IMPACT OF INDUSTRY TRANSFORMATION ON THE LIFECYCLE OF PHARMACEUTICAL PRODUCTS:
A Science and Risk Based Perspective

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Dedication

I dedicate this thesis: to my wife Amanda for her support, patience and devotion without whom none of this would be possible; to my children David and Amelia; to my parents for always encouraging me to strive for new heights.

And

To the memory of our grandparents who left fingerprints of grace on our lives; they shall not be forgotten!

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Author's Declaration

I declare that I do not have any financial or non-financial competing interests related to the content of the thesis.

Copyright Considerations

Abstract

The aim of this thesis is to explore the ongoing transformation in the pharmaceutical industry and its impact on pharmaceutical quality from the perspective of risk identification. This research was built upon three key pillars: Theoretical Evidence, Operational Evidence, and Opinion-based Evidence.

The regulatory environment is one of the most important external factors that affect a company's organization, processes and technological strategy. A quantitative analysis of regulatory events since 1813 revealed that the focus of regulators from 1813 to 1970s was centred on crisis management and public health protection. Since the 1980s a gradual move towards a greater focus on public health promotion, international harmonization, innovation, and agency modernization occurred.

The evolution of the pharmaceutical transformation was assessed through systematic review of the literature. Fourteen factors were identified that impact the pharmaceutical industry in future years. These factors, termed "transformation triggers", were considered as the theoretical evidence for the ongoing transformation. The relative importance ranking of the triggers was computed based on their prevalence within the articles studied. The four main triggers with the strongest theoretical evidence were: fully integrated pharma network, personalised medicine, translational research, and pervasive computing.

Operational evidence to verify existence of the transformation triggers was compiled through systematic collection of operational data. Trends in the operational evidence and the associated theoretical evidence were compared. Strong correlation between theoretical and operational evidence was found for the four transformation triggers listed above. Key areas of contrast included; healthcare management focus, adaptive trials and regulatory enforcement where the operational evidence was stronger than the theoretical evidence.

Expert opinion, obtained from a questionnaire-based survey on participants with recognised expertise in pharmaceutical regulation, product lifecycle or technology, validated the theoretical and operational evidence and supported the same four main pharmaceutical transformation triggers.

A quality risk model derived from the survey indicated a firm relationship between the pharmaceutical quality risks and regulatory compliance outcomes during the marketing approval and post-marketing phases of the product lifecycle and a weaker relationship during the pre-market evaluation phase.

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List of Acronyms and Abbreviations

Acd	Academic
ACS	American Chemical Society
CBER	Centre for Biologics Evaluation and Research
CDER	Centre for Drug Evaluation and Research
CDRH	Centre for Devices and Radiological Health
CFR	Code of Federal regulations
CIC	Cognitive Interview Comments
Con	Consulting
CRADA	Corporative Research and Development Agreements
CPI	Critical Path Initiative
CVM	Centre for Veterinary Medicine
EEC	European Economic Community
EU	Europe Union
EMEA	European Medicines Evaluation Agency
EMA	European Medicines Agency
FD&C	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GxP	Good Laboratory / Clinical / Manufacturing / Distribution Practices
GRP	Good Research Practice
Gov	Government
GAO	Government Accountability Office
Ind	Industry
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonisation
LJMU	Liverpool John Moores University
M&A	Merger & Acquisitions
NICE	National Institute for Health and Care Excellence
OCPP	Office of Critical Path Programs
ODA	Orphan Drug Act
OECD	Organisation for Economic Co-operation and Development
PAT	Process Analytical Technology
PDA	Parenteral Drug Association
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIL	Participant Information Leaflet
R&D	Research & Development
REC	Research Ethics Committee
Org	Research Organization
US	United States
WHO	World Health Organisation

Definitions

Adaptive Trials: in adaptive trials, information acquired during a particular clinical trial is used to alter the course of the trial without compromising its statistical validity.

Apothecary: a term often used between the 1600s and 1800s for individuals living in London who had passed the examinations of the Worshipful Society of Apothecaries of London. It does not refer to the chemist and druggist.

Bioinformatics: application of information technology and computer science to the field of molecular biology.

Biosimilar Products: as defined in HR 3590 is a product that is “highly similar” to the reference product “notwithstanding minor differences in clinically inactive components,” and for which there are “no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.”

Chemist and Druggist: a term first used to describe both chemical and drug merchants and practitioners of the emerging profession of pharmacy from the late 1700s.

Cloud Computing: computing model consisting of services that are commoditised and delivered in a manner similar to traditional utilities such as water, electricity, gas, and telephony. In such a model, users access services based on their requirements without regard to where the services are hosted or how they are delivered.

Drug Product: means a finished dosage form, for example, tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (source: FDA - 21 CFR Part 314).

Drug Substance: means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient (source: FDA - 21 CFR Part 314).

In-life Trials: leveraging emerging computation and communication technologies to replace Phase III trials.

Live Licensing: implies that the current Phase I to IV clinical testing process may eventually be selectively or wholly replaced by a system known as "in-life" testing or "live" licensing

Main Survey: is eliciting expert opinion on the transformation triggers and influence of proposed quality risks on regulatory compliance outcomes.

Open Innovation: in the pharmaceutical context is defined as leveraging external sources of innovation by collaborating with small biotechnology companies, universities, research partnerships, etc.

Operational Evidence: refers to systematic analysis of operational data that supports the concept of ongoing pharmaceutical transformation and hence the theoretical evidence. It is also the consolidated representation of the operational data in a graphical or tabular form.

Personalised Medicine: is concerned with the development and administration of treatments (based on a knowledge of genetic biomarkers or mutations) to patients who might best respond to an individually tailored treatment.

Pervasive Computing: an environment saturated with computing and communication capability

Pharmaceutical Chemist: a term that Pharmaceutical Society adopted in the 1840s, previously referred to mainly French scientists who promoted the use of chemical-based therapeutics.

Pharmaceutical Quality: a branch of regulatory science that is concerned with establishment and monitoring of internal standards to ensure product quality, patient safety and data integrity from the perspective of Good Laboratory / Clinical / Manufacturing / Distribution Practices (GxP).

Pharmaceutical Quality Risk: is defined as the potential adverse regulatory compliance outcomes relating to product quality, patient safety and/or data integrity during product lifecycle.

Pilot Survey: is the methodology used for testing the reliability and validity of the questionnaire used for the main survey.

Product Lifecycle: is defined as activities pertaining to product development, registration, manufacturing, distribution and product use. This from a regulatory compliance perspective equates to pre-market evaluation, marketing approval, and post-market surveillance events.

Progressive Licensing: see live licensing.

Regulatory Event: is defined as a legislative action or an initiative by regulatory authorities in response to a public health crisis or to promote a policy

Regulatory Science: refers to the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated medical products.

Systematic Review: refers to systematic nature of selecting and assessing articles against the acceptance criteria.

Theoretical Evidence: refers to systematic analysis of literature data that supports the concept of the ongoing pharmaceutical transformation.

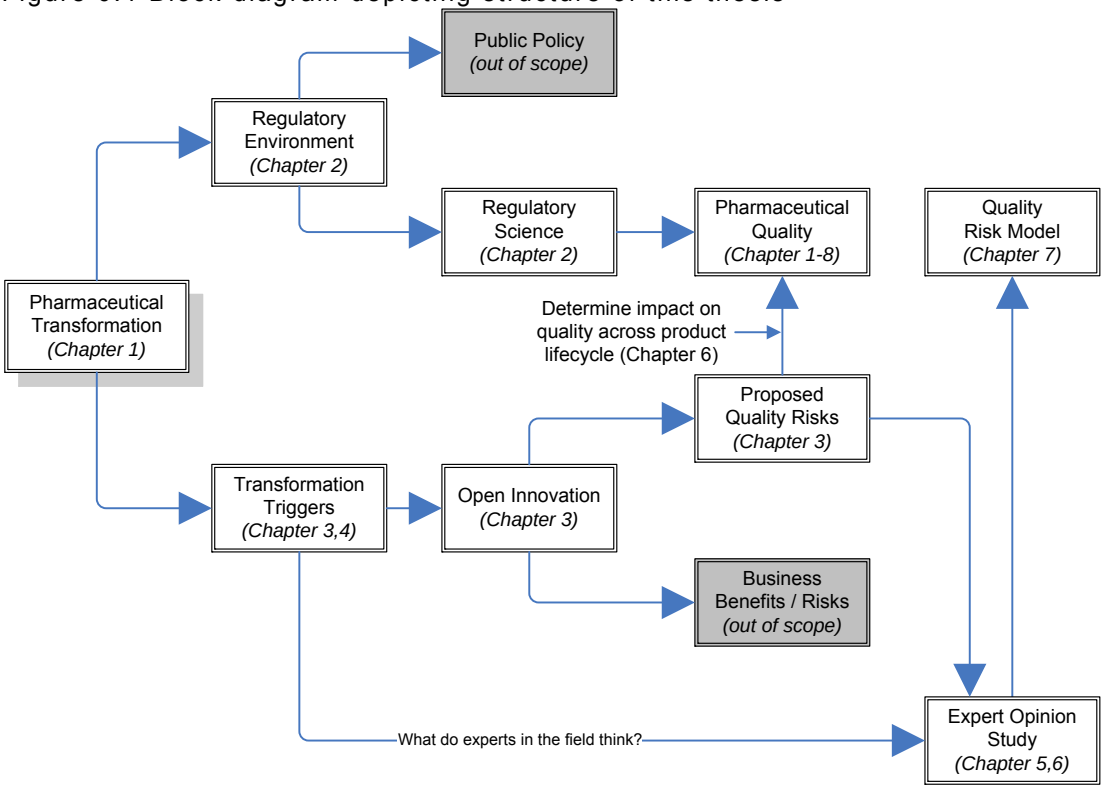
Transformation: the process by which the pharmaceutical industry intends to achieve and maintain advantage through changes in operational concepts, regulatory science, and technologies that will significantly improve its capability to innovate.

Translational Research: a bi-directional sharing of knowledge and ideas by the scientific and clinical disciplines to develop diagnostics that reliably selects the mechanisms leading to breakthrough therapeutics useful for practical applications that enhance human health and well-being.

Structure of This Thesis

This PhD thesis is structured around seven chapters and a final chapter on concluding remarks. The thesis starts with characterisation of the pharmaceutical industry and the regulatory environment (Chapters 1 & 2) within which the ongoing transformation is taking place. Thereafter the three pillars of this research are presented, which include: establishment of the theoretical evidence through identification and ranking of the transformation triggers (Chapter 3), establishment of the operational evidence through systematic analysis of existing product, regulatory, and technology related data (Chapter 4), and establishment of the opinion-based evidence through elicitation of expert opinion in the field (Chapter 5 & 6). The thesis concludes with a discussion on development of a pharmaceutical quality risk model (Chapter 7), implications from policy and practice standpoint, and recommendations for future research (Chapter 8). This is graphically illustrated in Figure 0.1.

Figure 0.1 Block diagram depicting structure of this thesis



The thesis starts with a historical overview of the development of the pharmaceutical industry and the associated regulatory environment. Since the pharmaceutical quality is a branch of regulatory science, it was important to understand key aspects of the regulatory environment within which the ongoing transformation is taking place. Chapter 2 was written to achieve this understanding. Knowledge gained in Chapter 2 was used to inform regulatory discussions, inform literature review coverage, and support conclusions presented in the last chapter.

The scope of this PhD research is limited to investigation of new and emerging quality risks induced by the on-going pharmaceutical transformation from the regulatory science perspective. Therefore detailed treatment of the following topics is out of scope:

- Public policy related to free movement of pharmaceutical goods, access to medicine, pricing of medicine, provision of healthcare, immunisation, etc.
- Business benefits/risks in the context open innovation relating to productivity, competition, intellectual property rights, etc.
- Drug safety practices relating to non-clinical laboratory studies
- Drug safety reporting relating to pharmacovigilance activities

Note: Although generally relevant to risk management within the pharmaceutical environment, the risks associated with drug safety and pharmacovigilance are known and in the context of regulatory science do not pose new or emerging quality risks. For this reason these two topics were not specifically treated as new or emerging sources of quality risk in this thesis.

Preface

After finishing my MSc in 1991, I remained at Liverpool University spending couple of years doing research in the department of industrial studies. During this time I collaborated with various companies and later joined R&D division of Mediva (a local biotechnology company) as a member of their process control team. My key responsibility was to validate the manufacturing processes and supporting technologies in the Hep-B vaccine pilot plant. In 1995 I joined Fisons Pharmaceuticals (later became RPR, Aventis, and now Sanofi) supporting various strategic projects including the development of inhalation, solid dosage, and chemical pilot plants and worldwide implementation of data management controls relating to pre-clinical, clinical, manufacturing, and regulatory processes. During my 20 years of pharmaceutical experience I have gained significant knowledge of pharmaceutical quality across various stages of the drug product lifecycle. Since 2009 I have assumed the responsibility for a team of experts, at corporate level, with the mission of helping the process owners in ensuring that systems they use during the product lifecycle are fit for their intended purpose. A key aspect of my mission is to predict regulatory controls for new and evolving technologies. This is achieved through internal/external benchmarking of evolving trends in pharmaceutical technology and regulatory science. As part of the external benchmarking, during the period 2007 - 2009, I attended various industry conferences designed to explore 21st century challenges to the pharmaceutical industry. The main focus of the discourse in these conferences was globalization and its impact on drug product lifecycle and also rapidly evolving technologies / emerging areas of science that could be applied to improve safety and efficacy of medical products. There were discussions around leveraging the knowledge gained from these emerging scientific fields to enhance the tools the industry and regulators use to evaluate drugs, biologics, and medical devices. Collaboration between all the stakeholders (federal agencies, patient groups, academic researchers, industry, healthcare practitioners, and others) was seen as a key success criterion. The general sentiment among the attendees was that the pharmaceutical industry is in the midst of a major transformation.

Through this exposure I learned that the emerging technologies offered improvement in many stages of the drug product supply chain. Areas of particular interest to me, from a pharmaceutical quality perspective, were testing and release of drug products in the manufacturing field and improved patient compliance in the clinical field. I also learned that the emerging scientific fields (e.g. genomics, imaging, and informatics) enabled development of targeted medicine – implying a shift from large-volume block buster paradigm to a small-volume specialised medicine targeted for a niche patient population. The experts in these conferences often argued that this type of transformation would mean

significant changes in the way drugs are developed, manufactured, approved, distributed and prescribed. My challenge at the time was to translate this learning into actionable knowledge supporting policy and practice from a pharmaceutical quality standpoint. The prerequisite for defining this actionable knowledge was a good understanding of the transformation-induced risks and in order to identify these risks one had to discern the factors that influenced the pharmaceutical transformation. My initial literature search revealed paucity of research on pharmaceutical quality risks in the context of the ongoing industry transformation. This gap in knowledge was the genesis of my PhD research proposal, which I presented to Professor James L Ford for consideration in early 2009.

CHAPTER 1: Introduction

The origins of medicines probably stemmed from observation that certain plants had effects other than fighting hunger and observation has always been the most important tool in the development of medicines (Royal Pharmaceutical Society, 2012). The favourable effects of medicines are likely to be accompanied by some adverse side effects. Therefore development, manufacture, distribution, prescription, and use of medicines also require an ethical framework to safeguard public health. In this chapter the origins of the pharmaceutical industry and drivers for the need for ethical framework in the form of regulatory oversight are described.

1.1 DEVELOPMENT OF THE PHARMACEUTICAL INDUSTRY

This section provides a historical account of how the pharmacy profession has evolved from its primitive days in Sumerian times into the modern pharmaceutical industry of today. The intent of this section is to provide the reader with basic knowledge of pharmaceutical industry and the associated regulations as the prologue to the rest of the thesis.

1.1.1 Early days of pharmacy (ancient times to 1100 AD)

Humans have been exposed to and have needed healing from disease, sickness and accidents since the beginning of time. The early practice of treating the symptoms in various civilisations resulted in the emergence of specialists often relying on methods based on pseudoscience and mysticism. Over time, based on trial and error and through the scientific exploration and enlightenment, these specialists acquired a body of knowledge that have progressively been augmented and refined (Anderson, 2005).

The pharmacy profession in its primitive form can be traced back to the Sumerian civilisation, later becoming part of the Persian Empire and now modern day Iraq. From around 4000 BC, Sumerians used medicinal plants such as liquorice, mustard, myrrh, and opium. The Sumerians wrote the earliest surviving prescriptions dating back to 2700 BC. There were specialists in the Sumerian society responsible for preparing medicines, a separate role from diagnosis and treatment, which was carried out by medics. In ancient Egypt Pharmacy was viewed as an important branch of medicine and had a high social ranking as a profession. Surviving papyrus scrolls, notably Ebers dating from 1500 BC includes listing of 700 drugs indicating that Egyptians made and used infusions, ointments, lozenges, suppositories, lotions, enemas, and pills in their treatments. In China (2000 BC), Shen Nung investigated medicinal value of

several hundred herbs wrote the first native herbal remedies containing descriptions of 365 plant-based drugs (Royal Pharmaceutical Society, 2012; Anderson, 2005). Meanwhile in Persia (300 AD) the academic centres like Jundishapur University were the scene for the union among great medical scientists from different civilizations. This tradition later produced great scientists such as Avicenna and Rhazes who contributed immensely to the field of medicine. Notable among their contribution was creation of creating the canon of medicine, identification and description of diseases such as smallpox and measles, and introducing the use of mercurial ointments (Anderson, 2005; Guthrie, 1945).

The shops selling medicinal goods existed around 1900 BC in the town of Sippara on the Euphrates River. This exemplifies first signs of organised preparation and dispensing of medicinal products for human use. People practicing this profession over the years have assumed many names including apothecaries, druggists, chemists and pharmacists (Anderson, 2005).

1.1.2 Pharmacy in the medieval times (1100 – 1617 AD)

These were difficult times in continental Europe, the period was littered with constant wars and frequent epidemics. Notable among them was Black Death that lasted for centuries. These existential conditions meant that new and effective remedies were needed to improve the health of the citizens and during this 500 year period significant progress was made in the field of medicine and pharmacy (Anderson, 2005; Guthrie, 1945).

The continuing migration of scholars from Persia to the west starting from the 8th century triggered creation of important centres of learning in Italy, Spain, France and England. An example is the medical school at Salerno which was the leading school of medicine and pharmacy in Europe (Anderson, 2005; Guthrie, 1945). The crusades (1095 to 1291) also had an impact in that it exposed Europeans to eastern culture and to new ideas on the practice of medicine and pharmacy. This included separation of medicine and pharmacy and compounding of drugs which was often practiced in large scale in Egypt. Other advanced practices, originally established in the Middle East, relating to government inspection of shops and markets run by pharmacists and herbalists were also adopted. The edict of Palermo by Fredrick II of Hohenstaufen (emperor of Germany and King of Sicily) in 1231 codified the separation of practice of medicine and pharmacy creating a clear distinction between responsibilities of physicians and those of apothecaries laying down regulations for their professional practice. This regulatory framework was intended to prevent exploitation of sick and was achieved through clearly defined responsibilities, creation of a predefined list of drugs to be used, limiting the number of premises to control price and imposition of storage time limits for

certain drugs to ensure efficacy (Anderson, 2005; Guthrie, 1945). Foundation of society of apothecaries in England (1617) is the key milestone towards the end of this era. The term apothecary, often used between the 1600s and 1800s, does not refer to the chemist and druggist. It was used for individuals living in London who had passed the examinations of the Worshipful Society of Apothecaries of London. Although the apothecary's practice included a strong dispensing element, it was more all-encompassing than the handling of drugs and chemicals. Following a ruling in the Rose Case (1701-1703/4), apothecaries became legally ratified members of the medical profession, able to prescribe as well as dispense medicines (Anderson, 2005; Royal Pharmaceutical Society, 2012; Guthrie, 1945).

1.1.3 Pharmacy in early modern times (1617 – 1841 AD)

From the perspective of practicing medicine and pharmacy this era was a period of transition in Europe. Challenges to occupational boundaries relating to dispensing and supply of medicines were common place, with regular disputes between physicians and apothecaries, and between apothecaries and chemists and druggists (Anderson, 2005).

Chemist and druggist was a term first used to describe both chemical and drug merchants and practitioners of the emerging profession of pharmacy from the late 1700s. Between the 1500s and 1700s, the differences between alchemy and medicinal chemistry were not at all clear but by 1841 some clarity emerged by pure scientific chemists establishing their own Chemical Society (Royal Pharmaceutical Society, 2012).

Pharmaceutical chemist, a term that Pharmaceutical Society adopted in the 1840s, previously referred to mainly French scientists who promoted the use of chemical-based therapeutics. After 1840s the term was being more widely applied to those interested in organic chemistry and in the skilled compounding of drugs (Royal Pharmaceutical Society, 2010).

During this period the systems of medical treatment in use included bloodletting, leeches, laxatives and purgatives (Royal Pharmaceutical Society, 2012). Many drugs were used as laxatives and diuretics but careful observation of their action led to refinement in their use. The most recognised application is the use of digitalis, by William Withering – an English chemist, for the relief of dropsy (oedema) in 1785; later recognised as treating the underlying heart failure. It took much longer to determine isolation of ascorbic acid (vitamin C) from citrus fruits after James Lind’s observation in 1747 that citrus fruits prevented scurvy in sailors on long voyages. These discoveries led to rapid expansion of surgery

from the battlefield into the hospital which included antiseptics and anaesthetics (Guthrie, 1945; Royal Pharmaceutical Society, 2012).

Homoeopathic medicine was also discovered in this period. The founder, Samuel Hahnemann (borne 1755) lived in Leipzig 1789 -1821 where he became a physician. In contrast to harsh treatments such as bloodletting, Hahnemann wanted to use more compassionate methods. In addition to homoeopathic medicine he stressed lifestyle changes for the patient such as improved sanitation, adequate rest, proper diet and regular exercise (Royal Pharmaceutical Society, 2012).

1.1.4 Role of bacteriology, physiology and pharmacology

In the nineteenth century a more logical approach to drug development was established and discoveries in other medically related disciplines were in the rise. The science of bacteriology grew rapidly and the role of micro-organisms in fermentation and disease was suggested. This linked to the work of an English physician in 1798, Edward Jenner, on the prevention of smallpox, which led to establishment of laboratories all over Europe to search for vaccines with the intent of both preventing epidemics and treating established disease. Another bacteriologist Paul Erlich, working on the selective staining of bacteria for identification purposes produced the first chemotherapeutic agent, arsphenamine (also known as “Magic Bullet”) against syphilis in 1910 (Anderson, 2005; Royal Pharmaceutical Society, 2012).

Chemical manufacturers, especially from the dye industry, at this time began to test synthetic chemicals against particular organisms in infected animals. This was a key driver for chemical companies to enter the pharmaceutical arena and became pharmaceutical companies as a result. Bayer exemplified this transition by successfully developing the dye prontosil red, active against streptococcal infections. This was soon shown to be the prodrug of sulphanilamide which was the first successful treatment for pneumonia and saved many lives. Alexander Fleming’s discovery of penicillin in 1928 is perhaps the most famous instance of discovery following chance observations that also occurred in the field of bacteriology. The development of penicillin as a commercial product as well as the search for other active substances produced by living organisms grouped together as antibiotics, were accelerated during the first world war by collaboration between the UK and US pharmaceutical industry. In 1944 one of the important discoveries derived from soil-based organisms was streptomycin which was active against tuberculosis, another major killer diseases of the nineteenth and early twentieth centuries. Unfortunately resistance to these early antibiotics soon built up and the pharmaceutical industry started to search for

synthetic modifications to combat this and increase stability to allow oral administration (Royal Pharmaceutical Society, 2012).

Another starting point for drug development was the development of human physiology[1], particularly the identification of glands whose hormone secretions were active throughout the body, and pharmacology, the study of the actions and uses of drugs. The isolation and analysis of the secretions led first to hormone replacement therapy with thyroid extracts (1890s) and insulin (1923) and later to more reliable therapy with synthetically produced material. The identification of various steroid molecules followed with cortisone in 1948 and the sex hormones in 1955 resulting in the first field studies of the contraceptive pill in 1960. In the second half of the twentieth century emphasis was again given to the relief of symptoms but this time with the support of science. Pharmacology was beginning to establish the mechanisms by which symptoms were produced even where the cause of the malfunction was still unknown. Oriented to studying impact of synthetic drug on pathological conditions, pharmacology was intimately linked with the rise of the pharmaceutical industry (Royal Pharmaceutical Society, 2012; Anderson, 2005).

1.1.5 The emergence of pharmaceutical industry (1860 – 1930)

The origin of the modern pharmaceutical industry traces back to i) apothecaries that transitioned into wholesale production of drugs in the middle of the 19th century and ii) dye and chemical companies that established research labs and discovered medical applications for their products starting in the 1880s. For example in 1668, Merck began as a small apothecary shop in Darmstadt, Germany and in the 1840s it began wholesale production of drugs. Similarly, Schering in Germany; Hoffmann-La Roche in Switzerland; Burroughs Wellcome in England; Etienne Poulenc in France; and Abbott, Smith Kline, Parke-Davis, Eli Lilly, Squibb, and Upjohn in the United States (US) all started as apothecaries and drug suppliers between the early 1830s and late 1890s. Other firms such as Agfa, Bayer, and Hoechst in Germany; Ciba, Geigy, and Sandoz in Switzerland; Imperial Chemical Industries in England; and Pfizer in the US began with the production of organic chemicals (especially dyestuffs) before moving into pharmaceuticals (Chemical and engineering News, 2012).

Pharmacy during American civil war - Most active pharmaceutical ingredients and raw material used in the US in the mid-1800s were imported. The healthcare system was very young and still evolving. A mounting struggle of such monumental size would call for a medical department ready to improvise and innovate quickly to meet the needs of a large standing army. Pharmacists were

[1] science of the mechanical, physical, and biochemical functions of humans, their organs, and the cells of which they are composed

engaged in every step of procurement of materials, inspection and preparation of finished drug products, distribution to warehouses and hospitals, and dispensing to patients. During the war, the Union established a network comprising as many as 30 depots, with key centres in New York and Philadelphia. The army relied heavily on a handful of large domestic drug companies for stable inventories and prices. Both the Union and Confederacy established laboratories to inspect raw drug materials and to prepare finished medicines. Both sides benefited from the expertise of talented and innovative chemists and pharmacists to ensure quality and efficiency (Hasegawa, 2000). Early manufacturers to grow their businesses relied on innovation in manufacturing rather than the discovery of new medicines. Leaders of the period, such as Edward Robinson Squibb, decided not to patent their innovations. This led firms to quickly copy the successes of other firms. The industry was relatively small, with most manufacturers providing items that pharmacists used in their compounding practices. The distinction between the manufacturers was the eponymous name of the owner, such as Squibb, Lilly or Abbott, guaranteeing quality. This state of the industry continued through the Civil War and into the early years of the 20th century (Worthen, 2003).

Emergence of pharmaceutical chemistry and pharmacology - the integration of apothecaries and dye/chemical companies into a distinct pharmaceutical industry took place in conjunction with the emergence of pharmaceutical chemistry and pharmacology as scientific fields at the end of the 19th century. This meant that the identification and preparation of synthetic drugs were linked with studying their impacts on pathological conditions. In 1980s, pharmaceutical companies in Germany and later in the US and England, established collaborative relationships with academic laboratories. These research partnerships and resulting research findings focused on dyes, immune antibodies, and other physiologically active agents that would react with disease-causing organisms. Synthetic organic chemistry emerged as an industrial discipline with a particular focus in the area of creating dyestuffs derived from coal tar. Transition from staining cells to making them more visible under microscopes to dyeing cells to kill them was a small evolutionary step. This transition enabled chemists to modify the raw dyestuffs and their by-products to make them more effective as medicines. In 1897, a chemist at Bayer, Felix Hoffmann, first synthesized aspirin (Chemical and Engineering News, 2012).

Impact of Chemical Industry - the important role of the chemist and chemical science in pharmaceuticals in the early-20th century is linked with the history of the American Chemical Society's (ACS) division of medicinal chemistry. Requirements for accurate analysis of medicines contained in the 1906 US Food & Drugs Act improved stature of US chemists and hence industrial employment. But US chemists rarely had the freedom to create new drugs, and relatively few companies manufactured complex therapies. Those activities were largely

dominated by German chemists working in conjunction with the major German chemical companies. World War I sanctions forced US chemists to copy German processes for producing drugs such as aspirin; Salvarsan for treatment of syphilis; and Veronal, a powerful hypnotic useful in easing the pain of battle wounds. In 1920, the focus from analysis to synthesis due to wartime changes, was a key driver for the ACS division to rename itself the Division of Medicinal Products (Chemical and Engineering News, 2012; Anderson, 2005).

Patent Drug-Makers - while largely unregulated by government bodies prior to the 20th century, the pharmaceutical industry faced challenges in differentiating its products from patent drug-makers whose secret recipes were not patented and they were peddled on the street by quacks. Wrongful claims made by the patent drug-makers concerning medical ingredients were tested against the national formularies and occasionally exposed by the professional bodies, including national physicians' associations, pharmacists' groups. For example the development of diphtheria antitoxin in the 1890s and subsequent cases of inactive or contaminated doses led the health authorities in Germany and France to test and oversee biologicals; similarly, the US Hygienic Laboratory was authorised to license manufacturers under the 1902 Biologics Control Act (Chemical and Engineering News, 2012; Royal Pharmaceutical Society, 2012). However in the US and Europe the authority of the government regulators to remove drug products from the market or constrain advertising claims were limited. Larger companies supported additional legislative interventions, including the 1906 Food & Drugs Act in the US and similar laws in several European countries that prohibited adulteration and forced manufacturers to reveal ingredients on product labels (Chemical and Engineering News, 2012). In spite of these regulations, in the early 1930s, most medicines were sold without a prescription and nearly half were compounded locally by pharmacists. Direct dispensing of medicine by the physicians to the patients was widespread and companies often supplied physicians with their favourite formulations. In the 1930s in Europe and America while the medical profession was well-established, the pharmaceutical industry was only beginning to develop medicines to treat pain, infectious diseases, heart conditions, and other ailments. Direct application of chemical research to medicine appeared promising, but only a few substances such as newly isolated vitamins and insulin, were more effective than treatments available at the turn of the century. Nevertheless the industry was at the crossroads of science, medicine, and growing health care markets set the stage for explosive growth (Chemical and Engineering News, 2012).

1.1.6 The modern pharmaceutical industry

Developments stated above led to the formal structuring of science, particularly chemistry, the rise of scientific research, and advances in technology and mass-production (Green-Templeton, 2009).

Second World War – during First World War in Britain, Burroughs Wellcome & Co. was alone in being able to supply many much needed drugs for military use, and other companies learned from this example. Several, including May & Baker, Nathan & Sons (Glaxo), and British Drug Houses developed research laboratories in the immediate post-war period. By the Second World War pharmaceutical companies in the US, Europe and Japan expanded rapidly after the Second World War by investing strongly in research, development and marketing (Green-Templeton, 2009; Chemical and Engineering News, 2012).

Post war reconstruction - the demands of the new National Health Service further stimulated the pharmaceutical industry. Many new therapies were developed, often by rational design based on increased knowledge of the underlying cellular mechanisms of drug actions. During this period the safety regulation increased in the US and Europe including the introduction of double blinded, clinically controlled trials for testing new medicines on the patients. This discovery boom by the 1970s was declining resulting in significant drop in the introduction of new drugs (Green-Templeton, 2009; Chemical and Engineering News, 2012).

The Genomic age - in the final decades of the twentieth century mergers and take-overs created large multi-national companies (Big Pharma), product diversification meant less reliance on medicinal products. Smaller biotechnology companies were established to accept the challenges of pharmaceutical development in the genomic age (Green-Templeton, 2009).

1.2 PHARMACEUTICAL REGULATORY ENVIRONMENT

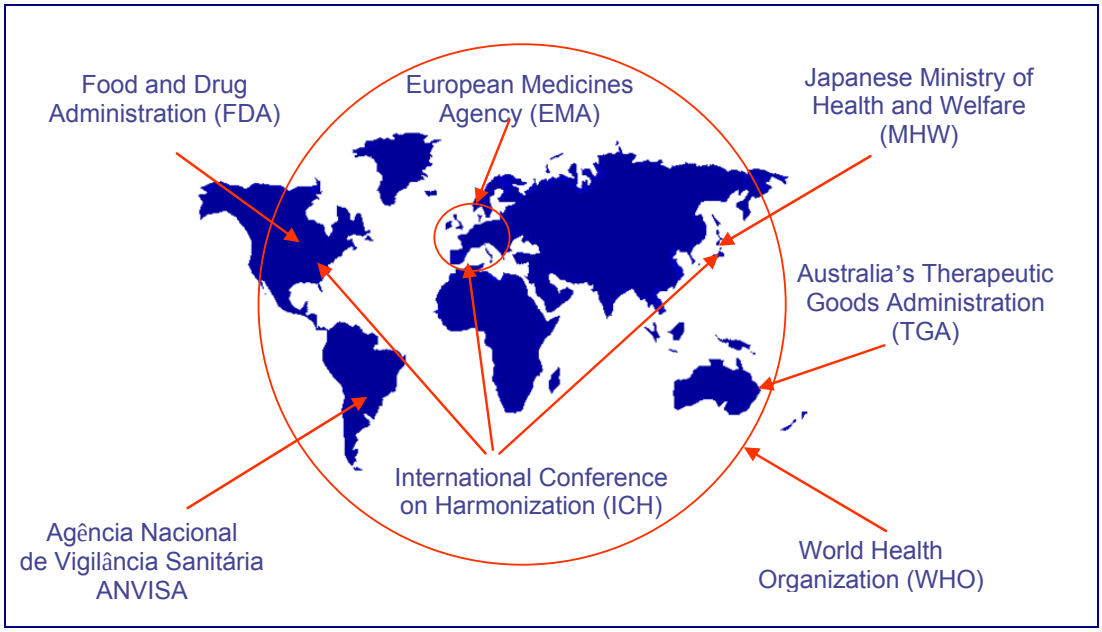
The evolution of the pharmacy from apothecaries to the genomic age has resulted in significant increase in industrialisation and technological complexity. This in turn has introduced ethical challenges impacting the drug product supply chain from the perspective of product quality, patient safety and related data integrity. Management of these ethical challenges are achieved through regulatory legislation and oversight, which collectively represents the pharmaceutical regulatory environment (see Chapter 2 for detailed description).

The pharmaceutical industry regulations, particularly in Europe Union (EU) and the United States (US), were established with the primary aim to protect and promote public health but also to respond to unexpected crisis. Since the pharmaceutical industry develops and manufacture products that affect patients'

quality of life, world governments have a keen interest in the industry and its products.

The regulatory landscape described in this section is limited mainly to the US and the EU with a brief description of the World Health Organization (WHO), see Figure 1.1. The main rationale for this approach is that pharmaceutical regulations globally are strongly influenced by US and the EU regulations due to the colossal size of the pharmaceutical markets in these important regions. Therefore description of the regulatory landscape for these two regions provides a good depiction of the historical evolution of the modern pharmaceutical regulatory environment. Another reason for restricting the scope to these two regions was to ensure that the research undertaken was feasible from a workload perspective.

Figure 1.1 Pharmaceutical regulatory bodies around the world



1.2.1 Regulatory environment in the EU

The regulatory environment in the EU is driven by the need to ensure free movement of goods and protection of public health (Hartmann, 2005). Fifty years ago, each European country had its own procedure for marketing authorisation of pharmaceutical products. Products from other European countries were not approved unless they went through the maze of local requirements. Since the 1960s, EU pharmaceuticals regulation has moved from legal harmonization, with the expectation of mutual recognition, to a complex system that joins national regulatory procedures and mutual recognition requirements with direct EU level regulation. The European pharmaceuticals regulatory agency (i.e. the EMA – formerly EMEA) was established in 1995 and later renamed as European

Medicines Agency (EMA). EMA has become an evaluation body with considerable authority and impact on regulatory decisions at the European level. Regulatory procedures have been standardised and the EMA has been empowered as a clearing house to approve medical products for all EU countries (Tanser & Mosseri, 2002; Li Bassi et al., 2003). The timeline of key regulatory events since 1965 is described in Table 1.1.

Table 1.1 The timeline of key EU regulatory events since 1965 (EURlex, 2012)

Timeline	Regulatory Event
1965	Crisis Management, the first pharmaceutical Directive 65/65/EEC was created as a reaction to the thalidomide disaster when thousands of babies were born with deformities as a result of usage of the drug during pregnancy. The directive aimed at harmonizing standards for approval of medicines in the European Economic Community (EEC). This was a pivotal event in the history of parmaceutical industry with a profound impact on practices relating to clinical trials, manufacturing, and post-marketing surveilance of drug products (see section 2.3.2 for more detail)
1975	After issuance of the first directive the evolution of EU regulatory landscape has been less about crisis management and more focused on establishments EU regulatory agencies and free movement of medicinal products for human and veterinary use. For example in 1975, the regulatory groundwork established ten yeas earlier was expanded through Directive 75/319/EEC to establish requirements for i) application for authorization to place medicinal products on the market, ii) examination of the said application iii) oversight of manufacture and imports coming from third countries, iv) safety reporting, and v) establishment of the Committee on Proprietary Medicinal Products.
1987	Biotechnology Products, complexity and cost of research for new biotechnology products that were emerging during the 1980s was the key driver behind Directive 87/22/EEC. Intent was to create a centralised procedure for authorizing European marketing of biotechnology products and making it mandatory for these products to be approved in one central location
1993	Centralised Procedure, the need for a single pharmaceutical regulatory agency in EU triggered the creation of Regulation (EEC) No 2309/93. This regulation established the European Medicines Evaluation Agency (EMEA) and laying down the centralised community procedures for the authorization and supervision of medicinal products for human and veterinary use.
1993	Decentralised Procedure, Directive 93/39/EEC laid down a parallel, decentralised alternative to the centralised procedure described above. Companies can apply for the simultaneous authorisation in more than one EU country of a medicine that has not yet been authorised in any EU country and that do not fall within the mandatory scope of the centralised procedure.
1995	Mutual Recognition Procedure, companies that have a medicine authorised in one EU Member State can apply for this authorisation to be recognised in other EU countries
2000	Orphan Drug Regulation, some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called ‘orphan’. Regulation (EC) No 141/2000 lays down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products.

Table 1.1 Continued

Timeline	Regulatory Event
2006	Paediatrics Regulation, before a medicinal product for human use is placed on the market in one or more Member States, it generally has to have undergone extensive studies, including preclinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population. Such studies may not have been undertaken for use in the paediatric population and many of the medicinal products currently used to treat the paediatric population have not been studied or authorised for such use. Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorization of, medicinal products for the paediatric population. Regulation (EC) No 1901/2006 lays down the requirements for providing necessary incentives to enable development and commercialisation of medicinal products for paediatrics use.
2007	Advanced Therapy Regulation, New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. This nascent field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body. Regulation (EC) No 1394/2007 lays down specific rules concerning the authorisation, supervision and pharmaco-vigilance of advanced therapy medicinal products.
2008	Variation Regulation, in the light of practical experience in the application of previous regulations impacting changes to terms of marketing authorization, Regulation (EC) No 1234/2008 intends to establish a simpler, clearer and more flexible legal framework for these types of changes, while guaranteeing the same level of public and animal health protection.

1.2.2 Regulatory environment in the US

In contrast to the EU, the regulatory environment in the US has been shaped by series of reactive steps of legislation adaptation in response to public health crises leading to creation of US Food and Drug Administration (FDA) (Borchers et al., 2007; Slater, 2005). States within the continental US exercised the principal control over domestically produced and distributed foods and drugs in the 19th century, control that was markedly inconsistent from state to state. The brief history timeline of key regulatory events since 1813 is described in Table 1.2.

Table 1.2 The timeline of key US regulatory events since 1813 (FDA History, 2012)

Timeline	Regulatory Event
1813	The Vaccine Act of 1813, though short-lived, was the first federal law dealing with consumer protection and therapeutic substances. Federal authority was limited mostly to imported foods and drugs. Adulteration and misbranding of foods and drugs had long been a fixture in the American cultural landscape, though the egregiousness of the problems seemed to have increased by the late 19th century (or at least they became more identifiable). By this time science had advanced significantly in its ability to detect this sort of fraud. Also, legitimate manufacturers were becoming more concerned that their trade would be undermined by purveyors of deceitful goods. Quinine-containing cinchona bark powder could be made less therapeutically effective-and much more profitable-by cutting it with just about anything, alum and clay masked poor wheat flour and thus netted a heftier return for the unethical company, and sufferers of any number of serious or self-limited diseases were relieved only of their finances by vendors of worthless nostrums. Even the so-called ethical drug firms were guilty of this practice.
1820	US Pharmacopeia, eleven physicians meet in Washington, D.C., to establish the U.S. Pharmacopeia, the first compendium of standard drugs for the United States.

Table 1.2 Continued

Timeline	Regulatory Event
1848	Drug Importation Act, this Act passed by the Congress requiring US Customs Service inspection to stop entry of adulterated drugs from overseas.
1862	The Bureau of chemistry was created, President Lincoln appoints a chemist, Charles M. Wetherill, to serve in the new Department of Agriculture. This was the beginning of the Bureau of Chemistry, the predecessor of the Food and Drug Administration.
1902	Biologics Control Act, this Act is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans. Congress appropriates $5,000 to the Bureau of Chemistry to study chemical preservatives and colours and their effects on digestion and health. Dr. Wiley's studies draw widespread attention to the problem of food adulteration. Public support for passage of a federal food and drug law grows.
1906	Food and Drugs Act, On 30 June 1906 President Roosevelt signed the Food and Drugs Act, known simply was the Wiley Act. This act, which the Bureau of Chemistry was charged to administer, prohibited the interstate transport of unlawful food and drugs under penalty of seizure of the questionable products and/or prosecution of the responsible parties. The basis of the law rested on the regulation of product labelling rather than pre-market approval. Drugs, defined in accordance with the standards of strength, quality, and purity in the
1912	Congress enacts the Sherley Amendment to prohibit labelling medicines with false therapeutic claims intended to defraud the purchaser, a standard difficult to prove. Mrs. Winslow's Soothing Syrup for teething and colicky babies, unlabeled yet laced with morphine, killed many infants.
1930	The name of the Food, Drug, and Insecticide Administration is shortened to Food and Drug Administration (FDA) under an agricultural appropriations act.
1938	Federal Food and Drug and Cosmetics (FDC) Act of is passed by Congress, containing new provisions: • Extending control to cosmetics and therapeutic devices. • Requiring new drugs to be shown safe before marketing-starting a new system of drug regulation. • Eliminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases. • Providing that safe tolerances be set for unavoidable poisonous substances. • Authorizing standards of identity, quality, and fill-of-container for foods. • Authorizing factory inspections. • Adding the remedy of court injunctions to the previous penalties of seizures and prosecutions.
1962	Good Manufacturing Practice is established, thalidomide, a new sleeping pill, is found to have caused birth defects in thousands of babies born in western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouse public support for stronger drug regulation. Kefauver-Harris Drug Amendments passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers are required to prove to FDA the effectiveness of their products before marketing them.
1971	Good Laboratory Practice established, National Centre for Toxicological Research is established. Its mission is to examine biological effects of chemicals in the environment, extrapolating data from experimental animals to human health.
1976	Medical Device Amendments passed to ensure safety and effectiveness of medical devices, including diagnostic products. The amendments require manufacturers to register with FDA and follow quality control procedures. Some products must have pre-market approval by FDA; others must meet performance standards before marketing.
1987	Investigational drug regulations revised to expand access to experimental drugs for patients with serious diseases with no alternative therapies.

Table 1.2 Continued

Timeline	Regulatory Event
1997	Food and Drug Administration Modernization Act reauthorizes the Prescription Drug User Fee Act of 1992 and mandates the most wide-ranging reforms in agency practices since 1938. Provisions include measures to accelerate review of devices, regulate advertising of unapproved uses of approved drugs and devices, and regulate health claims for foods.
1998	FDA promulgates the Paediatric Rule, a regulation that requires manufacturers of selected new and extant drug and biological products to conduct studies to assess their safety and efficacy in children.
2005	Critical Path Initiative (CPI), FDA's national strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured. Globalization, rapidly evolving technologies, and emerging areas of science are having a major impact on FDA-regulated medical products. CPI is leveraging the knowledge FDA has gained from these emerging scientific fields to enhance the tools it uses to evaluate drugs, biologics, and medical devices.

1.2.3 World Health Organization (WHO)

According to WHO National governments are responsible for establishing strong national medicines regulatory authorities with clear mission, solid legal basis, realistic objectives, appropriate organizational structure, adequate number of qualified staff, sustainable financing, access to up-to-date evidence based technical literature, equipment and information, and capacity to exert effective market control. The role of WHO in the area of medicines regulatory support is two-fold. One aspect relates to the development of internationally recognised norms, standards and guidelines. The second aspect relates to providing guidance, technical assistance and training in order to enable countries to implement global guidelines to meet their specific medicines regulatory environment and needs (World Health Organization, 2006).

1.2.4 The historical events driving the need for regulations

The history of the manufacture of medicines and health products is filled with incidents relating to their accidental or deliberate contamination. Public outcry after such occurrences has led to introduction or reinforcement of regulation and establishment of regulatory agencies to enforce the laws. Key events responsible for introduction or reinforcement of pharmaceutical regulations are listed in Table 1.3.

1.2.5 Pharmaceutical regulations and quality

Up to 1980s the focus of regulators was centred on crisis management and public health protection - a basic mission that has remained consistent over the years (US Supreme Court, 1969).

Table 1.3 Key events responsible for introduction or reinforcement of pharmaceutical regulations

Timeline	Reasons for Introduction of Pharmaceutical Regulations
1813	Control of smallpox
1848	Control entry of adulterated drugs from to the US
1902	Major issues with purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans
1906	Disclosures of insanitary conditions in meat-packing plants, the use of poisonous preservatives and dyes in foods, and cure-all claims for worthless and dangerous patent medicines. Journalists such as Samuel Hopkins Adams exposed in vivid detail the hazards of the marketplace. The nauseating condition of the meat-packing industry the final precipitating force behind both a meat inspection law and a comprehensive food and drug law.
1937	Elixir of sulphanilamide, containing the poisonous solvent diethylene glycol, kills 107 persons, many of whom were children, dramatizing the need to establish drug safety before marketing and to enact the pending food and drug law in the US.
1962	Thalidomide, a new sleeping pill, is found to have caused birth defects in thousands of babies born in Western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouse public support for stronger drug regulation in the US
1972	The talcum powder affair in Morhange during 1972, product contaminated by hexachlorophene, a bactericide sufficiently powerful to kill 36 children
1982	A "Tylenol scare" began when the first of seven individuals died in metropolitan Chicago, after ingesting Extra Strength Tylenol that had been deliberately contaminated with cyanide. Within a week, the company pulled 31 million bottles of tablets back from retailers, making it one of the first major recalls in American history
1987	The Therac-25 was a radiation therapy machine involved in at least six accidents between 1985 and 1987, in which patients were given massive overdoses of radiation. These accidents highlighted the dangers of technology validation and proving fitness for intended use

A review of the regulatory events indicates that since 1980s there has been a gradual change in regulatory direction towards a greater focus on public health promotion, international harmonization, innovation, and risk management (see Chapter 2).

The regulatory harmonization is achieved through the International Conference on Harmonisation (ICH) Launched 20 years ago; ICH brings together the drug regulatory authorities of Europe, Japan, and the United States, along with the pharmaceutical trade associations from these three regions, to discuss scientific and technical aspects of product registration. It is ICH's mission to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines (ICH, 2010).

Innovation in this context relates to establishment of a robust regulatory science program aimed at strengthening advances in biomedical sciences. Regulatory science is critical to effectively translate cutting edge developments in science and technology into promising products and therapies for the patients who need them. Just as biomedical research has evolved over the past few decades;

regulatory science must also evolve in important and powerful ways (FDA Strategic Priorities, 2010; EMA Roadmap to 2015, 2010).

Risk management is another key regulatory focus that intends to define a framework to improve regulator's ability to adjust the level of regulatory scrutiny commensurate with public health risk, a major component of which concerns inspection of pharmaceutical company's laboratory, clinical, manufacturing, and distribution practices.

There is a key difference between the pharmaceutical and other industries regarding product quality, safety and data-integrity. In the pharmaceutical industry quality practices are mandated by law and require establishment of an independent internal Quality Unit whereas in most other industries quality is often a voluntary activity. Within the pharmaceutical context, the health authorities accomplish their regulatory scrutiny through review of new product applications and inspection of laboratory, clinical, manufacturing, and distribution practices. The regulators rely on the industry to do internal supervision through their Quality Unit. The role of the Pharmaceutical Quality (through the Quality Unit) is to establish and monitor internal standards to ensure product quality, patient safety and data integrity from the Good Laboratory / Clinical / Manufacturing / Distribution Practices (GxP) perspective. The extent to which each pharmaceutical company meets GxP requirements has a direct impact on their ability to obtain approvals for their products and maintain the marketing authorization for those products.

Note: A pharmaceutical drug, also referred to as medicine or medication, is any biologically active substance intended for use in the medical diagnosis, cure, treatment, or prevention of disease. Vaccination in the other hand, is the administration of antigenic material (a vaccine) to stimulate an individual's immune system to develop adaptive immunity to a pathogen. Detailed discussion concerning public policy with respect to immunisation schemes and related safety events are outside the scope of this thesis.

1.3 CURRENT CHALLANGES IN THE PHARMACEUTICAL INDUSTRY

1.3.1 Ongoing industry transformation

The pharmaceutical industry since 1990 has experienced a decline in Research & Development (R&D) productivity, despite significant advancements in biomedical sciences and increasing R&D expenditure. According to the US FDA, the problem exists because the current medical product development path is becoming increasingly challenging, inefficient, and costly. The FDA, in its 2004 landmark publication "Innovation/Stagnation" (FDA Innovation or Stagnation, 2004)

illustrated that between 1993 and 2003 there was a significant drop in the number of new chemical and biologic applications submitted for approval. The FDA claims that this is because of the rising costs of product development that often force the innovators to focus their efforts on products with a potentially high market return. To address the innovation problem and ongoing evolutions in the regulatory landscape, the industry is making transformational changes to the pharmaceutical business. (See Chapter 3 for more detail). This consequently poses a major public health concern since fewer resources are deployed on products targeted for important public health needs such as rare diseases, prevention indications, or individualised therapies. This and other factors such as dramatic increase in number of overseas R&D and manufacturing facilities and diversity and complexity of medical products also play a key role in regulatory bodies to make transformational changes in how they work with the industry to protect and promote public health.

1.3.2 The regulators reaction

Both the FDA and EMA have strategic initiatives to address the innovation problem. The FDA's national strategy for transforming the way FDA-regulated medical products are developed, evaluated, and manufactured involves the Critical Path Initiative (CPI).

In Europe the EMA initially started by establishing the Innovation Task Force in 2001. EMA expanded this effort through the publication of its March 2007 report "Innovative Drug Development Approaches" with the aim of identifying scientific bottlenecks to the development of innovative medicines, both in the industry's R&D and in the academic environment.

Review of the outlined reports and related documents revealed the following common innovation enablers:

- Better product safety toolkit and standards - show that product is adequately safe for each stage of development
- Better product effectiveness toolkit and standards - show that product benefits people
- Better product manufacturing toolkit and standards – show product manufacturability, that it can go from laboratory concept to a manufacturable product
- Better product quality risk management toolkit and standards – show that the level of regulatory scrutiny can be adjusted commensurate with public health risk

1.3.3 The industry reaction

To address the innovation problem the industry has been going through significant transformational changes affecting the business model (R&D, manufacturing, etc.), regulatory compliance and technology. Open innovation (Chesbrough & Crowther, 2006) is a key characteristic of the ongoing industry transformation. In the open innovation paradigm centralised and internally focused approach to innovation is becoming obsolete and the pharmaceutical companies are not only trying to create value internally but increasingly leveraging external sources of innovation (small biotech, universities, research partnerships, etc.). Industry transformation triggers are characterised by the literature review conducted as part of this PhD effort. The important point to note is that the transformation triggers in the context of the open innovation paradigm pose challenges to Pharmaceutical Quality that needs further research, which is the main subject of this PhD thesis.

The industry is also fully engaged with the ICH effort on establishing international quality guidelines as an enabling toolkit to help improve innovation, as detailed above.

1.3.4 The role of the pharmaceutical quality

Achievement of the goals implied in the outlined common innovation enablers requires expertise throughout the drug product lifecycle, including contribution of the Pharmaceutical Quality (OECD, 1997; ICH E6, 1996; PIC/S, 2009). To harmonise practices for this contribution the regulatory agencies and industry started collaboration under the auspices of the ICH. This effort resulted in the following important quality guidelines that have been adopted internationally:

- Pharmaceutical Quality Risk Management – provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality (ICH Q9, 2005)
- Pharmaceutical Development – describes the process for presenting the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process (ICH Q8, 2005)
- Pharmaceutical Quality Systems - describes model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle (ICH Q10, 2008)

1.3.5 Rationale for the research and importance to the Pharmaceutical Industry

There is academic research in support of the common innovation enablers highlighted in section 1.3.2 above (NIH Research, 2009; EMA Research, 2010). The research is mainly concentrated on the safety and efficacy aspects. Although Pharmaceutical Quality is playing a key role however there is no academic research to support this fact. Furthermore there is no academic research exploring the quality risk model needed to cope with the new environment. Review of the 38 most cited quality management articles published between 1989 and 2009 revealed only 2 articles that studied pharmaceutical industry (Table 1.4). Neither of these articles focuses on the industry transformation. Therefore, there is a real need for research to characterise the regulatory evolution and industry transformation, identify the most important transformation triggers, determine the impact on Pharmaceutical Quality, and develop a quality risk model for the new environment.

Table 1.4 Prevalence of quality management articles by industry

Total Articles: *38* Author	# of companies in the study	Industry (Mixed - article includes multiple industries)	Sector (Mixed - article includes multiple sectors)	Country	# of citations
Bou-Llusar et al. (2009)	446	Mixed	Mixed	Spain	3
Curkovic et al. (2000)	526	Automotive	Manufacturing	US	8
Kaynak (2003)	214	Mixed	Mixed	US	177
Samson & Terziovski (1999)	1024	Mixed	Manufacturing	Mixed	363
Ahire & Dreyfus (2000)	418	Mixed	Manufacturing	US	15
Ahire & O'Shaughnessy (1998)	449	Automotive	Manufacturing	Mixed	49
Ahire et al. (1996)	371	Mixed	Manufacturing	US	591
Ahmad et al. (2009)	413	Pharma	Distribution	Pakistan	1
Anderson et al. (1995)	41	Mixed	Manufacturing	US	185
Antony et al. (2002)	32	Mixed	Mixed	Hong Kong	50
Badri et al. (1995)	424	Mixed	Mixed	UAE	107
Black & Porter (1996)	61	Mixed	Mixed	Mixed	408
Choi & Eboch (1998)	339	Electronics	Manufacturing	US	150
Cua et al. (2001)	163	Mixed	Manufacturing	Mixed	146
Das et al. (2000)	290	Mixed	Mixed	US	71
Douglas & Judge (2001)	193	Healthcare	Service	US	166
Dow et al. (1991)	698	Mixed	Manufacturing	Mixed	175
Flynn et al. (1994)	42	Mixed	Manufacturing	US	616
Forza & Flippini (1998)	43	Mixed	Manufacturing	Italy	90
Grandzol & Gershon (1998)	275	Engineering	Manufacturing	US	94
Ho et al. (2001)	25	Electronics	Mixed	Hong Kong	25
Joseph et al. (1999)	25	Mixed	Manufacturing	India	30
Kaye & Anderson (1999)	18	Mixed	Mixed	UK	60
Kontoghiorghes (2004)	2	Automotive	Manufacturing	US	8
Lai (2003)	304	Mixed	Mixed	Hong Kong	23
Lau et al. (2004)	600	Mixed	Mixed	China	12
Martinez-Lorente et al. (2000)	223	Mixed	Manufacturing	Spain	30
Miyagawa & Yoshida (2005)	52	Mixed	Manufacturing	China	3
Powell (1995)	19	Mixed	Manufacturing	US	903
Prajogo & Sohal (2003)	194	Mixed	Mixed	Australia	51
Rowley & Sneyd (1996)	22	Pharma	Manufacturing	UK	1
Rungtusanatham et al. (1998)	43	Mixed	Manufacturing	Italy	42
Sanchez- Rodriguez (2004)	306	Mixed	Purchasing	Spain	10
Saraph et al. (1989)	20	Mixed	Mixed	US	740
Sun (2000)	251	Mixed	Manufacturing	Mixed	18
Tamimi (1998)	173	Mixed	Mixed	US	35
Tan (2001)	310	Mixed	Mixed	US	37
Zu et al. (2008)	226	Mixed	Manufacturing	US	9

1.4 AIMS AND OBJECTIVES OF THIS THESIS

The aim of this thesis is to explore the ongoing transformation in the pharmaceutical industry and its impact on pharmaceutical quality from the perspective of risk identification. The following research questions and associated objectives were defined to achieve the above aim. The questions are based on researcher's industrial experience in pharmaceutical quality across drug product lifecycle and the preliminary review of the literature.

- What are the key triggers impacting pharmaceutical transformation?
- What will be the impact on regulatory science especially with respect to quality risk management?
- What is a plausible model for pharmaceutical quality risk suitable for the transformed environment?

1.4.1 Research Objectives

The above questions were explored by realizing the following objectives:

- Establish a good understanding of the pharmaceutical industry development from industrial and regulatory perspectives
- Characterise the pharmaceutical *regulatory environment* within which the ongoing transformation is taking place
- Identify and rank triggers impacting the pharmaceutical transformation in order to establish *theoretical evidence* in support of the ongoing pharmaceutical transformation
- Establish *operational evidence* in support of the transformation triggers
- Establish *opinion-based evidence* in support of the transformation triggers
- Develop the pharmaceutical quality risk model based on the knowledge gained from the analysis of the theoretical, operational and opinion-based evidence

Pharmaceutical quality risk in the context of this thesis is defined as the potential adverse regulatory compliance outcomes relating to product quality, patient safety and/or related data integrity during the product lifecycle. The term lifecycle includes activities pertaining to product development, registration, manufacturing, distribution and product use, which from a regulatory compliance perspective equates to pre-market evaluation, marketing approval, and post-market surveillance events. The term Regulatory Science refers to the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated medical products. This is based on the FDA definition provided in its science and research website (FDA Definition, 2010).

1.4.2 Overview of the methods used to accomplish the research objectives

Systematic review of the literature was the principal method used for characterising the regulatory environment and identifying the transformation triggers. This was done by focusing on qualitative content analysis of the articles and systematic literature search (Tranfield et al., 2003) for selection of articles. It is important to note that the intent of the literature review was not to perform a "systematic literature review", which is commonly used method to compare and contrast opposing views and opinions. Instead the intent of this research was to perform a systematic review of the literature to identify and rank likely triggers influencing pharmaceutical industry transformation and the factors that characterise the regulatory environment.

The use of the operational evidence is important as a verification mechanism in order to accept or repudiate the theoretical evidence based on the proof from the real world scenarios. The operational evidence was derived from data collected on pharmaceutical companies, products and technologies. Operational evidence was documented by consolidated representation of the operational data in a graphical or tabular form.

The opinion-based evidence in support of the theoretical and operational evidence was collected by surveying opinion of experts in the field. The study was a questionnaire based survey and was conducted in two phases of "pilot survey" and the "main survey".

Grouping of the relationships between theoretical, operational and opinion-based evidence constitutes the quality risk model in the context of pharmaceutical transformation. The relationship between theoretical and operational evidence was determined by computing the simple difference between the strength of the theoretical evidence and strength of the operational evidence. The fundamental backbone of the quality risk model is determining the relationship between transformation-induced quality risks (independent variables) and the corresponding regulatory compliance outcomes (dependent variables). This was accomplished by computing the covariance between the respective means of the transformation-induced quality risks and the regulatory compliance outcomes.

CHAPTER 2: *Characterisation of the pharmaceutical regulatory environment*

2.1 INTRODUCTION

As discussed in Chapter 1 the regulatory environment is one of the most important external factors that affect the organization, processes and technological strategy of a company especially in the case of the pharmaceutical industry where its products affect the quality of life for its consumers. The regulatory environment within the European Union (EU) is driven by the need to ensure free movement of goods and the protection of public health (Hartmann, 2005). Regulatory procedures have been standardised and the European Medicines Agency (EMA) has been established to approve medical products for all EU countries (Tancer & Mosseri, 2002; Li Bassi et al., 2003). In contrast, the regulatory environment in the United States (US) has been shaped by a series of reactive steps of legislation adaptation in response to public health crises – Examples include the legally marketed toxic elixir, which resulted in 107 US deaths in the 1930s, the thalidomide tragedy in Europe in the 1960s and faulty medical devices causing 10,000 injuries and 731 deaths in the mid 1970s in the US (Borchers et al., 2007; FDA Regulatory Information, 2007). In order to characterise the evolution of the regulatory environment, it is important to explore previous regulatory events, which should allow the identification of the key drivers behind legislations and enable the likelihood of future events to be predicted.

The goal of this chapter is to characterise the pharmaceutical regulatory environment. Since the requirements for pharmaceutical quality are driven by healthcare regulations, there is a need to describe the regulatory environment as a prerequisite to further studies. Therefore this chapter provides the backdrop to the regulatory discussions that will be covered in the subsequent chapters of this thesis – especially regarding the literature review coverage for identification of the transformation triggers in Chapter 3.

2.2 LITERATURE SEARCH AND REVIEW

The methodology used was composed of two key strands, the Literature Search described in Steps 1, 2 and 3 and Literature Review described in Steps 4, 5 and 6. This approach is illustrated in Figure 2.1.

2.2.1 Purpose and inclusion criteria (Step1)

The purpose of the literature review was to characterise the regulatory evolution and regulatory thinking that has in the past or is currently shaping the pharmaceutical regulations.

Since the US and EU are historically the largest pharmaceutical markets, US Food and Drug Administration (FDA) and European EMA were used as the two main sources of information for regulatory rulemaking and oversight in the pharmaceutical industry. In order to target better the article search, the 1999 to 2010 time-frame was selected. The starting point of 1999 as the acceptance criterion for article timeframe was chosen since around this time the initial ideas about pharmaceutical transformation were being discussed within the industry. EMA innovation taskforce (EMEA/SHMP, 2007) and FDA critical path initiatives (FDA Critical Path, 2007; FDA Innovation or Stagnation, 2007) are prime examples for which the preliminary deliberations started around 1999 but became official after year 2000. The 2010 endpoint for article selection was chosen since this was the year when the article search took place. It is important to note that after 2010 additional articles relating to regulatory environment (Chapter 1) and pharmaceutical quality (Chapter 7) were selected as references or for comparison purposes respectively.

Inclusion criteria incorporated two additional foci, i) a regulatory focus - centred on regulatory legislation, history, evolution and regulatory innovation and ii) a strategic focus - centred on the mission and key activities of the regulatory agencies with some forward looking coverage. Table 2.1 gives a list of the search phrases that were used during database and web searches.

Risks associated with the lifecycle activities such as drug safety and pharmacovigilance are known and in the context of regulatory science do not pose new or emerging quality risks. For this reason these two topics were not specifically treated as new or emerging sources of quality risk and therefore not listed as search phrases in Table 2.1.

2.2.2 Databases and search phrases (Step 2)

The databases used for this step were chosen because they contained three categories of article types, namely of peer-reviewed articles, those articles issued by regulatory agencies, and miscellaneous articles described as “Other”.

Peer-Reviewed Articles. Since the research scope is multidisciplinary, only the integrated search engines available through MyAthens or in the public domain were considered. Integrated search engines consolidate literature from multiple sources making the search process more efficient. The two databases that most

fit the outlined requirement were Web of Knowledge and Google Scholar and these search engines were used to search for the peer reviewed articles.

Regulatory Articles. The US FDA, EMA and International Conference on Harmonisation (ICH) websites were used to search for articles issued by the regulatory agencies within the timeframe described in Step 1 (Section 2.2.1).

Other Articles. The “other” category mainly included articles issued by industry, consulting, legal and research organizations. The general web search using Google was used to look for this category of articles.

Article Search Phrases. These are listed in Table 2.1, and are individual or combined text phrases that were used to look for articles in the databases. The selection of the search phrases was informed by the requirements described in Step 1 (Section 2.2.1). Execution of the search phrases provided an unfiltered list of articles that potentially met the acceptance criteria defined in Step1. Columns 2 and 3 of Table 2.1 show the number of articles found for each of the article search phrases during the article search process. Column 4 shows that, of the 358 articles found, 14 were selected as the *primary* articles and additional 16 were *derived* from the primary articles.

Figure 2.1 Process for article search, article selection and trend analysis of regulatory events

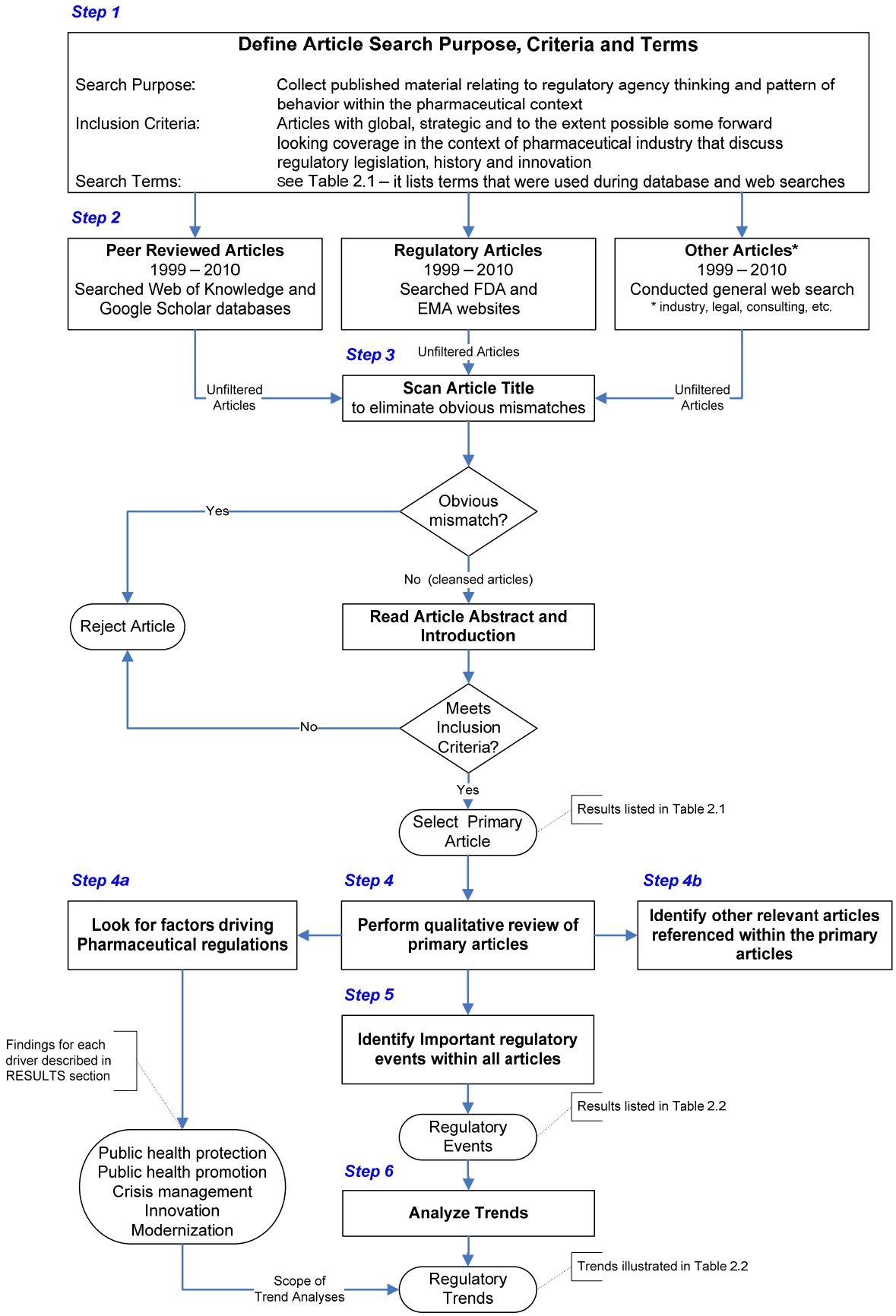


Table 2.1 Databases and article search phrases used in Step 2 and associated results

Article Search Phrases Search year: 2010	Google Scholar	Web of Knowledge	Selected Articles	Reference
“European Pharmaceutical Law”	26	3	1	Hartmann, 2005
“US Pharmaceutical Law”	4	0	0	-
“Pharmaceutical Regulations” AND Evolution	82	3	1	Tancer and Mosseri, 2002
“European Regulatory Policies” AND Pharmaceutical	31	3	1	Li Bassi, 2003
“US Regulatory Policies” AND Pharmaceutical	3	0	0	-
“The history and contemporary challenges” AND (FDA OR EMEA)	5	1	1	Borchers et al., 2007
“European Harmonisation” AND Pharmaceutical AND (FDA OR EMEA)	30	0	1	Abraham and Lewis, 1999
“US Harmonization” AND Pharmaceutical AND (FDA OR EMEA)	8	0	0	-
“International Collaboration” AND (“Drug regulatory Authorities” (FDA OR EMEA))	31	0	1	Epstein, 2009
“Regulatory Modernization” AND Pharmaceutical AND (FDA OR EMEA)	14	0	1	Merrill, 1999
"FDA Critical Path Initiative" AND “Pharmaceutical Industry”	65	1	1	Woodcock and Woosley, 2008
"Regulatory Thinking" AND Pharmaceutical AND (FDA OR EMEA)	36	2	1	Abraham and Davis, 2005
“Regulation and Innovation” AND “Cost benefit Analysis” AND (FDA OR EMEA)	0	0	1*	Schwartzman, 1976
FDA website > Downloads > “FDA Strategic Action Plan 2007”	0	0	1	FDA Strategic Action Plan, 2007
EMA website > Home > “Roadmap to 2010”	0	0	1**	EMA Roadmap to 2010, 2005
FDA website > Home > Science & Research > “Critical Path Initiative”	0	0	2	FDA Critical Path, 2007; FDA Innovation of Stagnation, 2004
Total	335	23	30***	

* General web search was conducted which resulted in reference 20

** As of October 2011 it reads Roadmap to 2015 but the Roadmap to 2010 can also be found in the same webpage

*** 14 primary and 16 derived articles.

2.2.3 Selection of primary articles (Step 3)

The titles of the unfiltered articles compiled in Step 2 (Section 2.2.2, Figure 2.1) were scanned to eliminate articles with obvious mismatches to regulatory topics in the pharmaceutical industry. For example, some articles dealt with topics related to the regulatory agencies but contained a main focus on the provision of healthcare services and economic or political issues rather than the regulation of pharmaceutical industry. Some of the articles had titles indicating that their scope were regulatory in nature but described non pharmaceutical industries. Articles with these types of titles were considered obvious mismatches and were eliminated from the list. The remaining articles (i.e. the cleansed list) were considered relevant for additional filtering as described below.

For each of the articles in the cleansed list, the abstract, introduction or the equivalent overview section of the articles were reviewed to determine if the article met the inclusion criteria as defined in Step 1 (Section 2.2.1). Any forward looking or strategic discussions, opinions or empirical evidence that were presented in these articles that related to pharmaceutical regulations from legislative, historical or innovation perspectives were considered central to meeting the inclusion criteria defined in Step 1 (Section 2.2.1). Those articles that met the inclusion criteria were tagged as "primary articles" and were selected for detailed review in Step 4 (Section 2.2.4).

2.2.4 Qualitative reviews of the primary articles (Step 4)

The content of all the primary and derived[2] articles were reviewed in detail, meaning that the entire article was read in the context of the inclusion criteria defined in Step 1 (Section 2.2.1). Particular attention was paid to texts that discussed the mission and key activities of the regulatory agencies that were responsible for and shaped the pharmaceutical regulations. Since the purpose of the literature review was to determine regulatory thinking and behaviour and typically these are manifest in agency mission and demonstrated in their actions, the most discussed mission and activities were classified into the six categories listed in Table 2.2. Subsequently each category was used i) as a driver of pharmaceutical regulations for which regulatory events identified in Step 5 (Section 2.2.5) were attributed to and ii) as the scale for the regulatory trends analysis in Step 6 (Section 2.2.6).

[2] See section 2.3.1 for more detail

2.2.5 Identification of important regulatory events (Step 5)

To identify important regulatory events all the primary and derived articles were reviewed and a description, year and country of each key regulatory event were recorded. A regulatory event is defined as a legislative action or an initiative by regulatory authorities in response to a public health crisis or to promote a policy. The outcome of this step is listed in Table 2.2.

2.2.6 Identification of regulatory trends with respect to key factors driving pharmaceutical regulations (Step 6)

Each of the regulatory events identified in Step 5 (Section 2.2.5) were studied in the context of the "drivers of pharmaceutical regulations" established earlier in Step 4 (Section 2.2.4). During review of each article every time a regulatory event was encountered that related to one of the six identified driving factors (Table 2.2), it was counted as one occurrence together with the date of occurrence. This process was repeated for each of the primary and derived articles and the regulatory trend analysis was performed using the regulatory events listed in Table 2.2.

2.3 RESULTS AND DISCUSSION

The article selection procedure resulted in 30 articles targeted for literature review (Table 2.1). The review of the literature resulted in the identification of six factors driving pharmaceutical regulations, namely: public health protection, public health promotion, crisis management, harmonization, innovation, and modernization. Important regulatory events were extracted from the selected articles and tabulated for analysis (Table 2.2). The number of articles found in Google Scholar and Web of Knowledge were 335 and 23 respectively of which 14 primary articles were selected and additional 16 articles were derived from the primary articles (Table 2.1).

Each Regulatory event was evaluated in detail paying particular attention to those texts supporting one or more of the six key factors. The results of the evaluation are mapped in Table 2.2 to determine the regulatory trends. The explanation of each of the six factors follows.

Table 2.2 Summary of regulatory events and six driving factors related to regulatory mission/activities

Regulatory Event	Year	Country of Origin	Six driving factors: Crisis Management	Public Health Protection	Public Health Promotion	Harmonization	Modernization	Foster Innovation
Vaccine Act	1813	US		x	x			
Drug Importation Act	1848	US		x				
Biologics Control Act	1902	US	x	x				
Food and Drugs Act	1906	US		x				
FDA takes it current name	1930	US						
Food, Drug, and Cosmetic Act	1938	US	x	x				
Factory Inspection Amendment	1953	US		x				
cGMPs Established (21 CFR Part 210/211)	1962	US		x				
EU Directive 65/65/EEC was established	1965	EU	x	x				
GLPs Established (21 CFR Part 58)	1975	US		x				
EU Directive 75/319/EEC was established	1975	EU		x				
Medical Device Amendments	1976	US	x	x				
Revision to cGMPs	1978	US		x				
EU Directive 87/22EEC was established	1987	EU				x		
Prescription Drug Marketing Act	1987	US		x				
Safe Medical Devices Act	1990	US		x				
EU Directive 91/356/EEC was established	1991	EU		x		x		
Generic Drug Enforcement Act	1992	US		x				
Prescription Drug User Fee Act (PDUFA)	1992	US			x		x	
EU Regulation 2309/93 was established	1993	EU		x		x		
EU Directive 93/93 was established	1993	EU				x		
ICH E6 GCP Guideline was established	1996	GL		x		x		
FDA Modernization Act	1997	US					x	
21 CFR Part 11 regulation was established	1997	US		x			x	x
ICH Q7 was established	1998	GL				x		
Medical Device User Fee & Modernization Act	2002	US			x		x	
21st Century GMPs – Risk Based Approach	2004	US			x		x	x
Process Analytical Technology	2004	US			x			x
EU Directive 2004/10/EC	2004	EU		x		x		
FDA Critical Path	2005	US			x		x	x
ICH Q8 was established	2005	GL				x		x
ICH Q9 was established	2005	GL				x		x
ICH Q10 was established	2007	GL				x		
FDA Transparency Initiative	2009	US					x	

2.3.1 Rationale relating to method selection

The characterization of the rationale and behaviour of the regulatory agencies required knowledge of the regulatory legislation, regulatory history, regulatory evolution and regulatory innovation within the pharmaceutical context. This knowledge was gained by review of relevant articles and notable regulatory events. The inclusion criteria were used as a filtering process for the selection of

articles in various steps of the search methodology (Figure 2.1). The inclusion criteria discussed in Step 1 (Section 2.2.1) were designed to enable the selection of all relevant articles that provided information on the events surrounding pharmaceutical regulation and initiatives. To focus the scope of the article search effort, i) regulatory agencies that significantly impact the pharmaceutical regulations globally and have enforcement presence in the largest pharmaceutical markets were studied, and ii) a blend of established and recent ariticles were selected in order to moderate between articles that reflected the evolutinery aspects of the regulations and those that better mirrored the current thinking of the regulatory agencies.

During the review of the primary articles in Step 4 (Section 2.2.4), papers referenced within the text (i.e. derived articles) that seemed relevant in scope to the primary articles were searched for within the outlined databases, they were read and if they met the inclusion criteria they were included in the regulatory trend analysis described in Step 6 (Section 2.2.6). Exceptions were made in two cases where each of the two articles met the inclusion criteria except for the timeframe (i.e. issued prior to 1999). This was only done when the article in question was pivotal. These articles were by US Supreme Court (1969) and Schwartzman (1976).

Examples of key regulatory events (Step 5, Section 2.2.5), tabulated in Table 2.2, included passage of new legislations or amendments to existing ones, creation or dissolution of regulatory organizations and establishment of global guidance for cross agency collaboration via ICH.

The regulatory trend analysis (Step 6, Section 2.2.6) was based on identification of the key regulatory events. The timeframe used for identification of the key regulatory events was 1813 to 2010. The 1813 starting point was used since this was the year when the first regulatory event took place (i.e. passage of Vaccines Act in the US). The 2010 end point was used since this was the year when the search was conducted and the latest regulatory event at that time was 2009 Transparency Initiative by the FDA.

2.3.2 Public health protection

Advances in new drugs, biopharmaceuticals, medical devices, and diagnostic-tools present significant opportunities for improvements in health care. Ensuring the safety and effectiveness of medical products is a key focus of the regulatory authority commitment to protect and promote public health. Approvals of new therapies are only granted if their benefits (lives saved, extended or enhanced) outweigh the risks they pose (these are blended statements from references cited in previous sections). Public health protection has been an overriding

purpose of the pharmaceutical legislations (US Supreme Court, 2007) in the past and will remain so in the future since the provisions for protection of public health is stipulated in pharmaceutical regulations as requirements (see trends in Table 2.2). A prime example is the 1962 Kefauver-Harris amendment (US Congress, 2010), which had a profound impact on drug development process especially in terms of methods used for design, conduct and analysis of clinical trials. The new authorities given to FDA by the Kefauver-Harris amendments:

- Required that manufacturers prove the effectiveness of drug products before they go on the market, and afterwards report any serious side effect
- Required that evidence of effectiveness be based on adequate and well-controlled clinical studies conducted by qualified experts. Study subjects would be required to give their informed consent
- Gave FDA 180 days to approve a new drug application, and required FDA approval before the drug could be marketed in the United States
- Mandated that FDA conduct a retrospective evaluation of the effectiveness of drugs approved for safety - but not for effectiveness - between 1938 and 1962
- Allowed FDA to set good manufacturing practices for industry and mandated regular inspections of production facilities
- Transferred to FDA control of prescription drug advertising, which would have to include accurate information about side effects
- Controlled the marketing of generic drugs to keep them from being sold as expensive medications under new trade names

Table 2.2 demonstrates the pervasive presence of public health protection in key legislations since 1813.

2.3.3 Public health promotion and advancement

A key mission of the regulatory agencies is commitment to the advancement of public health (US Supreme Court, 2007). An important aspect of this commitment is provision of an effective post marketing surveillance of medical products (US Government Accountability Office, 2006; FDA Strategic Plan, 2007). Several high-profile drug safety cases in recent years have heightened the importance of this topic (US Government Accountability Office, 2006). For example at a congressional hearings in September 2004, FDA was criticized for taking too long to tell physicians and patients about studies linking the use of antidepressants among children to an increased risk of suicidal behaviour. Similarly, at a congressional hearing in November 2004, it was alleged that FDA did not act quickly enough on evidence it obtained in 2001 about the cardiovascular risks of Vioxx, an anti-inflammatory drug that was developed and marketed by Merck pharmaceuticals. In the US, this has motivated the Government Accountability Office (GAO) to issue a report on the effectiveness of

FDA in managing post marketing surveillance of drug safety decision making (US Government Accountability Office, 2006). As a remediation strategy, the FDA has initiated cooperative programs that seek to bring safe and effective medical products to patients faster and improve communication of information about risks of drugs and devices (US FDA Strategic Plan, 2007). Concerning the latter, the US Congress in the fall of 2007 passed the FDA Amendments Act, mandating the FDA to establish an active surveillance system for monitoring drugs, using electronic data from healthcare information holders. The Sentinel Initiative is the response of the FDA to that mandate, which intends to "...create a new post-marketing surveillance system that will, by 2012, be using electronic health data from 100 million people to prospectively monitor the safety of marketed medical products" (Platt et al., 2009).

Internationally since 2007, the FDA and EMA cooperate closely to facilitate the sharing of documents and information related to assuring the safety, quality, and efficacy of pharmaceutical products (FDA Strategic Plan, 2007). This cooperative activity is intended to further enhance public health promotion and protection in the EU and the US (FDA Strategic Plan, 2007).

The future trends in public health advancement will likely involve evolutionary changes in patient communication, new enforcement tools, use of new labelling concepts, and post marketing surveillance (Platt et al., 2009; Psaty & Burke, 2006).

2.3.4 Crisis management

Historically governmental reaction to serious public health events has been the key driver for early landmark pharmaceutical legislations.
The congressional milestones (Table 2.2) include:

- The Federal Food, Drug, and Cosmetic Act (FD&C) of 1938, which was passed after a legally marketed toxic elixir, killed 107 people, including many children.
- The Kefauver-Harris Amendments of 1962, which were stimulated by the thalidomide tragedy in Europe, strengthened the rules for drug safety and required manufacturers to prove the effectiveness of their drugs.
- The Medical Device Amendments of 1976, which followed a U.S. Senate finding that faulty medical devices had caused 10,000 injuries, including 731 deaths. The law applied safety and effectiveness safeguards to new devices

Another landmark US legislation, The Patient Protection and Affordable Care Act (HR 3590), was signed into law on March 23, 2010. This time the motivation behind the legislation was a response to a different kind of crisis, which was the

expansion of healthcare coverage to over 30 million uninsured Americans. Although the legislation has largely received favourable response from the Pharmaceutical industry, provisions relating to an approval pathway for biosimilars have drawn a mixed response from the innovator-drug and generic-drug part of the industry (PhRMA, 2009). A "biosimilar" product as defined in HR 3590 is a product that is "highly similar" to the reference product "notwithstanding minor differences in clinically inactive components," and for which there are "no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product."

The trend in crises management, which was prevalent at early stages of regulatory evolution, is now changing. Since 1976, regulatory agency rule-making in the pharmaceutical industry is increasingly driven by international harmonization, fostering innovation and regulatory modernization (Table 2.2). According to the Institute of Crises Management (Institute of Crises Management, 2009), the Pharmaceutical industry hit the top-ten in the list of crisis-prone industries in 1999 and has remained there ever since. Examples of other crisis-prone industries include food, petroleum, automobile, and aircraft industries. The most recent report issued in 2009 ranks the industry at number seven (Institute of Crises Management, 2009). Based on the trends observed in Table 2.2 within the next decade the industry is likely to continue experiencing challanges largely due to introduction of new technologies and practices in an open innovation context that are advancing in a faster rate than the associated regulatory environment (discussed in Chapter 3). It is also important to note that the regulatory controls relating to these new and emerging technologies and practices are less mature than the existiting regulatory controls governing product safety and effiacy. However unlike some of the earlier events, the outcome may not involve landmark legislations that created the current regulatory environment. This is largely due to the existence of a mature regulatory framework in developed countries.

2.3.5 Harmonization

Collaboration between regulators and the industry will increasingly encourage further global harmonization with an ultimate goal of having one application per trial to all authorities (Funning et al., 2009). For example the FDA and the EMA cooperate closely with international partners, reinforcing the US and EU contribution to global harmonization (EMA Roadmap to 2010, 2005). In 2009, the FDA announced a collaborative agreement with the EMA for a Good Clinical Practices Initiative (Bass & Klasmeier, 2009). Under this new initiative, the two agencies will increase collaboration on inspection activities to ensure that clinical trials are conducted in a consistent, appropriate and ethical fashion

(Bass & Klasmeier, 2009). The agreement, signed in 2005, facilitates among the agencies the exchange of information relating to legal and regulatory issues, scientific advice, orphan-drug designation, inspection reports, marketing-authorization procedures and post-marketing surveillance (Bass and Klasmeier, 2009). The FDA and EMA also work closely with ICH on matters of harmonization. These agencies have already published numerous guidance documents on topics such as quality (Table 2.2) and various aspects of pharmacogenomics (Sudhop et al., 2008).

The majority of the interviewed scientists, regulatory managers and regulators in an empirical study of the pharmaceutical industry, believed that "European harmonization would either raise safety standards or at least maintain them as high as previous national standards" (Abraham & Lewis, 1999).

The FDA is trying to increase number of non-US pre-approval inspections for drug products manufactured within the developing countries. This is exemplified by establishing a close collaboration with China and India (Epstein et al., 2009). The FDA also works with international and inter-governmental bodies on the harmonization of international standards, guidance, recommendations, and risk analysis principles. Regional drug regulatory agencies have also embarked on harmonization schemes for pharmaceutical regulations (FDA strategic Action Plan, 2007; Epstein et al., 2009).

2.3.6 Fostering innovation

Empirical studies have shown that regulation is one of many external drivers that affect the technological strategy of a company (Schwartzman, 1976). Examples of other external drivers include the business environment (shaped by customers, competitors, and suppliers), new and emerging technologies, availability of skilled human resources, etc. Profitability may decrease as a result of regulation-induced costs. Several studies have been cited, which indicate an increase of 100 to 1000% in R&D costs per new chemical entity as a result of pharmaceutical regulation (Schwartzman, 1976). The regulators during the Seoul ICDRA conference suggested that technological innovation is essential for regulation to succeed and that focused attention by regulators is needed to encourage specific kinds of technological change (World Health Organization, 2006). They also recommended that national regulatory agencies should contribute to ensuring the right balance between the need for innovation and equitable access, and between commercial and public health interests (World Health Organization, 2006).

Within the pharmaceutical industry, regulatory agencies are responsible for advancing the public health by helping to speed innovations that make medicines

more effective, safer, and affordable. To this end they need to continually examine whether current regulations are still valid today and for future needs (US FDA strategic Action Plan, 2007; Carney, 2005). There is some evidence that this is happening in recent years. The ICH quality guidelines (Q8, Q9, Q10) and FDA's Critical Path initiative (Woodcock, 2007; Woodcock and Woosley, 2008) are some examples. Both FDA and EMA have issued reports on how they intend to foster innovation (FDA Critical Path, 2007; EMEA/SHMP, 2007; US FDA Innovation or Stagnation, 2004). Table 2.3 provides an overview of the key points.

The strategic investment by regulators in scientific areas such as those listed in Table 2.3 will contribute to medical product innovation. The investment is likely to produce some advanced scientific regulatory standards with the intent of providing predictability and enhancing efficiencies for product development (EMEA/SHMP, 2007; FDA Innovation or Stagnation, 2004). The ultimate goal of the strategic investment by the regulators is to increase public access to new medical products by helping the industry to shorten the medical product development time, identify doubtful products earlier in development, and get more promising products into the development pipeline (Table 2.3).

2.3.7 Modernization

The concept of modernization within regulatory authorities took root in mid 1990s. The aim is to expedite regulatory approval process so new pharmaceutical products could reach the market more quickly. Science-led modernization of regulatory processes will require modernised facilities to support more efficient operations with state of the art technologies. It will also require innovative approaches to expand access to scientific expertise to integrate emerging science into regulatory processes. Provision of modern information infrastructure and information management to enable improvements in data-driven regulatory decision processes is another key enabler (FDA Strategic Action Plan, 2007).

Within the US, the FDA Modernization Act of 1997 is enacted to extend earlier legislation designed to expedite the FDA approval process. The law also encouraged the harmonization of the regulatory process between the U.S., Europe, and Japan to avoid duplication, so patients would have greater access to new drugs worldwide (Tancer & Mosseri, 2002).

Modernization in the EU shares some similarity with the US approach but there are also major differences. A summary of key points for the US and the EU modernization activities are tabulated in Table 2.4 (Bass and Klasmeier, 2009; FDA Innovation or Stagnation, 2004; Merrill, 1999).

2.3.8 Discussion

In this chapter the regulatory environment was described in relation to key drivers behind the pharmaceutical regulations. Table 2.2 summarises the important regulatory events that have taken place since 1813 (Tancer & Mosseri, 2002, Borchers et al., 2007, Worthen, 2006). It is evident that from 1813 to 1970s the focus of regulators was centred on Crisis Management and Public Health Protection - a basic mission that has remained consistent over the years (US Supreme Court, 1964). Since the 1980s a gradual move in the regulatory environment towards a greater focus on Public Health Promotion, International Harmonization, Innovation, and agency Modernization may be seen. The change in focus is an important development since regulators consider the collaborative science-driven regulatory environment central to fostering innovation and enabling continuous improvements.

Although there is a positive trend in regulatory harmonization globally, there have been historical differences between various regulatory regions (e.g. US, EU, Japan, etc.) especially with regards to the pre-market review of the new drug applications. These differences have had public health implications - for instance according to a quantitative survey, over twice as many new prescription drugs were withdrawn from the market on grounds of safety between 1971 and 1992 in the UK as there were in the US. This was attributed to a more stringent US pre-market review standards, causing the FDA to release fewer unsafe drugs onto the market in the first place (Abraham & Davis, 2005).

Table 2.3 Key aspects of US and EU regulatory approaches to fostering innovation

FDA approach to fostering innovation (FDA Innovation or Stagnation, 2004)	EMA approach for fostering innovation (EMEA/SHMP, 2007)
• Developing better evaluation tools with a particular focus on biomarkers • Streamlining clinical trials • Harnessing bioinformatics • Moving manufacturing into the 21st century • Developing products to address urgent public health needs • At-risk populations – paediatrics	• Focus on biomarkers • Statistical methods and clinical study designs • Faster access tools – conditional approvals • Risk management plans • Clinical trials • Global harmonization • Interaction between industry and academia • Advanced therapies and emerging treatments

Table 2.4 Key aspects of US and EU approach to regulatory modernization

Key aspects of US FDA modernisation (FDA Innovation or Stagnation, 2004; Merrill, 1999)	Key aspects of EU EMA modernisation (EMA Roadmap to 2010, 2005)
• Renewal of the prescription drug user-fee program • Reforms of the FDA's drug approval process by integrating emerging science into regulatory processes • Changes in drug promotion and labelling rules • Expediting study and approval of fast-track drugs • Reforms in device regulation • Harmonization of regulation with international standards • Modernise FDA's Information Technology platform	Modernise EMEA by: • Efficient and transparent procedures • Top quality scientific assessment • Timely access to safe and effective innovative medicines • Continuous monitoring of medicinal products • Access to information

2.3.9 Summary of the salient points

As discussed in Section 2.2, purpose of the literature review and review of the regulatory events was to characterise the regulatory environment. The regulatory environment has two key elements; one that deals with public health policy and another is concerned with scientific methods. The first element is primarily concerned with political and socioeconomic issues particularly those relating to free movement of goods, access to medicine, drug product pricing, etc. The latter is primarily concerned with provision of science-based regulatory controls to ensure the safety and efficacy of pharmaceutical products for human use. Both elements have a profound impact on innovation and productivity of drug discovery and development processes.

Due to uncertainties and variations in the political landscape at the individual country level, a unified prediction of where the public heath policy will be in the future cannot be accurately estimated and also is outside the scope of this research. For example access to medicine in UK is based on the guidance of the National Institute for Health and Care Excellence (NICE) whose mission is to provide independent guidance to healthcare professionals and others to ensure quality and value for money. Whereas similar guidance and decision making in the US is largely performed by the healthcare insurance providers. However with respect to the second element, the regulatory actions to date indicate a move towards public health promotion, modernization and fostering innovation. Although this trend in regulatory thinking is likely to continue in the future it is also reasonable to posit that the industry transformation and dispersion of disruptive technologies (discussed in Chapter 3) will provide new regulatory challenges that will perhaps require crisis management responses to regulatory rule making from time to time.

CHAPTER 3: *Identification and ranking of triggers impacting the industry transformation: a systematic review of the literature*

3.1 INTRODUCTION

As described in Chapter 1 (Section 1.3) the productivity in the pharmaceutical industry has experienced a decline since 1990 despite increasing expenditure and investments in R&D (Cockburn, 2006; Cohen et al., 2004; Ahlborn et al., 2005; Peck wt al., 2007; Deloite white paper, 2009; Grabowski & Kyle, 2008). Challenging, inefficient, and increasingly costly product development is a key reason for the decline in productivity (FDA Innovation or Stagnation, 2004). According to the FDA the rise in costs of product development is forcing the innovators to focus their efforts on products with a potentially high market return (FDA Innovation or Stagnation, 2004).

To address the innovation problem stated above and the ongoing changes in the regulatory environment described in Chapter 2 (EMA Road Map to 2010, 2005*;* EMA Road Map to 2015, 2009; FDA Strategic Action Plan, 2004; Woodcock & Woosley, 2008; Milne, 2006), the industry is making transformational changes to the pharmaceutical business. In Chapter 1 transformation was defined as the process by which the pharmaceutical industry intends to achieve and maintain advantage through changes in operational concepts, regulatory science, and technologies that will significantly improve its capability to innovate.

A key feature of the ongoing industry transformation is open innovation. This means that pharmaceutical companies no longer rely solely on their centralised and internally focused R&D and are increasingly looking towards external sources of innovation such as research partnerships with small biotechnology companies, universities, governmental organizations, etc. (Enkel et al., 2009; Chesbrough , 2003; Talaga, 2009; Crommelin et al., 2010). Since 2001, some of the large pharmaceutical companies such as Glaxo, Pfizer and Lilly have experimented with the open innovation approach (Hunter & Stephens, 2010). Hunter and Stephens (2010) see open innovation as “a valuable model for large pharmaceutical companies” and argue that adopting an open innovation culture will require a change in operational concepts, deployment of new technologies and application of resources to nurture external collaborations and monitor their progress to ensure success.

Systematic review of the literature is a plausible method to characterise potential transformation triggers. The systematic discernment of patterns from a widely diverse set of studies and/or body-of-research requires analytical review

(Ginsberg & Venkatraman, 1985). In this study a literature review focusing on qualitative content analysis of the primary articles with systematic literature search (Tranfield et al., 2003) for selection of articles was used. It is important to note that the intent of the literature review was not to perform a "systematic literature review", which is commonly used method to compare and contrast opposing views and opinions. Instead the intent of this research was to perform a systematic review of the literature to identify and rank likely triggers influencing pharmaceutical industry transformation. The term "systematic review" refers to systematic nature of selecting and assessing articles against the acceptance criteria. The outcome of the literature review described in this Chapter is termed "theoretical evidence" and used throughout this thesis.

The aim of this Chapter is to identify and categorise pharmaceutical industry transformation triggers and associated theoretical quality risks by taking a systemic approach to reviewing the relevant literature.

In establishing the theoretical evidence in this chapter, the coverage of the article selection/review was influenced by the changes in the regulatory environment described in Chapter 2. As a reminder these changes included a greater focus on public health promotion, international harmonization, and innovation.

3.2 METHOD

A six step process was followed that was organised into three phases; article selection, article review and article classification.

Step 1: Selection of primary articles
Step 2: Review of the primary articles
Step 3: Selection of derived articles
Step 4: Testing for article diversity
Step 5: Searching for transformation triggers in all articles
Step 6: Ranking of transformation triggers

The selection phase involved development of a selection procedure, which identified articles that were considered relevant (Step 1 – Section 3.2.1, Step 3 – Section 3.2.3). The review phase involved the detailed review of the primary articles to discern likely triggers for pharmaceutical transformation (Step 2 – Section 3.2.2, Step 5 – Section 3.2.5) and testing of article diversity (Step 4 – Section 3.2.4) and the classification phase was performed to determine relative importance ranking of the transformation triggers with respect to their prevalence within the articles studied (Step 6 – Section 3.2.6).

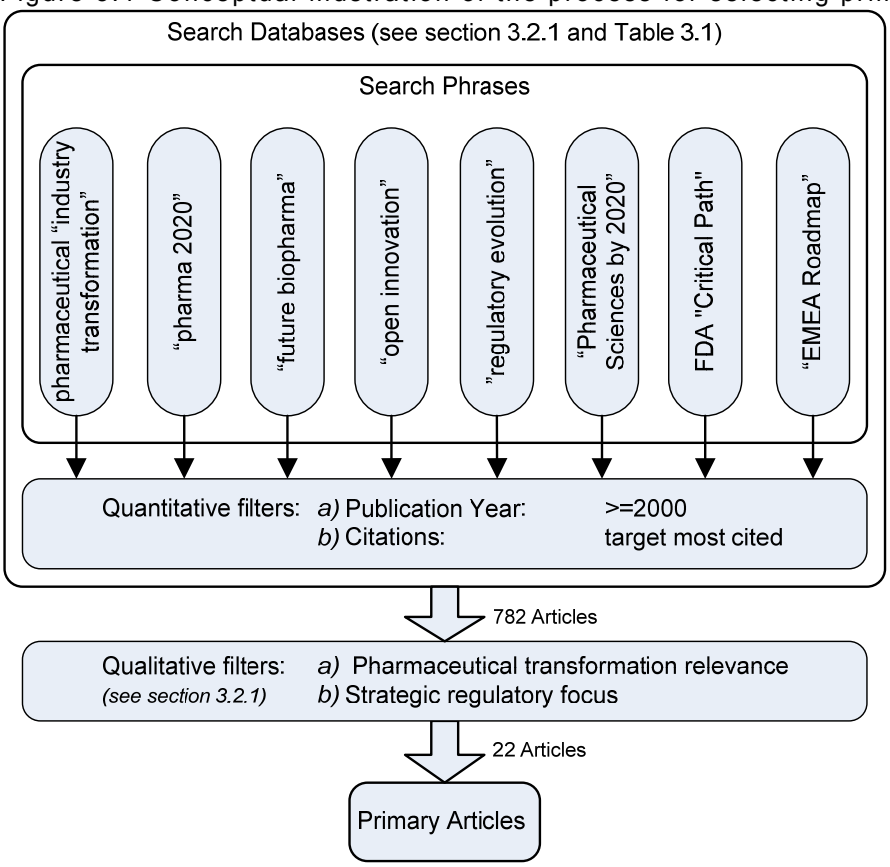
3.2.1 Selection of primary articles (Step 1)

As mentioned previously transformational change in a given industry is influenced by regulatory policy, industry environment and technological evolution (Meyer et al., 1990). It is therefore important that the selection procedure for the primary articles taps into the diverse body of literature that includes academic, industrial and government issued articles. The inclusion criteria and search phrases listed in Table 3.1 was used in the search procedure to identify the primary articles. The primary article selection procedure is conceptually illustrated in Figure 3.1.

Table 3.1 Inclusion criteria and search phrases used for selection of primary articles

Inclusion criteria	Search phrases
• Publication year (quantitative measure, >= 2000) • Citations (quantitative measure, targeted most cited) • Pharmaceutical transformation relevance (qualitative measure) • Strategic regulatory focus (qualitative measure)	• pharmaceutical “industry transformation” • “pharma 2020” • “future biopharma” • “open innovation” • ”regulatory evolution” • “Pharmaceutical Sciences by 2020” • FDA "Critical Path" • “EMEA Roadmap”

Figure 3.1 Conceptual illustration of the process for selecting primary articles



Database and Search Phrases - Since this PhD research involves topics that span multiple disciplines such as pharmaceutical transformation, pharmaceutical innovation, pharmaceutical technology, and pharmaceutical regulatory sciences, the search tools used had to be diverse. For peer-reviewed academic articles, Web of Knowledge, Science Direct, Wiley Online Library and JSTOR were used. Regulatory agency websites US FDA, European Medicines Agency (EMA), Health Canada and International Conference on Harmonization (ICH) were the main source of regulatory articles. Articles published by the consulting firms and other research organizations were collected through general Google Web Search or Google Scholar. The Google Scholar search was limited to articles in business, medicine, pharmacology and social sciences subject areas. The inclusion criteria and search phrases listed in Table 3.1 was used in the search procedure without truncation and in quotes when shown. Google Search is a web engine owned by Google Inc. The main purpose of Google Search is to look for specified text in publicly accessible documents offered by web servers and one of its key features is the ability to rank web pages that match a given search phrase.

Publication Year - the articles for each transformation trigger were selected from a period of time that was as recent as possible. This approach was based on the assumption that more recent articles reflect better the current thinking of the academic, consulting, governmental, industry and research organizations. The article search was performed in 2010 and included articles published from 2000 to 2010. Year 2000 was selected since the initial exploratory work on article selection revealed that forward looking opinions within the articles typically considered a 5 to 10 year time-horizon.

Number of Citations - this selection criterion represents the total number of citations per article. Frequency of citation of an article is a sign of its pervasiveness and hence its ability to influence current and future thinking. Its value is impacted by the year of publication. Therefore a balance between recentness (publication date) and pervasiveness (number of citations) was needed and was designed into the ranking procedure (Step 6 – Section 3.2.6). If available, the citation information was gathered from the publisher of the source journal, otherwise Google Scholar was used to determine the number of citations.

Pharmaceutical Transformation Relevance - the literature search was focused on articles that had relevance to the healthcare sector in general and the pharmaceutical industry in particular. This search was performed by review of the abstract and/or the introduction section of the articles which had met the initial criteria (publication date, containing the word “pharmaceutical” or “healthcare” in the title or abstract) and therefore considered an interesting article for further evaluation.

Strategic Regulatory Focus - the initial exploratory article search revealed that, within the US and the EU, the current and future thinking of the regulators is often articulated in their long term strategic plans. These plans dealt with the topics that are important from the perspective of public health protection and promotion. One such topic is the creation of a regulatory environment that enables the development of innovative life saving drugs, which regulators view as important to promotion of public health. The regulators use their long term strategic plans to communicate their current achievements and future actions relating to protection and promotion of public health. For these reasons the last two search phrases listed in Table 3.1 (i.e. FDA "Critical Path", “EMEA Roadmap”) were designed to discern articles that specifically dealt with forward-looking regulatory initiatives.

3.2.2 Review of the primary articles (Step 2)

Each primary article was reviewed in detail, meaning that the entire article was read focusing on views, opinions, actions and evidence that provided topics on pharmaceutical industry evolution from innovation and regulatory science perspective. Multiple occurrence of a particular topic relating to innovation or regulatory science was deemed important and was tagged as a transformation dimension. After review of all the primary articles (i.e. articles selected during the initial search) the identified transformation dimensions were classified into similar groups, which are termed “Transformation Triggers”.

3.2.3 Selection of derived articles (Step 3)

During review of the primary articles any referenced articles that were deemed relevant (i.e. covering similar topics as the primary article) were noted. After a review of the identified article’s abstract and/or introduction section, a determination was made whether the relevant articles were compliant with the same inclusion criteria as for the primary articles and if so they were considered as derived articles. The content of these articles were then searched for transformation triggers as described in Section 3.2.5 below.

3.2.4 Testing for article diversity (Step 4)

It was necessary to enhance generalization of results derived from the literature review to demonstrate that articles supporting each of the transformation triggers came from diverse sources but with similar sourcing characteristics, i.e. article type, age and pervasiveness. This goal was achieved through the design of the procedure for selecting articles and was tested through descriptive statistics and application of the Kruskal-Wallis H-test (Section 3.3.1; Chan & Walmsley, 1997).

3.2.5 Search for transformation triggers in all articles (Step 5)

The content of each article was searched using the search phrases listed in Table 3.2. Two or more search phrases were used for each transformation trigger. An article was deemed relevant to a transformation trigger if it covered at least one of the Related Search Phrases listed in Table 3.2. The intent was to focus the search effort on new and emerging pharmaceutical risk areas and not on the well-characterised risk topics relating to drug safety and pharmacovigilance.

Table 3.2 Search phrases related to the transformation triggers used in Step 5

Transformation Trigger	Corresponding search phrases
T1 - Healthcare Management Focused	• Healthcare Management • Health care Management • Biomarkers/Diagnostic-s • Drug/Device Combo
T2 – Fully Integrated Pharma Network	• FIPNet • Research Collaborations • Research Partnerships • External Partnerships • Externalization • In Licensing
T3 - Personalised Medicine	• Personalised medicine • Individualised medicine • Targeted Medicine • Open Innovation
T4 - Virtual R&D	• Virtual R&D • Virtual Discovery • Virtual Pharma
T5 - Translational Research	• Translational Research • Biomarkers • Predictive Medicine
T6 - Adaptive Trials	• Adaptive Trials • In-Life Trials
T7 - Global Harmonization	• FDA EMEA Partnerships • Global Harmonization
T8 – Science and Risk Based Regulations	• Risk Based Approach • Science-based regulations • Science-driven regulations
T9 – Live Licensing	• Live Licensing • Progressive Licensing
T10 – Enforcement	• Enforcement • Compliance
T11 – Biotechnology	• Biotechnology • Future of biotechnology
T12 – Nanomedicine	• Nanotechnology • Nanomedicine • Nanomaterials • Nanoscience
T13 - Bioinformatics	• Bioinformatics • Biocomputing • Virtual Lab
T14 – Pervasive/Cloud Computing	• Pervasive Computing • Cloud Computing • Ubiquitous computing • Biomedical Sensors

3.2.6 Ranking of transformation triggers (Step 6)

In order to highlight the relative ranking of each transformation trigger a weighted scoring approach was employed, similar to that described by Chan and Walmsley (1997). To achieve this, an importance weight score was applied to each attribute characterizing the article. These attributes include publication source, publication year, and number of citations per article, which are described below. The weighted score for each article with respect to each of the transformation triggers was computed based on the weighting scheme listed in Table 3.3.

Table 3.3 Weighting scheme used in Step 6 for relative importance ranking of the articles

Article Attribute	Importance Weight
Publication Year	Year Score (YS)
>2005	3
2000-2005	2
<2000	1
Article Source	Source Score (SS)
Gov	5
Acd	4
Con	3
Ind	2
Org	1
Citations	Citation Score (CS)
> 10	3
5 to 10	2
<5	1

i) Publication Source. Regulatory policy, the current thinking of the regulators, and their future plans are tangible examples of future regulatory direction and therefore were given the largest weight. Academic peer reviewed articles by definition are thoroughly vetted and therefore were given the second largest weight. Articles written by renowned consulting organizations typically reflect and influence the key stakeholders in the industry and therefore receive next priority weight. Articles written by industry practitioners not published in peer review journals and non-Pharma research organizations receive the lowest weight respectively.

ii) Publication Year. Articles published before 2000 (Pre) or on/after 2000 (Post). Pre was used to account for one derived article published in 1998 (Love, 1998) that was included as an exception since it met the acceptance criteria except for the publication date, which was close enough to 2000 and therefore was included.

iii) Number of Citations. This selection criterion represents the total number of citations per article. Frequency of citation of an article is a sign of its pervasiveness and hence its ability to influence current and future thinking. Its

value is impacted by the year of publication. Therefore a balance between recentness (publication date) and pervasiveness (number of citations) was needed and was designed into the ranking procedure (Table 3.3). If available the citation information was gathered from the publisher of the source journal, otherwise the Google Scholar was used to determine the number of citations.

The prevalence of the transformation triggers in the primary and derived articles was determined as described in Step 5 (Section 3.2.5) and their relative ranking was performed in accordance with the following computational procedure (Table 3.4).

In Table 3.4 Equation 3.1 was used to determine the geometric mean (central tendency) of the weighted scores for each article. In Equation 3.2 the weighted scores were multiplied by the geometric mean to determine a single Consolidated Weighted Score (CWS) for each article. Equation 3.3 was used to compute relative importance ranking of each of the CWS relative to the entire population of CWSs. Equation 3.4 was used to find the ordinal position of the CWSs. Some ordinal positions had the same value, which were termed “Ties”. Equation 3.5 and Equation 3.6 were used to compute the ordinal position of the CWS taking into account the Ties. Equation 3.7 was used to perform the ranking in reverse order. Equation 3.8 was used to calculate a single consolidated ranked score for each transformation trigger (by adding columns of the rank matrix). Larger the consolidated ranked score the higher the relative ranking of the transformation trigger.

Table 3.4 Procedure used in Step 6 for computing relative importance ranking of all articles

$GM_i = \sqrt[3]{(YS_i \times SS_i \times CS_i)}$	Equation 3.1: Geometric Mean
$Fw_{ij} = \Pi_i \times GM_i$	Equation 3.2: Consolidated weighted score
$R_{ij} = Rank(Fw_{ij}, Fw_{1j}, Fw_{nj})$	Equation 3.3: Rank including Ties
$OP = \left\{Sum\left(If\left(Fw_{ij} < Fw_{1j}, Fw_{nj}, 1, 0\right)\right)\right\}$	Equation 3.4: Ordinal Position
$TC = Count\{[R_{ij} \in (R_{1j}, R_{(i-1)j})]\}$	Equation 3.5: Tie Count (R_{10} is an empty cell)
$R_{ij} = OP + TC + 1$	Equation 3.6: Rank correction to account for Ties
$RR_{ij} = (n - R_{ij}) + 1$	Equation 3.7: Rank in Reverse order
$RankC_j = Rank(C_j, C_1, C_k)$	Equation 3.8: $C_j = \sum RR_{ij}$ where i=1..n and j=1..k

The structure of the ranking matrix is illustrated in Table 3.5. In this matrix the rows represent the primary and derived articles and the columns represent the transformation triggers. Scores per article and a given transformation trigger is

captured in the matrix, the corresponding weighted scores are calculated and finally the relative importance ranking is computed based on the procedure described above.

Table 3.5 Structure of the ranking matrix used in Step 6 for relative importance ranking of all articles

	C_1	C_2	C_j
		scores	
A_1	F_{11}	F_{12}	F_{1j}
A_2	F_{21}	F_{22}	F_{2j}
A_i	F_{i1}	F_{i2}	F_{ij}
		weighted scores	
A_1	Fw_{11}	Fw_{12}	Fw_{1j}
A_2	Fw_{21}	Fw_{22}	Fw_{2j}
A_i	Fw_{i1}	Fw_{i2}	Fw_{ij}
		ranked scores	
A_1	RR_{11}	RR_{12}	RR_{1j}
A_2	RR_{21}	RR_{22}	RR_{2j}
A_i	RR_{i1}	RR_{i2}	RR_{ij}
RankCj ➔	$C_1=\sum R_{i1}$	$C_2=\sum R_{i2}$	$C_k=\sum R_{ij}$

i = 1 ... n and j = 1 ... k

A - article; n - sample size; k - number of transformation triggers; F - trigger frequency (1 - present, 0 - absent); Fw - weighted trigger frequency; RR - reverse rank of each data point

3.3 RESULTS AND DISCUSSION

3.3.1 Results for article search and article diversity testing

The article selection procedure resulted in 22 primary articles targeted for literature review; and 60 derived articles from review of the primary articles (Table 3.6).

Testing of article source diversity (Section 3.2.4) was achieved using descriptive statistics provided in Table 3.7 and Kruskal-Wallis H-test for Transformation Triggers (H_{TT}). The null hypothesis was defined to mean that most articles have similar sourcing characteristics and the alternative hypothesis was defined to mean that most articles have diverse sourcing characteristics.

$$H=\frac{12}{N(N+1)}\left(\sum_{j=1}^{K}\frac{(SumR_j)^2}{n_j}\right)-3(N+1)$$

...Equation 3.9

R_j (Rank of each transformation trigger in Table 3.8; where j = 1 ... K)

n_j = (number of data points per transformation trigger in Table 3.8; where j = 1 ... K)

N = 146 (total number of data points for all transformation triggers)

K = 14 (number of transformation triggers)

df = (K-1) =13 (degrees of freedom)

H_{TT} = 13.02 (result of solving Equation 3.9)

Since H_{TT} =13.02 is less than the chi-squared H-test table value of 19.812 (Chan & Wamsley, 1997) the probability of occurrence i.e. the p-value is greater than 0.10. Hence the null hypothesis is accepted and it can be concluded that most articles have similar sourcing characteristics – meaning most articles are academic in nature, published after 2005 with less than 5 citations.

The qualitative assessment of views, opinions and evidence presented in the primary articles resulted in 14 transformation triggers. The relative importance ranking results for each of the transformation triggers are provided in Table 3.8.

3.3.2 Results of the literature review

Among the 14 transformation triggers, 4 triggers namely Fully Integrated Pharma Network (*Trigger 2*), Personalised Medicine (*Trigger 3*), Translational Research (*Trigger 5*) and Pervasive Computing (*Trigger 14*) were found to be the most prevalent within the articles studied. Note that the ordinal positioning of the transformation triggers in Table 3.8 (1 to 14) is different from their importance ranking provided at the end of the table. The 14 triggers are simply listed in the order of transformation topics that were addressed during the literature search and review process i.e. organization, product, regulatory and technology related topics respectively.

Information within the articles relating to transformation triggers were synthesised into statements that are presented below for each of the triggers. The proposed open innovation trends and the theoretical quality risks for each of the four main transformation triggers are also discussed below.

Trigger 1: Healthcare Management Focused - the main thrust of the discussions in the referenced articles seem to suggest that pharmaceutical industry is transforming from a mainly product-based industry to a healthcare management concept with more emphasis on preventative and life-style medicine and associated services. It is anticipated that the industry will integrate a larger health offering with sustainable pricing models for a wider array of products and services, including generics, diagnostics, disease management, prevention and knowledge management (Peck et al., 2007; Shah et al., 2009; Foster, 2008).

Trigger 2: Fully Integrated Pharma Network - a major theme within the literature pointed to a pharmaceutical business model that is based on a fully integrated global network that includes other pharmaceutical or biotechnology companies, universities, organizations, and even individuals in some cases (Woodcock & Woosley, 2008; British Telecommunications, 2007; Deloitte Consulting, 2002;

Hohman el al., 2009; Lundberg & Reilly, 2009; EMRC, 2005; Woosley & Cossman, 2007).

Trigger 3: Personalised Medicine - the literature (Humer, 2004; Jain, 2005; Phan et al., 2009; Aspinall & Hamermesh, 2007; Guidi & Lippi, 2009; Adams et al., 2006) points to the likely trends that specific treatments and therapeutics best suited for an individual are increasing in prevalence. There is no single definition for personalised medicine but one general theme among the articles suggested that personalised medicine is concerned with the development and administration of treatments (based on a knowledge of genetic biomarkers or mutations) to patients who might best respond to an individually tailored treatment (Humer, 2004; Jain, 2005; Phan et al., 2009; Aspinall & Hamermesh, 2007; Guidi & Lippi, 2009; Adams et al., 2006). This is exemplified by a quote from Adams et al. (Adams et al., 2006) “By 2015, a 21-year-old could undertake a whole genome test to identify risk factors for chronic conditions, such as a specific cancer or heart disease. It would also reveal the potential for adverse drug reactions to drugs. This knowledge will enable a new level of consumer responsibility.”

Trigger 4: Virtual R&D - the main argument in the referenced articles (Talaga, 2009; Hohman et al., 2009; Ginsburg & McCarthy, 2001; Shuchman, 2007; PricewaterhouseCoopers, 2008; Love, 1998) is that large pharmaceutical companies are shifting investment away from traditional in-house research activities and focusing more on developing superior deal-making and alliance capabilities to enable virtual R&D, which is also linked to the concept of open innovation.

Trigger 5: Translational Research - the referenced articles (Ahlborn et al., 2005; EMR, 20005; Phan et al., 2009; Mulder at al., 2008; Ginsburg & McCarthy, 2001; O’Connell & Roblin, 2006; Marrer & Dieterle, 2007; Michelson wt al., 2006; Zerhouni, 2007; Wehling, 2006) describe likely trends in translational research and define it as a bi-directional sharing of knowledge and ideas by the scientific and clinical disciplines to develop diagnostics that reliably select the mechanisms leading to breakthrough therapeutics. Some of the benefits argued by the articles include matching patients with therapy, improved compliance with therapy, reduced drug development costs, and reduced healthcare costs. Advances in computational tools such as predictive bio-simulation systems, *in-silico* modeling techniques and bioinformatics are also highlighted in some of the articles as playing a key role in enabling the realization of the translational research (Ahlborn et al., 2005; EMR, 20005).

Table 3.6 Article search phrases used during the selection procedure and the associated article selection results

Article search phrases	Source	Results*	Selected**	Reference
i) pharmaceutical “industry transformation”	Academic	77	1	(Cockburn, 2006)
ii) “pharma 2020”	Academic	31	0	–
iii) “future biopharma”	Academic	2	1	(Cooke, 2001)
iv) “Pharmaceutical Sciences by 2020”	Academic	2	2	(Crommelin et al., 2010; Shah et al., 2009)
v) FDA "Critical Path"	Academic	384	7	(Woodcock & Woosley, 2008; Woosley & Cossman, 2007; Jain, 2005; Aspinall & Hamermesh, 2007; Wehling, 2006; Miller et al., 2005; Calfee, 2006)
vi) “EMEA Roadmap”	Academic	6	2	(Milne, 2006; Heemstra, 2008)
Used the same search phrases above (i to vi)	Industry	174	5	(Peck et al, 2007; Deloitte, 2009; British Telecommunications, 2007; Mulder et al., 2008; PriceWaterhousecoopers, 2008)
Used the same search phrases above (i to vi)	Regulatory	106	4	(FDA innovation or Stagnation, 2004; EMA Road Map to 2010, 2005; EMA Road Map to 2015, 2009; FDA Strategic Action Plan, 2007)
Primary Articles: 22 ; Derived Articles: 60 ; Total Articles: 82				

* Number of articles meeting the initial search criteria

** Number of primary articles selected after review of abstract and/or introduction section

Table 3.7 Descriptive statistics supporting the testing of the article diversity

Article Type	No. of articles	%	Article Age	No. of articles	%	Citations	No. of articles	%
Government	6	7%	Before 2000	1	1%	5 to 10	10	12%
Industry	12	15%	2000 to 2005	24	29%	> than10	26	32%
Other	12	15%	After 2005	57	70%	< than 5	46	56%
Consulting	15	18%	-	-	-	-	-	-
Academic	37	45%	-	-	-	-	-	-

This table provides information on number of articles relating to type, age and citations. The corresponding percentage is calculated against the overall sample size (sample size = number of articles studied = 82)

Table 3.8 The pervasiveness and relative ranking of the transformation triggers in the primary and derived articles…….

	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8	Trigger 9	Trigger 10	Trigger 11	Trigger 12	Trigger 13	Trigger 14
n	11	16	22	6	15	8	7	8	7	5	7	6	11	17
Rank	7	**3**	**1**	12	**4**	13	9	6	11	14	8	10	5	**2**

n = pervasiveness of the trigger in all articles; sample size (total number of articles) = 82
See Appendix A for more detailed analysis

Trigger 6: Adaptive and In-life Trials - in adaptive trials, information acquired during a particular clinical trial is used to alter the course of the trial without compromising its statistical validity. In-life testing will leverage emerging computation and communication technologies and could replace Phase III trials. Such measures could shorten the developmental pipeline from the current 10 to 12 years to between 3 and 5 years (Boswell, 2002). Closer relationship with regulatory authorities is a key factor to ensure success (Ahlborn et al., 2005; Heemstra et al., 2008; Fraser, 2006; Miller et al., 2005; Boswell, 2002; Prendergast et al., 2004).

Trigger 7: Global Harmonization - harmonization discussions focus mainly on collaboration between regulators and the industry, especially in the ICH zone (North America, Europe and Japan). Referenced articles include predictive statements hoping for a level of global harmonization that may ultimately result in the seemingly unattainable goal of having one application per trial to all authorities (EMA Road Map to 2010, 2005; FDA Strategic Action Plan, 2007; Funning et al., 2009; Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting, 2009; Bass et al., 2009).

Trigger 8: Science and Risk Based Regulations - the articles examined argued that with the fates of the regulators and the industry more intertwined than ever, public health depends on regulatory innovation as much as on scientific progress. From the perspective of regulatory innovation an important step towards achieving the outlined goal involves international collaboration between regulators and industry (Calfee, 2006), which has been exemplified through ICH efforts manifested in issuance of a wide range of standards, particularly those related to Quality Risk Management, Pharmaceutical Development and Pharmaceutical Quality System (EMA Road Map to 2010, 2005; FDA Strategic Action Plan, 2007; Sneha & Varshney, 2009; Calfee, 2006; FDA Critical Path, 2006; Yu, 2008; Garcia et al., 2008).

Trigger 9: Live Licensing - discussions on this topic mainly have a conceptual tone due to uncertain commitment from the regulatory bodies. According to the literature live licensing implies that the current Phase I to IV clinical testing process may eventually be selectively or wholly replaced by a system known as "in-life" testing or "live" licensing (Health Canada, 2007; Visiongain, 2008). Those proposals involve cumulative testing of the drug throughout its lifecycle. In this paradigm the industry would continually test drugs with smaller, more focused clinical trials. If a trial shows efficacy and safety, a live license would be given, allowing the company to market the drug in a limited manner (Visiongain, 2008; Health Canada, 2007; Wright, 2007; Herbert, 2007; Lexchin, 2008).

Trigger 10: Enforcement – the articles studied anticipate a substantial increase in regulator's compliance and enforcement actions, particularly in the oversight

of inspections, product promotion and unapproved drugs (Boswell, 2002; Hamburg, 2009; Basile, 2009).

Trigger 11: Biotechnology - the recent applications of biotechnology will drive medical breakthroughs that will enable the people to improve their health and increase their longevity dramatically. To exploit potential of biotechnology and emulate successes of the biotech companies, large Pharma will likely structure themselves as a collection of biotechnology sites, which compete with each other and external biotechnology companies to supply compounds into a centralised development organization (Sager, 2001; US National Intelligence Council, 2000; Schmid & Smith, 2004; Cooke, 2001).

Trigger 12: Nanomedicine - generally the referenced articles (Wagner et al., 2006; European Science Foundation, 2006; Sahoo et al., 2007; Wiek et al., 2009) pointed to increasing use of nanobiotechnology by the pharmaceutical and biotechnology industries. Technical achievements in nanotechnology were applied to improve drug discovery and pharmaceutical manufacturing. Some argued that in the near future, it might be possible to model accurately the structure of an individual cell and to predict its function using computers connected to nanobiotechnology systems (Kewal, 2005). These futuristic statements imply that the detailed virtual representation of how a cell functions might enable scientists to develop novel drugs with unprecedented speed and precision, without doing any experiments in living animals.

Trigger 13: Bioinformatics - the referenced articles (FDA strategic Plan, 2007; Phan et al., 2009; Sneha & Varshney, 2009; Institute for Alternative Futures and the Draper Laboratory, 2005; Rauwerda, 2006; Ananthaswamy, 2003) largely focused on application of information technology and computer science to the field of molecular biology. Some also focused on bioinformatics from regulator's perspective implying that it involves use of modern computer systems to effectively manage the regulatory product-information supply chain.

Trigger 14: Pervasive Computing - the referenced articles (Saha & Mukherjee, 2003; Satyanarayanan, 2001; Clemensen at al., 2004; Scheffler & Hirt, 2005; Osmani et al., 2008; Floerkemeier & Siegemund, 2003; Pandian, 2008; Engin et al., 2005; Sriram at al., 2009) characterise pervasive computing as an environment saturated with computing and communication capability. Smart medication packaging, tiny wireless sensors implanted on the patient body to monitor various vital signs, and remote monitoring devices to determine how patients respond during clinical trials are just some examples. Another pervasive aspect of computing is provision of externally hosted services for management of data (e.g. clinical, manufacturing, product surveillance, etc.) and associated technical infrastructure. The concept is often times referred to as cloud computing (Orwat et al., 2008; Buyya et al., 2009; Sloan, 2009; Sneha &

Varshney, 2009), which is a computing model consisting of services that are commoditised and delivered in a manner similar to traditional utilities such as water, electricity, gas, and telephony. In such a model, users access services based on their requirements without regard to where the services are hosted or how they are delivered.

3.4 CONCLUSIONS

This systematic review of the literature has enabled identification of 14 triggers impacting the ongoing transformation in the pharmaceutical industry. Their importance-ranking reveal that of the 14 transformation triggers 4, namely Fully Integrated Pharma Network (*Trigger 2*), Personalised Medicine (*Trigger 3*), Translational Research (*Trigger 5*) and Pervasive Computing (*Trigger 14*) are considered as the most impactful.

The theoretical evidence presented in this Chapter against each of the transformation triggers was verified through operational evidence that is presented in Chapter 4.

CHAPTER 4: *Establishment of operational evidence in support of the transformation triggers: a systematic analysis of the operational evidence*

4.1 INTRODUCTION

This Chapter explores ongoing transformation in the pharmaceutical[3] industry and its impact on pharmaceutical quality from the perspective of risk identification. The 14 transformation triggers presented in this Chapter are findings of the systematic review of the literature performed in Chapter 3, which provided the *theoretical evidence* in support of these triggers and ranked their relative importance with respect to pharmaceutical transformation. Having established the theoretical evidence for the transformational triggers the aim of this Chapter is to determine the corresponding *operational evidence*. The operational evidence was derived from data collected on pharmaceutical companies, products and technologies. This approach is predicated upon the hypothesis that such data has the potential to provide valuable operational information about the transformation within the industry. Operational evidence is defined here as the consolidated representation of the operational data in a graphical or tabular form. The use of the operational evidence is important as a verification mechanism in order to accept or repudiate the theoretical evidence based on the proof from the real world scenarios. The key elements of this Chapter are description of the methods used for data collection, graphical presentation of the results and commentary on meaning of the results.

4.2 METHOD

The operational data on pharmaceutical products were collected from [redacted], ClinicalTrials.gov, FDA Orphan Drug database and from Table 2 of the paper by Wagner et al. (2006). Other types of operational data, not related to pharmaceutical products, were collected from databases listed in Section 4.2.2. These databases were selected because they were the leading and comprehensive source of data that was needed for this study.

4.2.1 Description of the product related databases

[redacted] - is owned by the [redacted] group, which is a world-leading provider of premium global business information, delivering independent data, analysis and opinion across many industries including pharmaceutical and

[3] The word pharmaceutical collectively refers to pharmaceutical and biopharmaceutical companies

healthcare industry. The PharmaViate Explorer search tool within the [redacted] database was used to collect operational data.

ClinicalTrials.gov - is a registry and results database of federally and privately supported clinical trials conducted in the US and around the world. ClinicalTrials.gov gives information about a trial's purpose, who may participate, locations, and phone numbers for more details. The advanced search tool within the Clinicaltrials.gov database was used to collect operational data.

Orphan Drug database – is owned by the FDA, which provides for granting special status to a product to treat a rare disease or condition. The combination of the product to treat the rare disease or condition must meet certain criteria. This status is referred to as orphan designation and drugs designated by the FDA as orphan are searchable in the Orphan Drug database. The search tool within the orphan drug database was used to collect operational data.

The paper by Wagner et al. (2006) is a global survey of companies pursuing nanomedicine application in the pharmaceutical and medical device industry. At the time of data collection this paper was the only comprehensive source of nanomedicine applications in the pharmaceutical industry. Information from Table 2 of this paper was used for compiling the operational evidence.

4.2.2 Operational data collection and analysis

The operational data were collected based on the search criteria described below for each of the 14 transformation triggers. The databases were searched according to the method and search attributes defined for each trigger in the following sections.

Data collection was performed between July and November of 2010 and therefore it excludes some months in second half of 2010 (details in the following Sections). In order to align the search timelines between the theoretical and operational evidence, the operational data search timeframe was set at year 2000 to 2010. For transformation triggers where a clear trend could not be established from the collected data the starting timeframe for the search was set at a timeline earlier than year 2000. For product related searches involving [redacted] database the scope of data collection also included the developmental drug products with a future launch date. In order to accommodate launch dates beyond 2010 the search timeframe for this type of search was extended to 2015.

Operational data related to pharmaceutical companies, products and technologies were exported into an excel spreadsheet for further classification

and analysis. The data were plotted and the resulting trends are presented in Section 4.3.

4.2.2.1 Trigger 1 - Healthcare Management Focused

The operational data for this Trigger was collected from the [redacted] database*. The objective was to verify theoretical evidence relating to diversification of the pharmaceutical industry (Chapter 3) from a diversified revenue perspective. Diversified revenues for 37 top pharmaceutical companies (Table 4.1 – based on size of annual revenue and the R&D portfolio) were collected. Timeline of 2000 to 2010 for actual diversified revenues and 2011 to 2015 for projected revenues were used. The researcher collected the operational data on 24 July 2010.

* [redacted] website: [redacted]

4.2.2.2 Trigger 2 - Fully Integrated Pharma Network

The operational data for this Trigger was collected from the [redacted] database. The objective was to verify theoretical evidence relating to diversification of the pharmaceutical industry (Chapter 3) from a product portfolio perspective. The product portfolio (i.e. R&D pipeline and product listing) of the top pharmaceutical companies was searched. Timeline of 2002 to 2010 for the marketed products and 2011 to 2015 for projected product pipeline was used. 2704 drug products were found, of which 1489 met "product sourcing" and "product age" search criteria listed in Table 4.2. The researcher collected the operational data on 24 July 2010.

Table 4.1 The top pharmaceutical companies used in [redacted] database search

Company name	Company name
Abbott	Lundbeck
Actelion	Menarini
Alcon	Merck
Allergen	Merck KGaA
Astra Zenica	Novartis
Boehringer Ingelheim	Mylan
Bayer	Novo Nordisk
Biogen Idec	Nycomed
Bristol Myers Squibb	Otsuka
Celgene	Pfizer
Cephalon	Roche
Daiichi Sankyo	Sanofi-aventis
Eli Lilly	Servier
Forest	Shionogi
Genzyme	Shire
Gilead	Teva
Glaxo	UCB
Johnson & Johnson	Watson
King Pharmaceuticals	

Table 4.2 [redacted] database search criteria for collection of product related operational data

Category	Criteria
Molecule type	Small molecule, therapeutic proteins, monoclonal antibody, vaccine
Therapeutic area	Cardiovascular, central nervous system, endocrine, metabolic & genetic, gastroenterology, genitourinary, haematology, immunology and inflammation, infectious diseases, musculoskeletal, oncology, respiratory
Product sourcing	Internal External (acquired, co-developed, in-licensed, merger & acquisition, other)
Company type	The following terms were derived from the [redacted] database: Big Pharma: Pharmaceutical companies with revenue in excess of $10 billion Mid Pharma: Companies with ethical product revenues between $1 and $10 billion, excluding Japanese and biotechnology companies Japan Pharma: Pharmaceutical companies legally registered in Japan Generics: Pharmaceutical companies that manufacture off patent drug products Biotech: Biotechnology companies specialised in research, development and manufacturing of biological drug products
Product age	(very old >15y, old 11-15y, recent 5-10y, new <5y
Product launch/expiry	Global, US, 5EU, Japan, Rest Of the World (ROW)

4.2.2.3 Trigger 3 – Personalised Medicine

The operational evidence for this trigger was collected from FDA Orphan Drug database*. The objective was to verify theoretical evidence that the pharmaceutical industry is increasingly focusing on research, development and commercialization of products and services targeted for individual patient needs (Chapter 3). Timeline of 1994 to 2010 was used. 2200 products with orphan drug designation status were selected for analysis. The FDA assigns an orphan drug designation status to a product when orphan drug designation request from a pharmaceutical company is deemed a good candidate for treating a rare disease. Upon satisfaction of regulatory requirements the FDA approves the designated orphan drug for commercial use. The researcher collected the operational data on 30 August and 20 October, 2010.

* Link to the US FDA Orphan Drug database:
http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

4.2.2.4 Trigger 4 – Virtual R&D

The operational data for this Trigger was collected from the [redacted] database. The objective was to verify theoretical evidence that pharmaceutical industry is externalizing the discovery and development of products (Chapter 3). The product portfolio of the top pharmaceutical companies was searched. Timeline of 2002 to 2010 for the marketed products and 2011 to 2015 for projected product pipeline was used. 2704 products met the “therapeutic area”, “product sourcing” and “company type” search criteria listed in Table 4.2. The researcher collected the operational data on 24 July 2010.

4.2.2.5 Trigger 5 – Translational Research

The operational evidence for this Trigger was collected from the FDA database on Biomarkers*. The objective was to use the prevalence of biomarkers as a surrogate indicator to verify the theoretical evidence relating to translational research in pharmaceutical industry (Chapter 3). Biomarker approval timeline of 1991 (earliest approved biomarker) to 2010 (year when the search was performed) was used to select 71 biomarkers that met the "FDA approved" search criteria. The researcher collected the operational data on 30 August 2010.

* Link to the FDA biomarker webpage: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. The webpage was replaced since the first visit and as of October 2011 the new link is: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

4.2.2.6 Trigger 6 – Adaptive Trials

The US Clinical Trials database* was used to collect the operational evidence to verify theoretical evidence and demonstrate if the use of the adaptive clinical trials is in the rise within the pharmaceutical industry (Chapter 3). Adaptive trials submission timeline of 2000 to 2010 was used to select 38 studies that met the "Adaptive design" search criteria in the database. The researcher collected the operational data on 30 August 2010.

* Link to the US Clinical Trials database website: http://clinicaltrials.gov/ct2/search/advanced

4.2.2.7 Trigger 7 – Regulatory Harmonisation

The International Conference on Harmonisation (ICH) website* was used to collect operational evidence to verify theoretical evidence and demonstrate if regulatory harmonization exists at the global level (Chapter 3). The ICH Guidance approval timeline of 1993 to 2010 was used to select 73 guidelines that met the "quality", "safety", "efficacy" and "multidisciplinary" search criteria. The researcher collected the operational data on 30 August 2010.

* Link to the ICH guideline webpage: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

4.2.2.8 Trigger 8 – Science and Risk Based Regulations

The FDA Cooperative Research and Development Agreements (CRDA) database* was used to collect the operational evidence to verify theoretical evidence and determine whether pharmaceutical regulations are increasingly being based on science and risk based approaches (Chapter 3). The content of 92 CRDA documents were examined for common themes relating to research topics that were designed to use science and risk based approaches to improve the regulatory oversight activities. The researcher collected the operational data on 2 September 2010.

* Link to the FDA CRDA webpage:
http://www.fda.gov/ScienceResearch/CollaborativeOpportunities/CooperativeResearchandDevelopmentA greementsCRADAs/ucm122820.htm

4.2.2.9 Trigger 9 – Progressive/Live Licensing

The FDA, EMA, and Health Canada websites were used to collect operational evidence to verify theoretical evidence that regulators intent to allow commercial use of medicinal products in a progressive fashion (Chapter 3). Extensive search of the websites resources such as position papers, strategic plans, guidelines, press releases, news, etc. was performed to indentify any official information relating to the intent of actual implementation of “Progressive Licensing” or “Live Licensing”. The search was performed on 2 September 2010.

FDA website:	http://www.fda.gov/
EMA website:	http://www.ema.europa.eu/ema/
Health Canada website:	http://www.hc-sc.gc.ca/index-eng.php

4.2.2.10 Trigger 10 – Regulatory Enforcement

The FDA Warning Letter database* was used to collect operational evidence to verify theoretical evidence relating to regulatory enforcement in pharmaceutical industry (Chapter 3). The FDA warning letter issuance timeline of 2000 to 2010 was used to select 664 warning letters that met the “CGMP”, “Clinical”. “Active Pharmaceutical Ingredients” and “Devices” search criteria. The researcher collected the operational data on 10 November 2010.

* FDA Warning Letter database webpage-
http://www.accessdata.fda.gov/scripts/warningletters/wlSearchExcel.cfm

4.2.2.11 Trigger 11 – Biotechnology

The [redacted] database was used to collect the operational evidence to verify theoretical evidence and demonstrate if drug products based on large molecules are in the rise (Chapter 3). The drug product portfolio with a launch timeline of 2002 to 2015 was searched and 2704 developmental and commercialised products that met the “molecule type”, “therapeutic area”, and “product launch/expiry” search criteria (Table 4.2) were selected for analysis. The researcher collected the operational data on 24 July 2010.

4.2.2.12 Trigger 12 – Nanomedicine

The paper by Wagner et al. (2006) was used to collect the operational evidence to verify the theoretical evidence and determine if nanotechnology based drug products prevalence on the market are rising (Chapter 3). List of nanomedicine products on the market from Table 2 of the paper was used to select 36 nanomedicine based drug products. The researcher collected the operational data on 24 July 2010.

4.2.2.13 Trigger 13 – Bioinformatics

The US and EU Patent Office websites* were used to collect the operational evidence to verify the theoretical evidence and determine if Bioinformatics related technologies are prevalent in the pharmaceutical industry (Chapter 3). The approved patents for timeline of 2000 to 2010 was used to select 55 US patents that met the [(((SPEC/Bioinformatics AND SPEC/Therapy) AND ACLM/computer) AND ISD/20000101->20100101)] search criterion, 72 EU patents that met the [“Bioinformatics” in Title field] search criterion, and 20 EU patents that met the [“Bioinformatics” AND “Computer” in Title/Abstract field and “2000:2010” in the Application Date field] search criterion. The researcher collected the operational data for US patents on 24 July 2010 and EU patents on 20 October 2010.

*US PO - http://patft.uspto.gov/netahtml/PTO/search-adv.htm
*EU PO – http://worldwide.espacenet.com/quickSearch

4.2.2.14 Trigger 14 – Pervasive/Cloud Computing

The US and EU Patent Office websites* were used to collect the operational evidence to verify the theoretical evidence and determine if pervasive and cloud computing technologies are prevalent in the medical field (Chapter 3). The approved patents for timeline of 2000 to 2010 was used to select 323 patents that met the search criteria stated in Table 4.3. The researcher collected the

operational data for US patents on 1 September 2010 and EU patents on 20 October 2010.

*US PO - http://patft.uspto.gov/netahtml/PTO/search-adv.htm

*EU PO – http://worldwide.espacenet.com/advancedSearch?locale=en_EP

Table 4.3 Search criteria used to collect operational data from the US and EU Patent Offices on Pervasive/Cloud computing

Database Search Criteria	Patents
US Patent Office:	
(TTL/telemedicine AND ISD/20000101->20100901)	11
(((TTL/(implantable AND device) AND SPEC/(computer AND sensor)) AND ACLM/(Drug AND Delivery)) AND ISD/20000101->20100901)	14
(TTL/(implantable AND biosensor) AND ISD/20000101->20100901)	6
(SPEC/(((intelligent AND embedded) AND Medication) AND Package) AND ISD/20000101->20100901)	41
(ABST/(((Remote AND patient) AND monitoring) AND Clinical) AND ISD/20000101->20100901)	9
European Patent Office:	
"Telemedicine" in the title AND 2000:2010 as the publication date	90
"Implantable drug delivery device" AND "sensor" in the title or abstract AND 2000:2010 in the publication date field	13
"Remote patient monitoring" AND "Clinical" in the title or abstract AND 2000:2010 in the publication date field	18
"Implantable biosensor" in the title AND 2000:2010 in the publication date field	90
"Electronic" AND "medication" AND "patient" in the title or abstract AND 2000:2010 in the publication date field	31

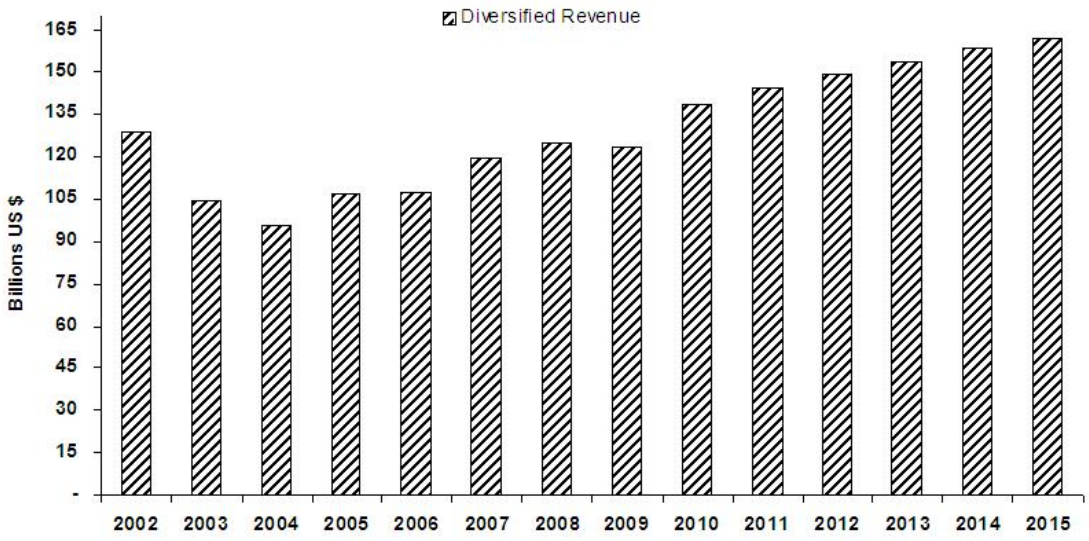
4.3 RESULTS AND DISCUSSION

The theoretical evidence for the 14 triggers listed below was established in Chapter 3. The corresponding operational evidence is established in this Chapter and the results presented below. The discussion for each trigger reflects the interpretation of the operational evidence as illustrated in Figures 4.1 to 4.12. Raw data upon which the Figures 4.1 to 4.12 were constructed are presented in Appendix A

Trigger 1: Healthcare Management Focused - an increase in pharmaceutical revenues from products or services other than from the traditionally strong prescription drug sales would mean that the pharmaceutical industry is diversifying and that *Trigger 1* is taking root. Revenue information relating to non-prescription drug products (drug products that do not require written instructions from a physician or dentist to a pharmacist) of 37 pharmaceutical companies was used as the primary indicator of diversification in the pharmaceutical industry. Since diversification is divergence from established

core products/services, of the 37 pharmaceutical companies listed, only those that had “non-prescription drug” and “other” revenue information were selected for trend observation. This limited the final list to 16 pharmaceutical companies. The actual and projected revenue information was collected for financial years 2002 to 2015. Operational trends observed in Figure 4.1 for non-prescription drug products and services show a substantial increase in diversified revenue.

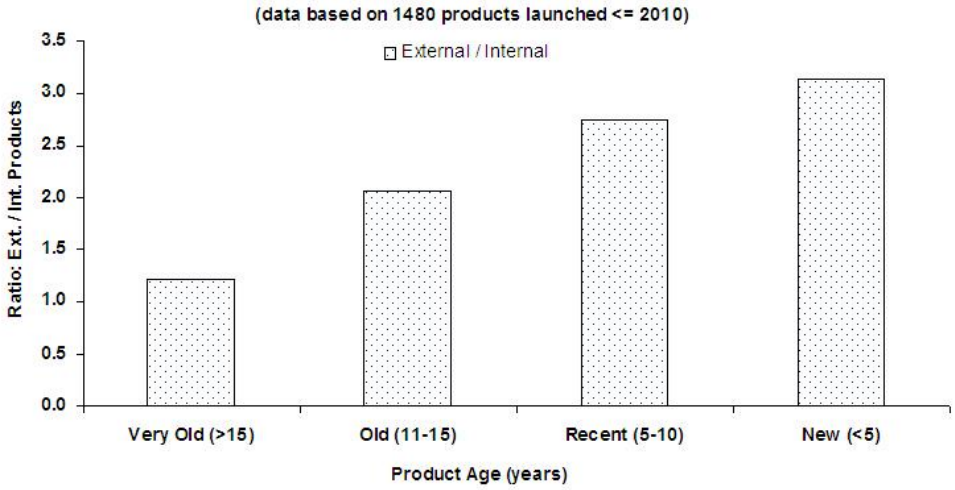
Figure 4.1 Pharmaceutical diversification - increase in pharmaceutical revenues from non-traditional products or services (Trigger 1)



Trigger 2: Fully Integrated Pharma Network - the ratio of internally developed versus externally developed drug products is an indication of the degree to which the pharmaceutical industry is leveraging external sources of innovation. To determine this trend the [redacted] database was searched for products that were launched or to be launched between 2002 and 2015. Sources of launched or to be launched products in the database were clearly tagged in the excel spreadsheet and categorised as “internal”, “acquired product”, “co-developed”, “M&A”, “other external”, “in-licensed” and for products in development phase “n/a”. The word *Internal* means that the products were developed in house. *Acquired product* means that the product was purchased from another organization. *Co-developed* means the product was co-developed with another pharmaceutical company under specific agreement. *M&A* means the product was inherited through merger and acquisition. *In-licensed* product refers to transfer of a license by agreement from another organization in order to develop or market the particular product. *Other external* refers to acquisition of products externally by other means than explained above. The term “n/a” means not applicable and is used for products in the development phase. The acquired product, co-developed, M&A, in-licensed and other external were collectively consolidated into a single category called “external”. For the purposes of this analysis “n/a” was excluded. The age of the drug product was categorised into very old >15 years, old = 11-15 years, recent = 5-10 years, new<5 years. The prevalence of

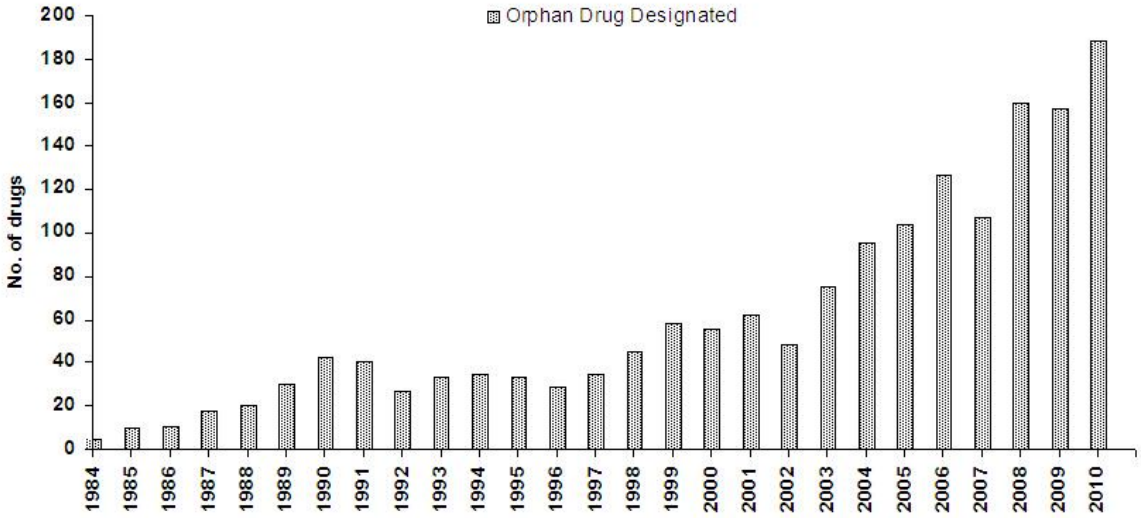
external sources of products for the newer products would be a positive indication that Trigger 2 is taking root. The trends observed in Figure 4.2 show a substantial increase in external sourcing for newer products.

Figure 4.2 Product sourcing - ratio of internally developed versus externally developed drug products (Trigger 2)



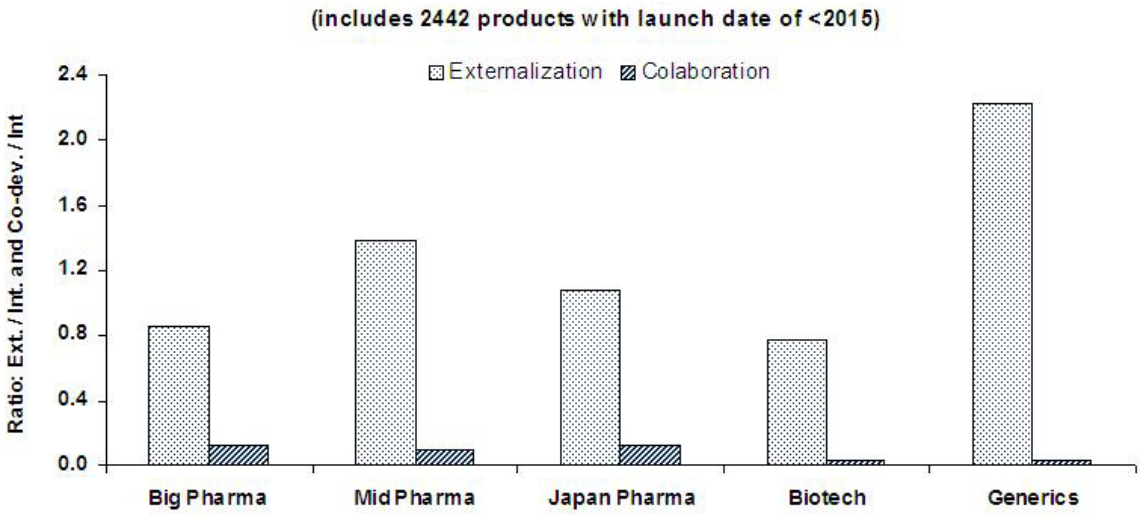
Trigger 3: Personalised Medicine - since personalised medicine, by definition, is concerned with the development of drugs for *niche* patient populations (Chapter 3), designation of orphan drugs by the FDA is a good indicator of trends in personalised medicine. In exceptional cases some personalized medicines may target larger segments of the population; for instance oncology products such as Herceptin exemplify this for treatment of breast cancer. Data collection focused on drugs that had received orphan drug designation between 1993 and 2010. Trends observed in shows a substantial increase in FDA orphan drug designations (Figure 4.3), gradual increase in FDA approved Biomarkers (see Trigger 5), and gradual increase in Launch of biological (large-molecule) drugs (see Trigger 11).

Figure 4.3 FDA orphan drug designation for drug products with niche patient populations (Trigger 3)



Trigger 4: Virtual R&D - a key feature of virtual R&D involves outsourcing research activities to third parties or in some cases co-development with other pharmaceutical companies (Chapter 3). In order to investigate the likely trends in Virtual R&D the collected data were classified into three categories of i) drug products developed through Internal R&D or ii) drug products developed externally through third party agreements or iii) drug products developed through partnerships with other pharmaceutical companies. The externalization and collaboration trends for Big Pharma, Mid Pharma, Japan Pharma, Biotech, and Generics (Pharma industry classifications as defined by [redacted]) were derived by calculating the ratio of externally developed drug products to internal drug products and co-developed drug products to internal drug products. The trends observed in Figure 4.4 show that Mid Pharma and Generics play leading roles in externalization of research and that collaboration among pharmaceutical companies is low in general but slightly more pronounced in Big Pharma.

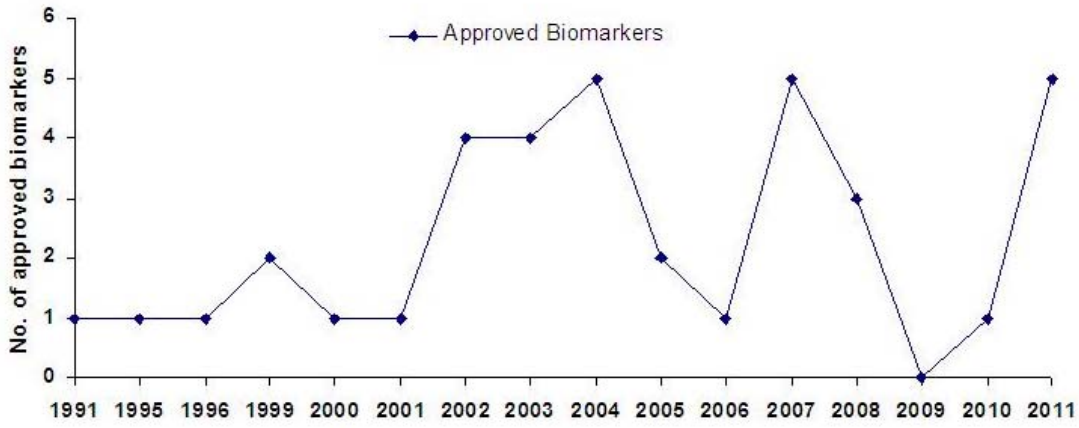
Figure 4.4 Research outsourcing and collaborative R&D (Trigger 4)



Trigger 5: Translational Research - the goal of translational research is to facilitate exchange of information between preclinical scientists and clinical practitioners to implement in-vivo measurements that more accurately predict drug effects in humans (Chapter 3). Prevalence in regulatory approval of biomarkers is a good indication that translational research is increasing. In order to prove this point, a list of approved biomarkers by the FDA (i.e. in-vivo measurements) was analyzed to determine the number of products associated with approved biomarkers and date of biomarker approval for trending purposes. Since the FDA does not publish explicit approval date for biomarkers, the date of the earliest published research related to the prototypic drugs (drug associated with the label information defining the biomarker context) was used as a surrogate indicator – see the web link in Section 4.2.2.5 for a list of valid approved biomarkers published by the FDA. The word "valid" is described by the FDA as a biomarker that is measured in an analytical test system with well

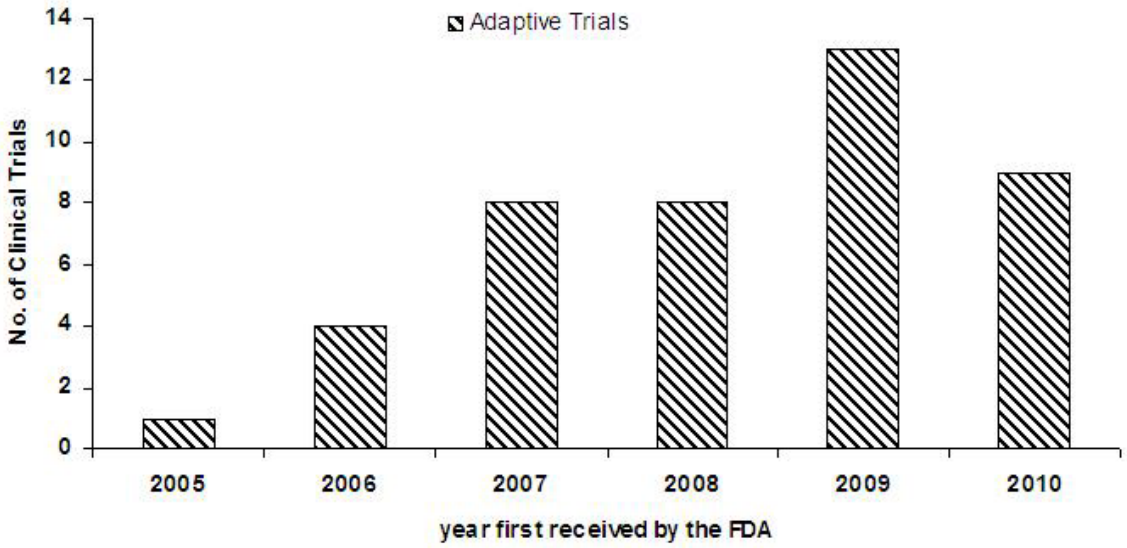
established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiological, toxicological, pharmacological, or clinical significance of the test results. Although sporadic at times, Figure 4.5 shows a general upward trend in the number of valid biomarkers over the last two decades.

Figure 4.5 Approved biomarkers as an indicator for prevalence of translational research (Trigger 5)



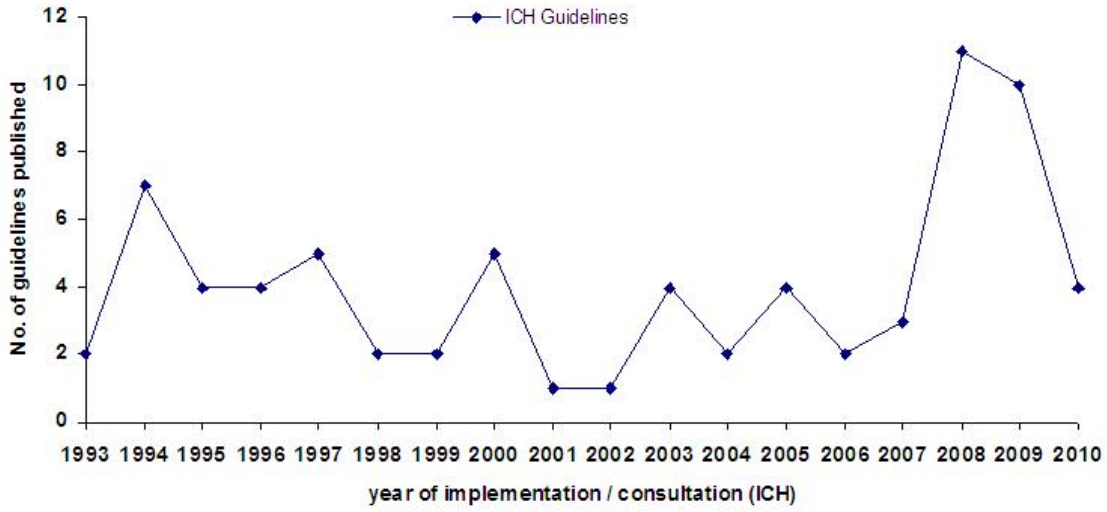
Trigger 6: Adaptive Trials - information about clinical trials is often maintained in registry and results databases frequently managed by governmental organizations. One such database that is publically available and also contains information on adaptive trials is Clinicaltrials.gov. This database was searched for studies containing the phrase “adaptive design” in Phase I, Phase II and Phase III clinical trials that were first submitted to the FDA between 2000 and 2010. Figure 4.6 shows a steady increase in the number of adaptive clinical trials since 2005 and a sharp decline in 2010 is apparent. From a public policy perspective emerging approaches such as UK’s patient access scheme is boosting early access to medicine, which is likely to impact the design and conduct of clinical trials. It is noteworthy to mention that currently this approach is localized to UK and not adopted globally.

Figure 4.6 Prevalence of adaptive clinical trials (Trigger 6)



Trigger 7: Global Harmonization - creation and deployment of international guidelines is the direct indication of regulatory and industry commitment to global harmonization. To validate this assertion the ICH guidance database was searched for evidence of harmonization relating to safety, efficacy and quality of drug products. Trends observed in Figure 4.7 shows that the activities on global regulatory harmonization have remained more or less constant during the last 2 decades except for a large spike in 2009 and 2010.

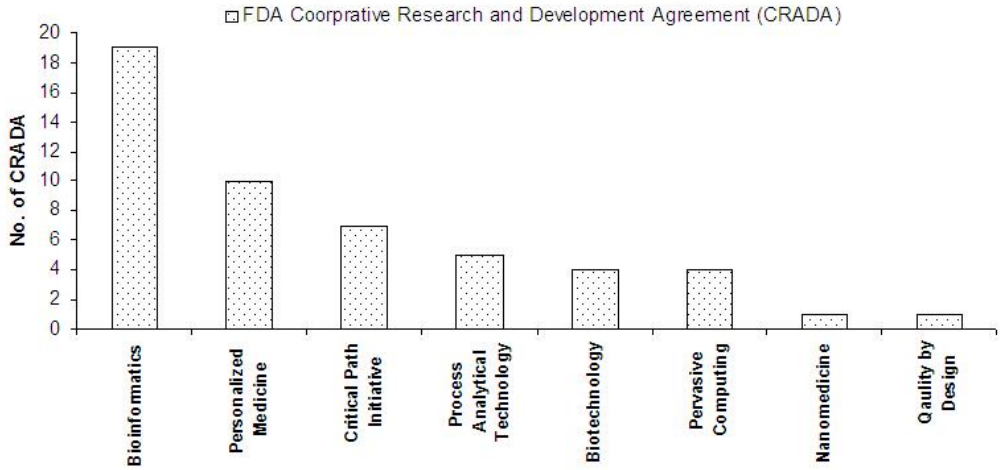
Figure 4.7 Trends in regulatory harmonization based on ICH publications (Trigger 7)



Trigger 8: Science and Risk Based Regulations - research conducted by regulators in cooperation with the industry and other research organizations was used as a surrogate indicator that regulatory rule making is likely to benefit from results of such cooperation. The FDA database containing a list of cooperative research and development agreements was searched. The review of FDA's CRADA agreements resulted in a classification of research focus into one of the

following categories: Bioinformatics, Personalised Medicine, Critical Path Initiative, Process Analytical Technology, Biotechnology, Pervasive Computing, Nanomedicine, Quality by Design and Other categories. The trends observed in Figure 4.8 shows that the agreements are largely focused on bioinformatics, personalised medicine and in support of FDA's critical path initiative.

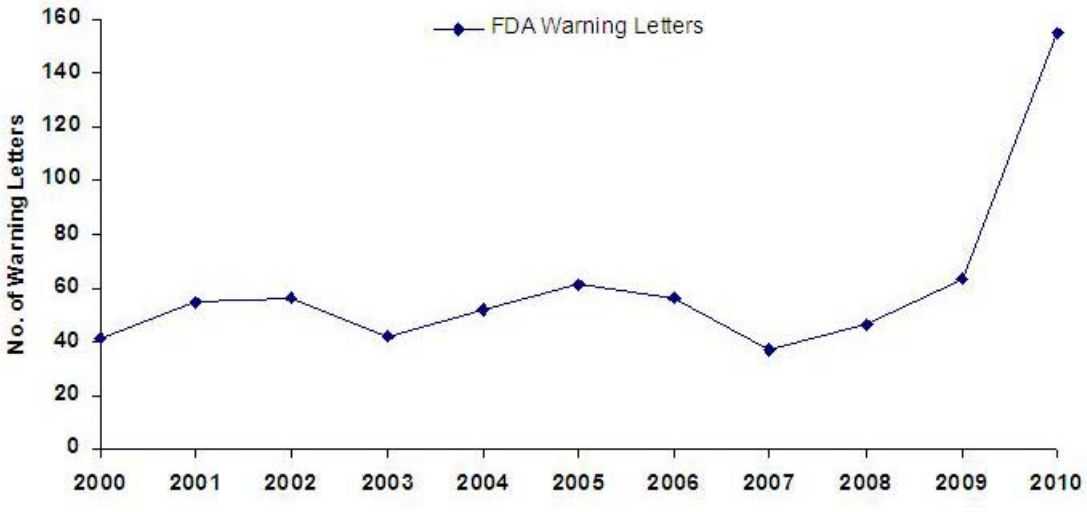
Figure 4.8 FDA's cooperative research and development agreements (Trigger 8)



Trigger 9: Progressive/Live Licensing - the FDA, European Medicines Agency (EMA) and Health Canada websites were extensively searched for evidence of procedures for drug product licensing that allowed progressive use of medicinal products, i.e. starting the commercial use in Phase III clinical development under certain conditions. Although there were some forward looking statements in the Health Canada website, there was no indication in any of these regulatory websites that medicinal products intended for human use are awarded progressive marketing authorization while in the clinical development phase. There was no operational evidence in support of this transformation trigger.

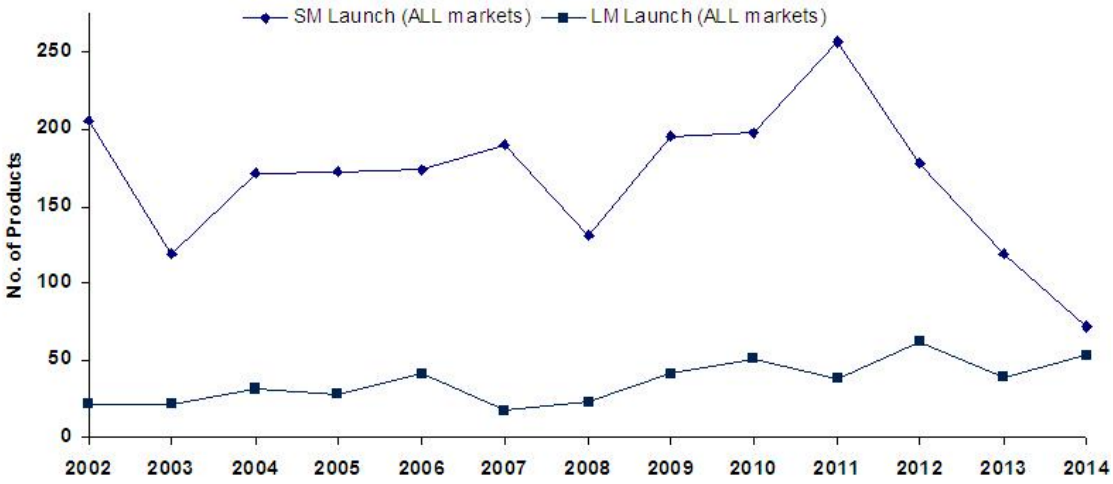
Trigger 10: Regulatory Enforcement - the Issuance of observations by the regulators to pharmaceutical companies is an indication of their enforcement of applicable regulations (Hamburg, 2009). Although this takes place in the US, EU and other regulated markets, due to freedom of information act in the US only FDA warning letters are available publicly. Trends observed in Figure 4.9 shows that the issuance of FDA warning letters seemed cyclical since 2000 with a sharp increase in 2009.

Figure 4.9 FDA enforcement pharmaceutical regulations (Trigger 10)



Trigger 11: Biotechnology - trends in commercialization of small molecule drug products (chemical basis) compared with large molecule drug products (biological basis) in the pharmaceutical market can be used as an indicator to determine the position of biotechnology in the pharmaceutical industry. To substantiate this, launch information for small and large molecule drug products for Global, US, 5EU, Japan, and Rest of the World markets was extracted form the [redacted] database and analyzed. Trends observed in Figure 4.10 shows that the number of drug products containing small molecules has risen since 2002 with a sharp decline in 2011. At the same time number of drug products containing large molecules increased gradually and the projected convergence with small molecule drug products can be seen by 2014.

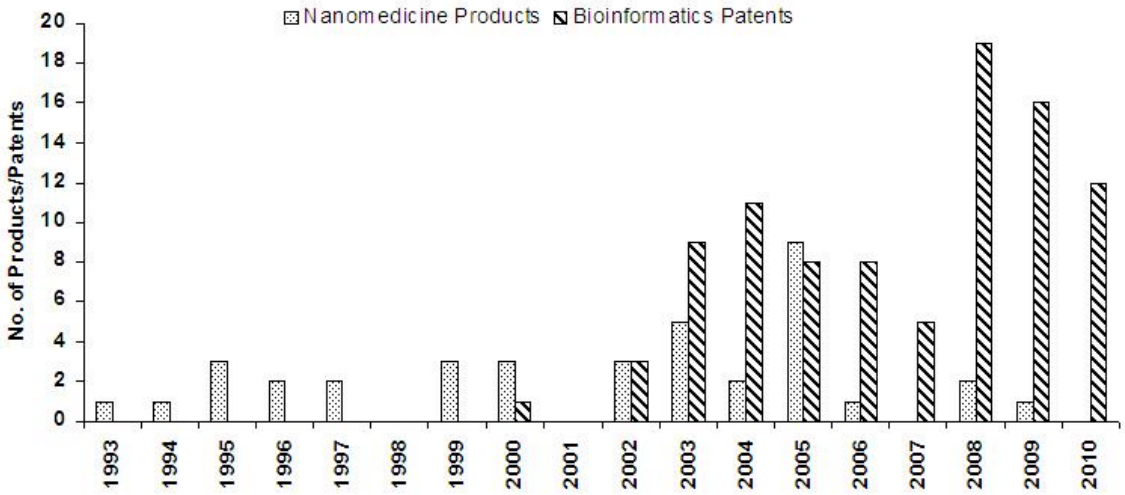
Figure 4.10 Small versus large molecule drug product launches (Trigger 11)



Trigger 12: Nanomedicine - each nanomedicine product listed in the work of Wagner et al (2006) was classified into 9 therapeutic categories (Cardiology, Central Nervous System, Genitourinary, Immunology & Inflammation, Infectious Diseases, Metabolic Disorders, Musculoskeletal, Oncology, Ophthalmology). The

number of nanotechnology based drug products for each therapeutic category was determined. The trends observed in Figure 4.11 show uneven peaks and troughs in marketing of nanotechnology based drug products since 1993 with an isolated rise in 2005.

Figure 4.11 Prevalence of Nanotechnology based drug products and Bioinformatics in the pharmaceutical industry (Trigger12 and 13)



Trigger 13: Bioinformatics - examining patent information on a particular technology can provide evidence of its prevalence and likely future trends. To test this assertion the bioinformatics search keywords below were searched in the US and EU patent databases. Trends observed in Figure 4.11 show a rise in bioinformatics patents since 2000 with peaks at 2004 and 2008. The 2010 data do not represent the full year.

Trigger 14: Pervasive/Cloud Computing - examining patent information on a particular technology can provide evidence of its prevalence and likely future trends. To test this assertion the pervasive computing search phrases were grouped into five themes of Telemedicine, Implantable Drug Delivery, Implantable Biosensors, Intelligent Medication Package and Remote Patient Monitoring. These themes were derived from Chapter 3 as the possible areas of pharmaceutical applications. The US and EU patent databases were searched according to the search criteria stated in Section 3. The trends observed in Figures 4.12 and Table 4.4 shows a substantial rise in number of pervasive computing patents since 2000 with key areas of focus on intelligent medication package and telemedicine. Note that 2010 data does not represent the full year.

Figure 4.12 Pervasive computing trends in pharmaceutical industry (Trigger 14)

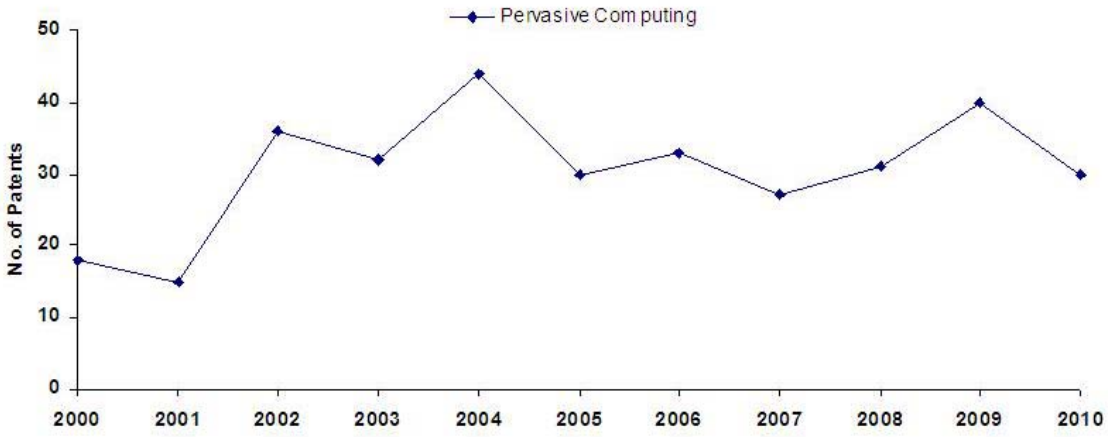


Table 4.4 Application of pervasive computing technology in the pharmaceutical Industry

Pervasive Computing Pharmaceutical Application	Number of Patents
Implantable Biosensors	24
Implantable Drug Delivery	27
Remote Patient Monitoring	40
Telemedicine	101
Intelligent Medication Package	131

4.3.1 Discussion

The operational evidence presented in Section 3 provides substantive evidence in support of pharmaceutical industry transforming from a prescription drug-centric industry to a diversified healthcare industry (Figure 4.1). Changes in the pharmaceutical business model are also evident in that there is more focus on external sources for supplementing the product portfolio (Figure 4.2). The newer drug products are three times as likely to be sourced externally as developed internally. The pharmaceutical industry move towards individualised medicine is supported by orphan drug designation (Figure 4.3), development and availability of valid genomic biomarkers (Figure 4.5) as well as industry shift from a small-molecule blockbuster drug strategy to a large molecule based targeted drug strategy (Figure 4.10). For virtual R&D the operational evidence can be interpreted in two ways: a) healthy increase in externalization in that the pharmaceutical companies are increasingly exploiting external sources of innovation (Figure 4.4) and b) comparatively less enthusiasm on collaborative drug discovery and development among pharmaceutical companies (Figure 4.4). The modest but steady increase in the number of approved clinical biomarkers (Figure 4.5) is apparent and is a surrogate indicator that clinicians and scientists are working closely in the context of translational medicine to develop products tailored for specific populations. The operational data in support of translational research exclude additional evidence, which was not known during the initial data collection (August 2010) i.e. 14 biomarkers that currently are in the review and consultation stage within the FDA (Woodcock et al., 2011). There is enough

operational evidence to support the concept of adaptive clinical design (Figure 4.6) however it is a small[4] proportion of all the clinical studies that are conducted within the same time period. Although regulatory harmonization relating to common safety, efficacy and quality guidance (Chapter 3) is firmly supported by the operational evidence (Figure 4.7) however the current data collection found no evidence to suggest that the different regulatory authorities will eventually fully harmonise the pre-market evaluation and post market surveillance of drug products. Operational evidence for science and risk based regulations is mainly limited to efforts of US FDA's corporative research agreements and EMA's innovation taskforce, which are largely focused on personalised medicine, translational research and bioinformatics topics (Figure 4.8). Progressive product licensing although a revolutionary concept has not been implemented in practice; this was confirmed since at the time of data collection no operational data was found to substantiate this activity. It is likely that this topic will remain in the conceptual phase until there are robust methods to firmly assure product safety at early stages of product development, which may be possible in the arena of the personalised medicine. Regulatory enforcement data are only based on the US FDA due to freedom of information act in the US; enforcement data for EMA were not publicly available during the data collection period. The operational data point to cyclical enforcement profile except a sharp increase in 2009 (Figure 4.9); this is widely attributed to FDA commissioner's tough stance on effective regulatory enforcement (Woodcock et al., 2011). Application of biotechnology is supported by strong evidence that the projected pharmaceutical product portfolio within the next five years will have equal number of large and small molecule drug products (Figure 4.10). This supports the literature assertion that pharmaceutical industry is focusing more and more on biologics (Chapter 3), which is also consistent with industry move towards personalised medicine (Chapter 3). The operational data in support of nanotechnology are somewhat erratic (Figure 4.13). Clearly there is evidence that nanotechnology plays a role in drug development however the amount and consistency of operational data does not indicate a steady rise. Bioinformatics as an enabling technology (Chapter 3) supporting translational research and personalised medicine is taking root and its prevalence in the healthcare industry can be noticed in analysis of the worldwide patent data since 2000 (Figure 4.11). The operational evidence supports the literature assertion that pervasive computing will increasingly play a key enabling role in pharmaceutical industry with a particular focus on patient support activities such as intelligent medication, telemedicine and remote patient monitoring (Table 4.4, Figure 4.12).

[4] As of 17 September 2012 there are 132,526 clinical trials with locations in 179 countries clinicalstrials.gov

4.3.1.1 Proposed theoretical quality risks:

The assessment of the theoretical evidence presented in Chapter 3 from an open innovation and quality risk management perspectives have resulted in the following proposals that were validated and the outcomes are presented in Chapter 6.

Trigger 2: Fully Integrated Pharma Network - the open innovation trends for this transformation trigger will likely impact selection and employment of external research and commercial partnerships and in-licensing of products. These changes will result in quality risks that will require establishment of effective due diligence and product transfer processes to mitigate the potential risks.

Trigger 3: Personalised Medicine - the open innovation trends for this transformation trigger will likely impact research, development, manufacturing, distribution, marketing and surveillance of novel and complex products such as combination, biological and biotechnology products. From the perspective of quality risk management these novel and complex products, which require convergence of multiple scientific and technological disciplines, will challenge the regulators, industry, and healthcare professionals in their safe and effective use. The resultant theoretical quality risks will require provision of multidisciplinary regulatory knowledge and skills to mitigate the potential risks.

Trigger 5: Translational Research - the open innovation trends for this transformation trigger will likely impact research partnerships and research information sharing. The resultant theoretical quality risks will require establishment of effective due diligence for research partnerships and provision of robust data management policies and procedures to mitigate the potential risks.

Trigger 14: Pervasive Computing - the open innovation trends for this transformation trigger will likely result in prevalence of smart implantable devices for product tracking, patient monitoring and drug delivery and outsourcing of information systems for management of clinical and product data (e.g. for clinical trials, drug safety surveillance, customer complaints, etc.). The resultant theoretical quality risks will require establishment of effective validation procedures to ensure reliability of smart devices and provision of data management procedures to ensure security and integrity of outsourced data to mitigate the potential risks.

4.4 CONCLUSION

In this Chapter the operational evidence has been provided for all the 14 transformation triggers except for Trigger 9 “Progressive Licensing” for which no operational data was found. The quantitative comparison of theoretical versus operational evidence will be provided in Chapter 8. Although this Chapter verifies the theoretical evidence, it does not validate the proposed quality risks derived from the theoretical evidence. In addition, given that the literature results take time to publish, there is a difference in knowledge within the literature and those of experts in the field. Therefore there was a need to augment the theoretical and operational evidence by creating a view of the current situation in the field. This was done by eliciting opinion of experts with operational knowledge of the industry transformation and the associated quality risks. The validation of the proposed quality risks, from the perspective of opinion-based evidence, is the subject of Chapter 5 and 6, which will be described next.

CHAPTER 5: *Development of the Survey for the Study of the Expert Opinion*

5.1 INTRODUCTION

The theoretical evidence for factors influencing the ongoing transformation in the pharmaceutical industry was established in Chapter 3 and corresponding operational evidence was provided in Chapter 4. A set of pharmaceutical quality risks proposed in Chapter 3, were considered likely to have been induced by the four main transformation triggers. The opinion-based evidence in support of the theoretical and operational evidence was collected by surveying the opinion of experts in the field (i.e. recognised experts in the field of pharmaceutical regulation, product lifecycle, or pharmaceutical technology – see section 6.2.2). The aim of this Chapter is to describe the development of the method that was used for elicitation of expert opinion presented in Chapter 6. The study was a questionnaire based survey and was conducted in two phases, namely: "pilot survey" and the "main survey". This Chapter describes details of the pilot survey that was performed to ensure reliability and validity of the study design (Robson, 2002; Carmines & Zeller, 1979).The intent of the pilot survey was to test the study design and processes and make the necessary improvements to enable the commencement of the main survey. The outcome was to create the main survey questionnaire (Chapter 6) by improving the pilot questionnaire.

5.2 METHOD

Methods described in this section are applicable to the expert opinion study. Although the remainder of this section will focus on the methods for the pilot survey, however there are aspects of the methods that also apply to the main survey – namely: questionnaire anonymisation and ethical considerations.

5.2.1 Pilot survey design overview

The design approach for the pilot survey was based on cognitive interviewing using verbal probing technique. Data were collected using the interview notebook. Collected data were analyzed using qualitative description of the emerging themes, quantitative description of the classified observations, and quantitative analysis of the responses to the pilot survey questionnaire (Appendix B2).

5.2.2 Pilot survey participants

Participants for the pilot survey were selected from the researcher's employer (Sanofi, a global pharmaceutical company). The criteria for selection of pilot survey participants included:

- The number of participants should be in the range of 6 to 10
- There should be at least one representative from each of key phases of the product lifecycle (i.e. pre-clinical development, clinical development and manufacturing)
- The participants should have at least 10 years of experience in the pharmaceutical industry
- The participants should have operational experience with products based on chemical synthesis or biological process
- The participants should have good understanding of the drug products lifecycle and the regulatory environment
- The participants should have operational knowledge of quality activities within the product lifecycle

5.2.3 Pilot Survey questionnaire design

The pilot survey questionnaire (Appendix B2 - improved version of the pilot questionnaire was also used in the main survey, see Section 6.2.5) contained a number of closed-ended questions based on the Likert Scale with four options (Leal et al., 2007): 1. Very Unlikely 2. Unlikely 3. Likely 4. Very Likely including an option for Don't Know. The rationale behind choosing a four-interval measurement scale was to avoid gravitation towards the centre and encourage the participants who were recognised experts to take a clear stance. The questions were categorised into the following four sections with an additional section focusing on participant instructions and definition of terms (Appendix B2). The questions presented in each of the sections were based on the information derived from: Chapter 3 for transformation triggers and open innovation, Chapter 4 for proposed transformation-induced quality risks and associated compliance outcomes, and this Chapter for the participant details and the overall methodology for the survey.

- Participant Details
- Pharma Transformation Triggers and Risks
- Open Innovation and Regulatory Compliance
- Assessment of Transformation-Induced Quality Risks

Piloting the Questionnaire - The questionnaire was piloted using the cognitive interviewing method (Wallis, 1999) by interviewing participants. During piloting the questionnaire, the cognitive interviewing method was applied using the

verbal probing technique (Wallis, 1999). The focus of the verbal probing was the survey questions. A one-hour interview with each participant was performed during which the participant answered the survey question, the interviewer then asked for other specific information relevant to the questions, or to the specific answer given. In general, the interviewer "probes" further into the rationale and basis for the response. The key benefit was to improve the pilot questions and hence the main survey questionnaire by exploring issues relating to participant comprehension and identify structural problems such as erroneous skip patterns (procedures that direct respondents to answer only those items relevant to them) and unclear layout during the interview process. The pilot interview notebook was used to collect the observations. The notebook contained the questions, participant's response to the questions, and classification of any comments (Table 5.1) that the participant made related to the question or the survey procedure. This interview captured two types of data, namely participant responses to the survey questions and participant comments to the assessment of survey reliability and validity.

Table 5.1 Classification of the Cognitive Interview Comments for the pilot questionnaire

Comment Category	Comment Classification
Reliability related	Survey procedure
	Logical layout and flow of the questions
	Clarification for better understanding
	Spelling or grammatical errors/suggestions
Validity related	Appropriateness of the measurement scale
	Challenges to the usefulness/validity of the question

5.2.3.1 Reliability and Validity Assessment

Reliability and validity were performed in three areas relating to:

i) Reliability of the data collection method

ii) Validity of the data collection method

iii) Qualitative description of the emerging themes

i) *Reliability of the data collection method* - pilot data relating to participant comments were analyzed with the aim of improving the reproducibility of the survey questionnaire.

ii) *Validity of the data collection method* - the aim of the validity assessment was to improve fitness of the questionnaire for its intended use. This involved assessment of validity with respect to questionnaire content, structure and participant sampling - collectively termed as external validity.

Construct validity is evidence that the measurement scale within the questionnaire is appropriate for the study (Robson, 2002). Construct validity was

assessed and improved during pilot survey based on the information collected from the cognitive interviewing.
Content validity is the extent to which the content of a survey questionnaire is representative of the research domain it is intended to cover (Robson, 2002). Content validity was derived from the literature review (Chapter 3).

iii) *Qualitative description of the emerging themes* - the data from the cognitive interviewing was categorised into themes, which in turn informed the actions needed to improve the questionnaire and the associated survey procedures.

5.2.3.2 Questionnaire Anonymisation

The pilot questionnaires were anonymised according to the following pseudo-code procedure (designed by the researcher) and a link file containing the participant details and the corresponding anonymised code. The pseudo-code was composed of five elements each with two characters represented in EE-SS-CC-RR-NN format. Details of each of the five elements are:

- EE: Expert's second letter of first name and second letter of last name
- SS: BP for Big Pharma / SP for Small Pharma / CO for Contract Organization / CN for Consulting organization / OT for Other
- CC: First two letters of participant's organization name
- RR: Regulatory Domain of Expertise; US for FDA / EU for EMA / UE for both
- NN: Participant ID. A sequential number assigned based on the order in which the questionnaires were sent to the participants

The anonymisation procedure was also applied to the main survey.

5.2.4 Ethical considerations

The expert opinion study protocol (Appendix B4) for the survey was submitted to Liverpool John Moores University (LJMU) Research Ethics Committee (REC) for review. The pilot survey did not commence recruitment until unconditional approval was received.

Informed Consent - informed consent for pilot survey participants was performed in compliance with the LJMU procedure on "Obtaining Informed Consent for Research Participation". Initially verbal consent of the participant was secured during the awareness discussions (via telephone). Subsequently an e-mail containing a brief statement referencing the summary of the telephone conversation and that the candidate had verbally consented to take part in the survey was sent to the participant. In addition a statement was included in Participant Information Leaflet (PIL - Appendix B1) and the questionnaire to clearly indicate its voluntary nature and the fact that returned completed questionnaire implies participant's consent.

5.3 RESULTS FOR THE PILOT SURVEY

The results for the pilot survey were classified into three categories that characterise participant profiles, describe participant interview outcomes, and enhance reliability of the questionnaire. The remainder of this Section provides an overview of the results relevant to each classification and introduces the respective tables that contain the raw data.

5.3.1 Participant profiles

The pilot interviews included total of six participants whose profiles are based on the data from Section B of the pilot questionnaire and summarised in Table 5.2.

Table 5.2 Participant details for the pilot survey

Section B of Pilot Questionnaire	Regulatory domain of expertise	Organization type	Pharma experience	Years of experience	Quality domain of expertise	Sum	%
US FDA	6					6	100
EU EMA	4					4	67
Other	4					4	67
Big Pharma		6				6	100
Pharmaceutical			4			4	67
Biopharmaceutical			3			3	50
15+ years				6		6	100
Good Laboratory Practice					2	2	33
Good Manufacturing Practice					5	5	83
Good Clinical Practice					1	1	17
GxP[5]					1	1	17

5.3.2 Pilot interviews

The pilot interviews composed of responses from six participants. Each interview lasted approximately 1 hour. During pilot interviews interaction with the participant was performed in accordance with the cognitive interview process described in Section 5.2.3. All remarks made by the participants during the interview were captured as embedded comments within the excel version of the questionnaire in Appendix B3 and summarised in a table in Appendix B5. Due to participant preference scripted verbal probing was not used. Instead, the objective of the verbal probing, the role of the interviewer and the role of participant were explained at the beginning of each interview. The participants were encouraged to freely challenge the questionnaire content, style (layout and

[5] GxP – Good Laboratory, Clinical, Manufacturing, Research Practices

format of the questions) and the measurement scale during the interview. All the comments made by all the participants during the cognitive interview process were attributed to a section or a question within the pilot survey questionnaire. There were 59 comments of which 90% were related to content of the questions, 7% to style of the questions and 2% to the measurement scale. Cognitive interview comments guided improvements of the questionnaire, which resulted in reducing the number of questions from 36 to 30.

The impact of these comments on the questionnaire design is discussed in Section 5.4.1 and 5.4.2.

5.3.3 Category and frequency of cognitive interview comments

All the comments made by all the participants during the cognitive interview process were attributed to a section or a question within the pilot survey questionnaire and listed in Appendix B5. The frequency of participant comments by category (Content, Style, and Measurement) is also provided in Table 5.3. During pilot interviews interaction with the participant was performed in accordance with the cognitive interview process described in Section 5.2.3. All remarks made by the participant during the interview were captured as embedded comments within the excel version of the questionnaire.

5.4 DISCUSSIONS AND CONCLUSIONS OF PILOT SURVEY

5.4.1 Pilot interviews

Participant Profiles - analysis of the participant profiles indicates that they all have extensive professional experience (15+ years) in the pharmaceutical industry. They have strong expertise in the US and EU regulations with some knowledge of other regulatory environments such as France, Germany, Japan, Brazil, and Canada regulatory environment. They have gained most of their operational experience in the context of big Pharma industry, which is evenly distributed between pharmaceutical (67%) and biopharmaceutical (50%) business. The regulatory expertise for the majority of the participants is focused on the manufacturing quality, followed by laboratory quality; clinical quality and research quality (Table 5.2).

Cognitive Interview Comments – a great majority of the participant comments from the cognitive interview relate to the content of the questions with few remarks relating to style and composition of the questions and only one comment concerning the measurement scale as illustrated in Table 5.3.

5.4.2 Improving the pilot questionnaire

To identify questions that needed the most improvement the questions were classified into tiers of priority. This was done by sorting the questions in descending order of priority using the respective frequency of the cognitive interview comments provided in Table 5.3. Questions with the most comments required the most attention and hence placed in Tier 1:

Table 5.3 Frequency of participant cognitive interview comments by category for the pilot survey

Question	# of Participant Comments	Comment Category		
		Questions Content	Question Style	Measurement Scale
Section A	1	1	0	0
Section B	1	0	1	0
Section C	0	0	0	0
Section D	0	0	0	0
Section E	13	7	6	0
Count	15	8 (53%)	7 (47%)	0 (0%)
Q6	1	1	0	0
Q7	4	4	0	0
Q8	8	6	2	0
Q9	11	11	0	0
Count	24	22 (92%)	2 (8%)	0 (0%)
Q10	1	1	0	0
Q11	3	3	0	0
Q12	1	1	0	0
Q13	0	0	0	0
Q14	2	1	1	0
Q15	5	5	0	0
Q16	2	2	0	0
Q17	4	4	0	0
Q18	2	2	0	0
Q19	6	5	1	0
Q20	2	2	0	0
Q21	2	2	0	0
Q22	1	1	0	0
Q23	3	2	1	0
Q24	0	0	0	0
Q25	2	2	0	0
Q26	3	2	1	0
Q27	1	1	0	0
Q28	1	1	0	0
Q29	0	0	0	0
Q30	1	1	0	0
Q31	4	4	0	0
Q32	4	3	0	1
Q33	3	3	0	0
Q34	0	0	0	0
Q35	1	1	0	1
Q36	4	4	0	0
Count	59	53 (90%)	4 (7%)	2 (3%)

Tire 1 – Q19,Q15,Q17,Q36,Q32,Q31,Q33,Q23,Q11,Q26 (Order: left to right)
Tire 2 – Q20, Q35, Q16, Q25, Q14, Q18, Q21
Tire 3 – Q22, Q27, Q10, Q12, Q30
Tire 4 – Q24, Q34, Q13, Q29

The improvements to the questionnaire are most effective by studying the cognitive interview comments and applying the potential enhancements to the survey. This approach for improving the pilot questionnaire was applied with a particular focus on Tier 1 & 2 questions. The summary of changes made to the pilot questionnaire is listed in Table 5.4.

Table 5.4 Improvements made to the questionnaire due to pilot survey

Question	Changes made to pilot questionnaire
Question 6	Added Good Research Practice (GRP) to the list
Question 8	Replaced “Externalization of S/W Applications” with “Outsourcing of Data Management”
Question 9	Added help comments
Questions 11, 15, 17	None of the comments suggest rephrasing of the questions
Question 16	Removed the word “Smarter”
Questions 18 to Q36	Reduced number of questions from 18 to 12. The composition of the questions was changed to achieve an open-ended style. The measurements scale was revised to measure the likelihood of adverse compliance outcomes for i) each of the transformation-induced risks and ii) areas within the product lifecycle that are most impacted.

5.4.3 Conclusion

The results presented in this Chapter confirm the reliability of the survey questionnaire subject to improvements in some areas (Section 5.4.2). The questionnaire for the main survey was built to reflect these improvements and is presented in Chapter 6.

CHAPTER 6: Establishment of opinion-based evidence in support of the transformation triggers

6.1 INTRODUCTION

The aim of this Chapter is to present the results of the expert opinion survey developed in Chapter 5. The survey was performed to elicit expert opinion on the i) proposed transformation triggers and associated quality risks identified in Chapter 3, and ii) relationship between the proposed quality risks and the regulatory compliance outcomes present during drug product lifecycle. Expert opinion was sampled using the main survey questionnaire with participants who were experts in the fields of pharmaceutical regulation, pharmaceutical product lifecycle or pharmaceutical technology.

6.2 METHOD

The questionnaire design, anonymisation, and ethical considerations of the main survey are based on the methods described in Chapter 5. Additional methods specific to the main survey are provided in this section.

6.2.1 Main survey design overview

The survey design was based on the relational non-experimental fixed method (Robson, 2002). The word “relational” means that the survey was set up to specifically explore relationships between particular variables (i.e. the relationship between transformation-induced quality risks and the regulatory compliance outcomes). The survey was non-experimental in that the researcher did not deliberately change or manipulate the variables during the conduct of the main survey. It was a fixed method since the survey design was fully defined before the data collection took place. Data were collected using the main survey questionnaire.

6.2.2 Main survey participants

The participants of the main survey were recognised experts in the field of pharmaceutical regulation, product lifecycle, or pharmaceutical technology. They had strategic view of the pharmaceutical quality in their respective organization, were typically the “go-to” person on matters of quality and regulatory compliance and often represent their companies in external academic or industrial

organizations. They had multidisciplinary quality expertise with exposure[6] to quality issues affecting the drug product lifecycle[7], and experience in the pharmaceutical or biopharmaceutical industry as an employee or as a service provider. They represented their respective organisation in external departments listed in the sampling frame (Section 6.2.3). Assignments of members was based on expert knowledge of the members on the subject matter that the department was commissioned to undertake. Therefore the survey participants selected from these departments are considered experts.

A combination of purposive (the primary sampling method) and snowball sampling (Mack et al., 2005; Robson, 2002) was used for participant selection. Purposive sampling groups participants according to preselected criteria relevant to a particular research question. The sample was taken from the organizations that make up the sampling frame (Section 6.2.3). Snowball sampling was used as an aid to the purposive sampling, which requires the participants to identify other potential candidates from the sampling frame.

6.2.3 Sampling frame

The sampling frame is the source of the eligible population from which the survey sample was drawn. Potential candidates for this study were recruited from the organizations listed in Table 6.1. These organizations were representative of pharmaceutical experts who gather and formulate solutions to challenging regulatory problems and publish their work. The key criteria for selecting the four organizations listed in Table 6.1 were i) focus on pharmaceutical science, technology and regulations in the context of drug development, approval, and manufacturing ii) diverse membership that included industry professionals, industry service providers, regulatory agencies and academia iii) active involvement in regulatory science topics and iv) a specific focus on pharmaceutical quality from the perspective of Good laboratory, manufacturing, clinical or pharmaco-vigilance Practice and risk management. Inclusion of consulting professionals from service providers to the pharmaceutical industry was important for enhancing sample diversity since these professionals experience a wide range of industry practices during their service offerings. None of the consulting professionals had any working relationship with the researcher or were offered consulting engagements with the collaborating organisation as part of their survey participation.

[6] Exposure to quality issues affecting two or more elements of the drug product lifecycle
[7] Lifecycle: laboratory studies > clinical studies > product approval > product manufacturing > product distribution > product surveillance

Table 6.1 Target participant organizations from which the main survey participants were selected

Organization	Department
International Society for Pharmaceutical Engineers (ISPE)	Board of directors
	Good Automated Manufacturing Practice forum
Parenteral Drug Association (PDA)	Science Advisory Board
	Biotech Advisory Board
	Regulatory and Compliance Advisory Board
	Quality Risk Management Interest Group
Research Quality Association, formerly BARQA	GMP, GLP, GCP, PV Committee Leaders
American Association of Pharmaceutical Scientists (AAPS)	Quality By Design (QBD) Working Group

6.2.4 Main survey participant inclusion criteria

The candidates meeting the following criteria were selected for the survey.

- Those who had quality and compliance knowledge in good laboratory, clinical, and/or manufacturing practice AND
- Those who had experience with US (FDA) regulations and/or EU (EMA) regulation AND
- Those who had current working knowledge of quality relevant to medicinal products based on pharmaceuticals and/or biologics

Participants were allowed to withdraw from the study at any time.

6.2.5 Main survey questionnaire

The main survey questionnaire (Table 6.3) is the revised and enhanced version of the pilot survey questionnaire (Appendix B2) discussed in Chapter 5.

6.2.6 Ethical consideration

The REC approval was obtained for the revised version of the questionnaire, which was based on the improvements identified during the pilot study. The ethical approval for the main survey followed the process described in Chapter 5 except for the informed consent for the participants from the PDA. The informed consent for this population was secured via collaboration with the PDA in order to comply with PDA's privacy policy for their members. There was no fundamental change to process approved by the REC. The only adjustment involved the PDA assigning a coordinator to interact with the participants in place of the researcher. The researcher trained the PDA coordinator on requirements of the approved study protocol (including informed consent) prior to commencement of the survey.

6.2.7 Procedure for performing the main survey

The survey procedure had two key steps: i) participant awareness and informed consent ii) questionnaire completion. Potential candidates were contacted by telephone to secure their verbal consent to participate in the survey. The telephone conversation was intended to last up to 30 minutes and focused on explaining the information leaflet, instructions on how to complete the main questionnaire and addressing any process related questions that candidates may have had. During the telephone conversation it was explicitly stated that participation in the survey was voluntary and there was no obligation to contribute to research study. The telephone conversation stopped at this point and if the candidate consented he/she was considered as a "participant" in the study. Prior to the teleconference meeting, an e-mail containing electronic copy of the information leaflet and the questionnaire was sent to the candidates. After the phone conversation, an e-mail containing a brief statement referencing the summary of the phone conversation and that the candidate had verbally consented to take part in the survey was sent to the participant. The participants were asked to complete the questionnaire offline and return the completed electronic or scanned copy to the principal investigator. The questionnaires were checked for completeness upon receipt and the participant contacted to address any gaps. The main survey conduct was deemed closed once all the completed questionnaires and subsequent communication to address issues were received within a six month period from start (March 2012) of the main survey study. The main survey study was closed on September 2012.

For participants from the Parenteral Drug Association (PDA) the survey conduct was somewhat different. For this population Survey Monkey (an online survey application) was used to inform, seek consent and collect participant responses to the main survey questionnaire online. This approach was taken to conform to the privacy policy of the PDA and to ensure equivalence to the paper process the Survey Monkey questionnaire and associated communication procedure were aligned to the study protocol approved by the LJMU REC. The alignment was achieved by comparing the questions, instructions and layout of the online survey with that of the approved paper questionnaire.

6.2.8 Definition of key terms

The following are definition of key terms used to describe the main survey data.

- The *interval* scale (Table 6.2) was used to capture participant scores to multiple choice (Likert) questions in the questionnaire
- The *binary* scale (Table 6.2) was used to capture participant scores to simple Yes or No questions in the questionnaire

- The *mean* is the arithmetic average of participant scores for each question in the questionnaire
- The *dataset* refers to participant scores for questions in the questionnaire that use interval (Likert) scale for measurement (i.e. Q10 to Q30 except Q24 of the main questionnaire)
- The *dataset mean* is the average participant scores for the entire dataset

Table 6.2 Measurement range for interval and binary scales

Scale	Measurement Range	
Interval	Very Unlikely	0 to 25
	Unlikely	25 to 50
	Likely	50 to 75
	Very likely	75 to 100
	Don't Know	0 to 100 (the participant does not know enough to respond but the potential answer could be within the full range of the scale)
Binary	Yes / No	100 / 0

6.3 RESULTS FOR THE MAIN SURVEY

The results for the main survey were classified into three categories that characterise participant profiles, supply descriptive statistics for survey questions, and summarise participant comments to survey questions. The remainder of this section provides an overview of the results relevant to each classification and introduces the respective tables that contain the raw data.

6.3.1 Participant profiles

The main survey included 80 participants of which 33 (41%) responded to the questionnaire. Respondent profiles - based on their answers to questions in Section B in the questionnaire - are summarised in Table 6.4.

Table 6.3 Main Survey questionnaire definitions, participant details and transformation related questions

SECTION A – Definitions	
GxP – Good Laboratory, Clinical, Manufacturing, Research Practices	
ICH – International Conference on Harmonization	
Innovation – the introduction of new technologies or methodologies	
Open Innovation - the practice of leveraging the discovery of others and not rely exclusively on own R&D for innovation	
Pervasive Technologies – smart implantable devices used for product tracking, remote patient monitoring or drug delivery	
Pharma Transformation - is concerned with ongoing disruptive changes currently shaping the operational concepts, organization, and technologies impacting pharmaceutical innovation and the ability to meet the demands of a changing healthcare environment	
Post-market Surveillance – Regulatory agency risk assessment activities that take place after approval of the drug product	
Pre-market Assessment – Regulatory agency risk assessment activities that take place prior to approval of the drug product	
Product Lifecycle - all phases in the life of the product from the initial development through marketing until the product's discontinuation	
Quality – the degree to which a set of inherent properties of a product, system or process fulfils requirements	
Quality Risk – a GxP activity that if not performed properly may have the potential to result in adverse events impacting product quality, data integrity or patient safety	
SECTION B - Participant Details	Likert scale used?
1. Expert identification code:	No
2. Organization name:	No
3. Regulatory domain of expertise:	No
4. Organization type:	No
5a. Experience in:	No
5b. Years of Experience:	No
6. Quality domain of expertise:	No
SECTION C – Pharmaceutical Transformation Triggers and Risks	

Table 6.3 Continued

7. Which of the following is a key driver for the current Pharmaceutical Transformation? • Business Environment • Regulatory Environment • Open Innovation • Other (please specify):	No
8. Which of the following Open Innovation trends do you think is currently practiced in the pharmaceutical industry? * e.g. Clinical Studies, Safety Reporting, IT Data Centres, etc. • Commercial Partnerships • Increased In Licensing • Research Partnerships • Research Information Sharing • Focus on Combination Products • Focus on Biological Products • Focus on Pervasive Technologies • Outsourcing of Data Management • Other (please Specify):	No
9. Lack of which of the following will pose a GxP Risk in an Open Innovation environment? • Effective Due Diligence • Effective Product Transfer • Multidisciplinary Regulatory Knowledge (e.g. for combination products) • Effective Product Characterization • Data Security and Integrity • Technology Validation (means obtaining proof of fitness for intended use) • Other (please Specify):	No
SECTION D – Open Innovation and Regulatory Compliance	
10. Open Innovation will have significant impact on external partner/alliance selection and oversight?	Yes
11. Open Innovation will have significant impact on legal framework for exchange of research information?	Yes
12. Open Innovation will have significant impact on data management in the context of data security, integrity and privacy?	Yes

Table 6.3 Continued

13. Biological/Biotech products will become major part of the project and product portfolio?	Yes
14. Prevalence of pervasive technologies will require multidisciplinary knowledge and skills to deal with convergent scientific disciplines (e.g. smart implantable drug delivery devices)?	Yes
15. Existing regulatory approaches are adversely impacting the innovation drive in the industry?	Yes
16. Regulatory approach that is responsive to new discoveries while maintaining safety and efficacy standards will improve innovation drive?	Yes
17. Regulatory initiatives such as FDA's Critical Path and EMA's Innovation Task force (ITF) will have a significant impact in industry's innovation drive?	Yes
SECTION E – Assessment of Transformation-Induced Quality Risks	
a) GxP Due Diligence of External Partners and Alliances	
18. What is the likelihood that problems with due diligence process will result in adverse GxP compliance outcomes when selecting external alliances / partners?	Yes
19. What part(s) of the product lifecycle is most at risk of adverse compliance outcomes?	No
b) Product Transfer	
20. What is the likelihood that problems with product transfer* process will result in adverse GxP compliance outcomes? *Internally within a company or between the company and external partners.	Yes
21. What part(s) of the product lifecycle is most at risk of adverse compliance outcomes?	No
c) Multidisciplinary Regulatory Approach	
22. What is the likelihood that insufficient multidisciplinary quality knowledge/expertise across a range regulatory situations* will result in adverse GxP compliance outcomes? *e.g. combination products that may require regulatory knowledge of diagnostics, drugs and devices	Yes
23. What part(s) of the product lifecycle is most at risk of adverse compliance outcomes?	No
d) Biological/Biotech Products	
24. Are Biological/Biotech products more complex and difficult to characterise than chemically synthesised products? • Yes / No	No
25. What is the likelihood that poor process understanding and product integrity* controls will result in adverse GxP compliance outcomes? * contamination controls, stability controls, sterility assurance	Yes

Table 6.3 Continued

26. What part(s) of the product lifecycle is most at risk of adverse compliance outcomes?	No
e) Data Security and Integrity	
27. What is the likelihood that externalization of GxP data creation, storage and maintenance will result in adverse GxP compliance outcomes?	Yes
28. What part(s) of the product lifecycle is most at risk of adverse compliance outcomes?	No
f) Technology Validation	
29. What is the likelihood that technology* validation supporting product lifecycle will result in adverse GxP compliance outcomes? * relating to manufacturing and laboratory automation and information management systems	Yes
30. What part(s) of the product lifecycle is most at risk of adverse compliance outcomes?	No

Likert measurement scale was used for questions in Table 1 that are tagged as “Yes”. For questions 19, 21, 23, 26, 28, 30 the following response options were used:

- Pre-market Evaluation / Marketing Approval / Post-market Surveillance / Don’t Know

Table 6.4 Participant details for the main survey

Participants: 80 Respondents: 33 Response rate: 41% Participant responses to Section B questions	Regulatory domain of expertise	Organization type	Pharmaceutical experience	Years of experience	Quality domain of expertise	Participant profiles (%)
US FDA	31					44.3
EU EMA	24					34.3
Other	15					21.4
Big Pharma		10				26.3
Small Pharma		5				13.2
Consulting		16				42.1
Contract Research/Manufacturing Org.		5				13.2
Other		2				5.2
Pharmaceutical			31			55.4
Biopharmaceutical			20			35.7
Other			5			8.9
10-5 years				1		3.0
10-15 years				2		6.1
15+ years				30		90.9
Good Laboratory Practice					11	19.7
Good Manufacturing Practice					31	55.4
Good Clinical Practice					5	8.9
Good Research Practice					4	7.1
Other					5	8.9

Response rate varies by question since each respondent was allowed to choose multiple options for Section B questions with the exception of the question relating to “Years of Experience” where participants were only allowed to choose one option.

6.3.2 Descriptive statistics for the main survey

The frequency of the participant responses to Section C questions - covering questions relating to transformation triggers, open innovation, and transformation-induced quality risks - is tabulated in Table 6.5. Some participants provided multiple suggestions (discussed in Section 6.4) for the open ended element of these questions, which are counted separately and reflected in the response frequency calculations.

Table 6.5 Response count for transformation related questions for the main survey

Section C	Question	Trigger / Risk	Response Count	Response Rate %
Pharma Transformation Triggers	Q7	Business Environment	27	47
		Regulatory Environment	20	35
		Open Innovation	8	14
		Other (please specify):	2	4
		Total	57	100%
Open Innovation	Q8	Commercial Partnerships	20	19
		Increased In-licensing	17	16
		Research Partnerships	13	12.5
		Research Information Sharing	2	2
		Focus on Combination Products	13	12.5
		Focus on Biological Products	16	15
		Focus on Pervasive Technologies	3	3
		Outsourcing of Data Management	18	17
		Other (please Specify):	3	3
		Total	105	100%
Pharma Transformation Risks	Q9	Effective Due Diligence	18	19.5
		Effective Product Transfer	19	20
		Multidisciplinary Regulatory Knowledge	13	14
		Effective Product Characterization	16	17
		Data Security and Integrity	9	10
		Technology Validation	14	15
		Other (please Specify)	4	4.5
		Total	93	100%

Response rate varies by question since each respondent was allowed to choose multiple options for questions listed in column 2.

The responses to questions in Sections C, D and E were standardised (see Table 6.2) for all participants and mean of the standardised scores and respondent comments per question is included in Table 6.6.

The frequency of participant responses for transformation-induced quality risks (independent variables) and compliance outcomes (dependent variables) is captured in Table 6.7 and Table 6.8 respectively.

Table 6.6 Participant response statistics for the main survey

Transformation Triggers and Risks	Mean of standardised scores	No. of Participant comments
Q7	55.56	2
Q8	38.64	3
Q9	44.95	4
Q24	30.30	2
Compliance Outcomes (dependent variables)	Mean of standardised scores	No. of Participant comments
Q19	32.58	2
Q21	28.79	2
Q23	30.30	2
Q26	32.58	2
Q28	32.58	2
Q30	30.30	3
Quality Risks (independent variables)	Mean of standardised scores*	No. of Participant comments
Q10	65.91	2
Q11	64.39	2
Q12	65.23	0
Q13	70.83	2
Q14	73.11	1
Q15	62.50	3
Q16	66.67	2
Q17	59.85	3
Q18	69.32	0
Q20	67.42	3
Q22	68.94	4
Q25	75.00	2
Q27	56.82	2
Q29	57.20	2
*analysis dataset for Likert scale questions ➔	Mean: 65.94 SD: 17.75	

Table 6.7 Participant response count for questions relating to quality risks for the main survey

Question	Very Unlikely	Unlikely	Likely	Very Likely	Don't Know	Skipped
Q10	0	2	17	9	1	4
Q11	1	2	13	10	3	4
Q12	1	2	14	10	1	4
Q13	0	1	11	15	2	4
Q14	0	0	10	17	2	4
Q15	0	6	12	9	2	4
Q16	1	4	9	14	1	4
Q17	2	6	11	9	1	4
Q18	0	1	13	13	1	5
Q20	0	2	15	11	0	5
Q22	0	1	18	11	3	3
Q25	0	1	7	20	0	5
Q27	0	7	13	4	4	5
Q29	0	9	13	5	1	5
Total	5	44	176	157	22	60

Table 6.8 Participant response count relating to compliance outcomes for the main survey

Question	Pre-market Evaluation	Marketing Approval	Post-market Surveillance	Don't Know	Skipped
Q19	5	11	16	6	5
Q21	2	10	18	3	5
Q23	2	12	16	4	6
Q26	6	11	15	3	8
Q28	6	10	16	5	6
Q30	4	11	14	5	6
Total	25	65	95	26	36
	11.85%	30.81%	45.02%	12.32%	17.06%

Response rate varies by question since each respondent was allowed to choose multiple options for questions listed in column 1.

6.3.3 Respondent comments on the main survey questions

The following is commentary on remarks that the respondents made on the various questions within the questionnaire. The exact text provided by respondents is enclosed in quotation marks.

Respondent comments on questions 7 - 9:

Quality risk on the one hand and overly prescriptive standard promulgation and an exaggeration of risk on the other were identified as opposing opinions and additional drivers of industry transformation. One participant stated that "open innovation trends currently practiced in the industry include virtual organizations, contract manufacturing and professional consortiums". Other areas of risk identified by participants include i) duration of research partnerships versus duration of the product development lifecycle ii) supply chain management in its broadest context iii) management understanding of quality rather than just compliance and iv) product adulteration and drug counterfeiting.

Respondent comments on questions 10 - 17:

Concerning the impact of open innovation on external partner/alliance selection, two participants suggested that companies were already downsizing and outsourcing various activities and that more scrutiny in partner selection was needed. One participant thought that "legal framework for open innovation should probably be established, but was not sure if it would happen" and another participant had an opposing view stating that "legal framework is pretty well developed already". Regarding the prevalence of biological/biotechnology products one participant believed that this was already part of project and product portfolios of pharmaceutical companies and this is a trend that will accelerate. In contrast another participant suggested that biological/biotechnology products tended to be highly expensive targeted drugs and current trends in healthcare management may not embrace these products as a first line of therapy. On multidisciplinary knowledge/skills one participant stated that "what is required from a compliance point of view are more

individuals with medical experience making judgments regarding patient care and less involvement of bureaucrats to encourage peer review and ensure attention to fundamental scientific principals". On regulatory approach to compliance and innovation one participant suggested that "compliance is all too often a self-fulfilling prophecy in which a perceived problem is blown out of proportion to risk. Overbearing regulation for years has been used to control respective markets leading to difficulty in introducing newer technologies particularly those that rely on unique drug delivery systems, are customised to a specific patient, or are multifaceted in one way or another. Overbearing regulation would result in a loss of innovation, the swallowing up of smaller, entrepreneurial organizations, drug shortages of some medicines, and perhaps even the curtailment of generics". Another participant focused more on the legal aspect stating that "concern about adverse publicity and legal issues (potential class action lawsuits) are leading to conservative decision making in portfolio management and regulatory review". Another participant summarised the regulatory approach as "the bar for safe and effective is increasing". One participant stated that "regulators have no incentive in making anything easier for anyone and was not optimistic that the regulatory apparatus, which has evolved in Europe and the USA in particular, can support an innovative environment". Concerning regulatory initiatives one participant opined that "these initiatives may work if regulators provide flexibility in regulatory filings". A couple of the participants expressed a more sceptical tone opining that regulation never leads to innovation or innovation drive, regulation should focus on one thing and one thing only, making sure that there is a supply of safe medicine for everyone and that new ideas gain market access at the appropriate pace. Such initiatives to date have tended to be largely political and seem to lack the strategic partnership needed with all sectors of the Pharmaceutical Industry (i.e. Big Pharma as well as Generics).

Respondent comments on questions 18 - 30:

On GxP due-diligence for external partners/alliances one participant commented that "all the phases of the product lifecycle were at risk as long as the focus remains on regulatory compliance rather than real compliance". The participant defined real compliance as "developing and manufacturing safe and effective medicines from a strong ethical base focusing on combating unethical and criminal elements of the healthcare product supply chain". With respect o product transfer one participant stated that "potential GxP compliance risks will depend a lot on quality of product transfer planning and execution". Another participant stated that "the GxP compliance was a moving target, which often has absolutely nothing to do with product safety". One participant proposed "inadequate knowledge management and process characterization continue to be major roadblocks in early commercialization". One comment focused on contractual process expressing a great deal of concern during the technology transfer process from one organization to another and that the "contract giver discovers it takes much more time and resource than they had imagined".

Another comment attributed inadequate knowledge of dosage form processes to “poor inspections outcomes stating that there is a direct relationship between industry implementation of innovative technology and more regulatory scrutiny”. Concerning multidisciplinary regulatory knowledge/skills one participant stated that “the compliance risks are high after the initial product approval since firms’ compliance and quality systems trend to deteriorate during the commercial manufacturing”. Regarding complexity of the biological/biotechnology product characterization, couple of the participants opined that the process is the product and in some cases they are more difficult to characterise chemically or biochemically, but in some cases they aren't. Further explaining that “complex biologics have been used safely for decades; there is no reason to be hung up on complexity”. One comment focused on regulators understanding of contamination control and stating that the “recent drive to manufacture even non-sterile drugs in classified clean rooms as a complete waste of money and regulatory effort”. Another comment attributed majority of regulatory product recalls to “poor understanding of product performance long term, especially with product component interactions”.

With respect to externalization of GxP data management one comment stated that “some aspects of data collection, and storage has been in place for decades and compliance problems have been comparatively rare” and another comment focused more on use of social media in the industry implying that “it may present a larger quality and compliance risk than internal data management systems”. Concerning technology validation one comment discussed the new technology adoption in the industry saying that the “pharmaceutical and biopharmaceutical industries have lagged behind other technological industries in the adaptation of modern information and process management technologies”. The commenter attributed this lag largely to “misplaced regulatory concerns and unfortunate regulatory requirements”. Another comment focused on computer validation approaches noting that they “have not changed significantly in 20 years and therefore the current methodologies are unprepared for use of new "cloud based" computing”.

6.4 DISCUSSIONS AND CONCLUSIONS

The results of the main survey relating to each section of the questionnaire are discussed. The supporting data for the following discussion is provided in Tables 6.4 to 6.8.

6.4.1 Participant details (questions 2 to 6 of main survey questionnaire)

Analysis of the participant profiles indicated that they all had extensive experience (15+ years) in the pharmaceutical industry (Q5a, Q5b in Table 6.3). They had expertise in the US and EU regulations with some knowledge of other regulatory environments such as Australia, Brazil, Canada, Japan, New Zealand, Switzerland, the Pharmaceutical Inspection Co-operation Scheme and the World Health Organization (Q3 in Table 6.3). Most of the respondents linked their operational experience with Big Pharma and Consulting companies serving mainly the pharmaceutical and biopharmaceutical business (Q4 in Table 6.3). The regulatory expertise for majority of the participants focused on the manufacturing quality, followed by laboratory quality; clinical quality and research quality (Q6 in Table 6.3).

The 41% response rate (Table 6.4) is appropriate since the respondent profiles characterise the participant population (i.e. the 80 participants). The following key characteristics of the participant population are strongly represented in the respondent profiles as demonstrated in Table 6.4:

- Participants with operational experience in pharmaceutical industry and as service providers
- Participants with operational knowledge of the US and EU regulatory environment
- Participants with operational knowledge of good laboratory and manufacturing practice. In practice the drug product quality and associated patient safety concerns are more prominent during product approval and routine use of the drug product than during the research and development phase. Therefore it is appropriate that most respondents have experience in good laboratory and manufacturing practice

The participants were selected - by the researcher or the PDA coordinator in the case of PDA participants - from specific departments within the organisations listed in Table 6.1. The word “department” is used to collectively refer to terms such as advisory board, committee, working group and interest group. The departments listed in Table 6.1 have a specific mission and their members were assigned by their respective organisations. Assignments of members was based on expert knowledge of the members on the subject matter that the department

was commissioned to undertake. Therefore the survey participants selected from these departments are considered experts.

One potential area of improvement is additional expertise in the clinical quality arena. More participants with this expertise would have provided a sharper image of quality risk and compliance outcomes associated with the pre-market evaluation phase of the product lifecycle.

6.4.2 Transformation triggers and risks (questions 7 to 9 of main survey questionnaire)

In addressing questions relating to pharmaceutical transformation most participants agreed that the *Business* and *Regulatory* environment play the leading role in the ongoing transformation within the industry with open innovation playing somewhat of a lesser role (Q7 in Table 6.5). Among the open innovation trends commercial partnerships, outsourcing of data management activities, focus on biological products and in-licensing received the most attention. Participants also suggested increase in other open innovation trends that include virtual organizations, contract manufacturing and professional consortiums (Q8 in Table 6.5). From the perspective of quality risks, the participants gave the highest importance to effective due diligence, product transfer and product characterization activities followed by technology validation and multidisciplinary regulatory knowledge (Q9 Table 6.5). Provisions for data security and integrity received the lowest score (Q9 Table 6.5).

6.4.3 Open innovation and regulatory compliance (questions 10 to 17 of main survey questionnaire)

There was support amongst participants that open innovation would have a significant influence on selection and oversight of external partners (Q10 in Table 6.7) and management of data from the perspective of data security, integrity and privacy (Q12 in Table 6.7). The prevalence of biological and biotechnology products in pharmaceutical companies' project and product portfolios (Q13 in Table 6.7) and prevalence of pervasive technologies requiring multidisciplinary knowledge/skills (Q14 in Table 6.7) received the most likelihood of occurrence from the participants. Participants did not agree that existing regulatory approaches adversely impact pharmaceutical innovation (Q15 in Table 6.7) and there was modest support for the assertion that the current regulatory initiatives such as "Critical Path" of the US FDA and "Innovation Task Force" of EMA had significant positive impact on pharmaceutical innovation (Q17 in Table 6.7).

6.4.4 Assessment of transformation quality risks (questions 18 to 30 of main survey questionnaire)

Poor process understanding for biological / biotechnology products and problems with due diligence process for external partners/alliances was seen as posing the most quality risks followed by lack of multidisciplinary quality knowledge and expertise across a range of regulatory situations (Q18, Q22, Q25 in Table 6.7). Externalizing management of GxP related data and lack of effective technology validation processes were deemed important but comparatively less important as sources of quality risks (Q27, Q29 in Table 6.7). According to the experts (Table 6.8) the outlined quality risks from a GxP compliance perspective are most noticeable during the post marketing surveillance and marketing approval phases of the product lifecycle. In comparison, the participant responses suggest that quality risks are less impactful during pre-market evaluation phase and that most of the impact is focused on due diligence of external partners/alliances, biological/biotechnology product characterization and externalization of GxP data management.

6.4.5 Conclusion

Given that literature results take time to publish, there is a difference in knowledge within the literature (i.e. with respect to the theoretical evidence presented in Chapter 3) and those of experts in the field. Therefore there was a need to have a view of the current situation by eliciting opinion of experts with operational knowledge relating to industry transformation and associated quality risks. The main survey has closed this gap by providing valuable field information that is used to determine the pharmaceutical quality risk model presented in Chapter 7.

CHAPTER 7: *General Discussions & Development of a Pharmaceutical Quality Risk Model*

7.1 INTRODUCTION

The pharmaceutical industry, since 1990, has experienced a decline in research and development productivity, despite significant advancements in biomedical sciences and increasing R&D expenditure (Section 1.3.1). The productivity decline consequently poses a major concern since fewer resources are deployed on products targeted for important public health needs such as rare diseases, prevention indications, or individualised therapies. This prospect has motivated both the industry and the regulators to make transformational changes to the way drug products are discovered, developed, approved, and used – with the ultimate aim of producing innovative products to protect and promote public health (Sections 2.3.2 and 2.3.3).

During the design and implementation of these transformational changes, a key consideration for the pharmaceutical industry and regulators is to ensure that risks associated with quality of products, safety of patients and integrity of related data (collectively termed "pharmaceutical quality risks") are effectively addressed. In the pharmaceutical industry the *quality unit* – mandated by law – plays a key role in addressing these risks (Section 1.2.5). Therefore an important goal for the *quality unit* should be to determine potential risks introduced by the ongoing pharmaceutical transformation and devise a plausible quality risk model to identify areas within the product lifecycle that require the most attention.

This original research (see Section 7.4.3) set out to study the ongoing pharmaceutical transformation with the aim of i) establishing theoretical evidence for key triggers influencing the pharmaceutical transformation, ii) identifying transformation-induced quality risks, iii) accumulating operational evidence so as to confirm or deny the theoretical evidence, iv) eliciting opinion of expert practitioners to acquire field knowledge of the transformation-induced quality risks and their relationship to regulatory compliance outcomes, and v) using this information to propose a pharmaceutical quality risk model for the drug product lifecycle. To accomplish the above aim this PhD research was built upon the following three key pillars:

- Theoretical Evidence - represented by transformation triggers derived from the systematic review of the literature
- Operational Evidence - represented by Figures 4.1 to 4.12 derived from the systematic analysis of operational data
- Opinion-based Evidence - represented by results of the expert opinion survey

The identification and ranking of importance of the triggers impacting pharmaceutical transformation, termed “theoretical evidence”, were performed in Chapter 3. The importance ranking of the fourteen transformation triggers (listed below) resulted in selection of four triggers (Trigger 2, 3, 5, and 14) as the basis for proposing potential quality risks impacting the pharmaceutical quality.

Trigger 1: Healthcare Management Focused
Trigger 2: Fully Integrated Pharma Network
Trigger 3: Personalised Medicine
Trigger 4: Virtual R&D
Trigger 5: Translational Research
Trigger 6: Adaptive Clinical Trials
Trigger 7: Regulatory Harmonisation
Trigger 8: Science and Risk Based Approach
Trigger 9: Progressive/Live Licensing
Trigger 10: Regulatory Enforcement
Trigger 11: Biotechnology
Trigger 12: Nanomedicine
Trigger 13: Bioinformatics
Trigger 14: Pervasive/Cloud Computing

The corresponding “operational evidence” - backing the theoretical evidence from the perspective of industrial practice - was provided in Chapter 4. The next step was to propose a plausible model for pharmaceutical quality risk. To do this it was necessary to elicit expert opinion in the field (Chapter 6) regarding the theoretical evidence and use experts’ knowledge to determine the relationship between the proposed quality risks and the compliance outcomes.

The aim of this Chapter is to discuss the findings of the previous chapters, compare them with findings in the literature and use the survey data from the expert opinion study to determine the relationship between the proposed quality risks and the compliance outcomes.

7.2 METHOD

The methods described in this section are used to: i) determine the strength of the operational evidence, ii) determine the tripartite relationship between expert opinion, theoretical evidence and operational evidence, iii) construct a pharmaceutical quality risk model using data from the main survey, and iv) identify other research similar to this PhD research for the purposes of comparison.

This section is reliant on Chapter 6 since the descriptive statistics for the main survey data referenced here are described in Chapter 6.

7.2.1 Determining strength of theoretical evidence and operational evidence

The method for measuring strength of the theoretical evidence was based on the ranking of the transformation triggers (i.e. the higher the ranking, the higher the strength of the theoretical evidence). However in order to ensure a simple comparison between the theoretical and operational evidence, the measurement scale for strength of the theoretical evidence was converted into an interval scale (Flynn et al. 1994) with ten equal intervals with values between 0 and 100 (Table 7.1). Since the theoretical evidence rankings are in descending order the highest strength values are assigned to the lowest ranking numbers (Table 7.2, 7.3)

Table 7.1 Measurement scale to show the strength of the theoretical evidence

Theoretical Evidence Rank Interval	Theoretical Evidence Strength Interval
1.0 – 1.4	90 – 100
1.4 – 2.8	80 – 90
2.8 – 4.2	70 – 80
4.2 – 5.6	60 – 70
5.6 – 7.0	50 – 60
7.0 – 8.4	40 – 50
8.4 – 9.8	30 – 40
9.8 – 11.2	20 – 30
11.2 – 12.6	10 – 20
12.6 – 14.0	0 –10

The strength of the operational evidence was determined through visual examination of the Figures 4.1 to 4.12 and the observed trends were converted into a simple strength scale to enable direct comparison with the strength of the theoretical evidence. In order to facilitate this simple like-for-like comparison, the measurement scale for the operational evidence and theoretical evidence were aligned.

The method for measuring strength of the operational evidence was based on the interval scale (Flynn et al. 1994) with values from 0 to 100. The scale was divided into seven equal intervals with “None” at the lowest end and “Very Strong” at the highest end of the interval (Table 7.2). Seven intervals were chosen to provide maximum precision in allocating the strength values for the operational evidence. Each interval qualitatively defines the amount of operational evidence present for transformation triggers. The “Very Strong” interval was subdivided into two tiers to differentiate between evidence from multiple versus single operational indicator. The word “indicator” refers to the category of operational data that was used to build the operational evidence (see

Section 4.3). Three indicators were used to build the operational evidence for transformation Trigger 3 (personalised medicine) and hence the operational evidence for this trigger was assigned the highest strength value (Table 7.3).

Table 7.2 Measurement scale to show the strength of the operational evidence

Strength of Operational Evidence	Interval Scale
Very Strong (tier 1): significant amount of operational evidence from multiple indicators exist	86 – 100
Very Strong (tier 2): significant amount of operational evidence from a single indicator exists	71 – 86
Strong: reasonable amount of operational evidence exists	57 – 71
Medium: some operational evidence exists	43 – 57
Weak: little operational evidence exists	29 – 43
Very Weak: very little operational evidence exists	14 – 29
None: no operational evidence exists	0 – 14

7.2.2 Relationship between theoretical evidence and operational evidence

The relationship between theoretical and operational evidence was determined by computing the simple difference between the strength of the theoretical evidence and strength of the operational evidence.

The similarity between the theoretical and operational evidence was deemed *excellent* if computed difference was 0 to 10; *Good* if 10 to 20; *Acceptable* if 20 to 30; and *Weak* if > 30. The "computed difference" was based on the argument that numerical distance between strength of the theoretical and operational evidence is a simple indicator of their similarity or contrast. The lower values of "computed difference" mean high similarity in strength between the theoretical and operational evidence and conversely the higher values of the "computed difference" indicate low similarity in strength between the theoretical and operational evidence.

7.2.3 Relationship between theoretical evidence, operational evidence, and expert opinion

The sum of respondent comments on the questions mapped against each transformation trigger was considered as the primary indicator of respondents' level of interest on a transformation rigger and hence it's perceived importance. This is based on this researcher's observation during cognitive interview sessions of the pilot study where respondents focused more on topics that were directly related to their respective area of expertise or topics that they had a particular interest and hence tended to provide more commentary on those topics. This survey variable was therefore used in determining strength of correlation between the expert opinion and the corresponding theoretical and operational

evidence. The correlation between the transformation triggers and the main survey questions was determined as follows:

The main survey questions that addressed topics related to a transformation trigger was mapped to that trigger (Table 7.4). For each transformation trigger the strength of the expert opinion was determined by computing the sum of the respondent comments to mapped questions. For each transformation trigger the ranking and strength of the theoretical evidence, the strength of the operational evidence, and the strength of the expert opinion were tabulated in Table 7.3 and 7.4. The correlation between the expert opinion strength and each of the other columns within Table 7.4 was computed using Equation 7.1. In this case, correlation (Table 7.3) rather than covariance was used because the measurement scale for the variables is in different units. Correlation between theoretical evidence (Transformation Triggers) and the expert opinion was computed using CORREL (Equation 7.1), which is Microsoft Excel functionality (Microsoft Corporation, 2012).

CORREL ([expert opinion strength] $^{1 \text{ to } T}$, [X] $^{1 \text{ to } T}$) ...*Equation 7.1*

Where T is the number of transformation triggers = 14 and X = Column 3 or 4 in Table 7.4, representing “theoretical evidence strength” and “operational evidence strength” respectively.

7.2.4 Relationship between quality risks and regulatory compliance

The relationship between the transformation-induced quality risks and the regulatory compliance outcomes for the main survey was determined by computing their covariance. Individual mean of main survey questions for the transformation-induced quality risks (independent variables) were calculated (Table 7.6). Individual mean of survey questions for the regulatory compliance outcomes (dependent variables: i.e. pre-market evaluation, marketing approval, and post-market surveillance) were calculated (Table 7.6). Covariance between the independent and dependent variables was computed using Equation 7.2. Covariance between independent and dependent variables was computed using COVAR (Equation 7.2), which is Microsoft Excel functionality (Microsoft Corporation, 2012).

COVAR ((([Quality Risks] $^{1 \text{ to } I}$, [Y] $^{1 \text{ to } D}$) ...*Equation 7.2*

Where I and D are the number of main survey questions relating to independent and dependent variables = 4 and Y = Column 4 or 5 or 6 in Table 7.6, representing “pre-market evaluation” or “marketing approval” or “post-market surveillance” respectively.

7.2.5 Method for identifying other research similar to this PhD research

This section describes the method used to identify other research similar to the work presented in this thesis. The search method focused on identifying articles that dealt with topics related to “Industry Transformation” and “Quality Risk Management/Model” in the context of the pharmaceutical industry. These topics were used to perform the article search within the search timeframe of 2000 to 2013. The article search databases used included JSTOR, Cambridge Journals, Emerald, IngentaConnect, Nature, Science Direct, Taylor & Francis, Oxford Journals, and Google Scholar. The “Industry Transformation” and “Quality Risk Management/Model” were used as search phrases in the title of the articles. The search was performed in February 2013. Article relating to service industry and non-profit or governmental organisations were excluded. The intent was to find research articles targeting industries that have some similarity to the pharmaceutical industry, especially those with substantive R&D operation. Articles that generally covered topics of interest from a theory or practice point of view were considered as “relevant” and were considered. Articles that were written in the context of the pharmaceutical industry were considered as “directly relevant”.

The article search method for the “Quality Management” topic is described in Section 1.3.5.

7.3 RESULTS

The results presented in this section are intended to provide insight into the relationships between the theoretical, operational and opinion based evidence presented in previous chapters. This covers two key aspects, i) Relationship between the *Theoretical*, *Operational* and *Survey* evidence, and ii) Relationship between *Independent* and *Dependant* variables - the grouping of these relationships constitutes the quality risk model in the context of pharmaceutical transformation, which is presented in Section 7.3.3.

7.3.1 Relationship between theoretical and operational evidence

The relationship between the theoretical and operational evidence was established by a simple comparison of the strength of the theoretical evidence and strength of the operational evidence. The results of this comparison are tabulated in Table 7.3. The importance ranking of theoretical evidence is captured in Column 2 and the corresponding strength values are captured in

Column 3. The observed strength of the operational evidence is captured in Column 4. The outcome of the "computed difference" between strengths of the theoretical and operational evidence indicating degree of their similarity is captured in Column 5.

Table 7.3 Relationship between theoretical and operational evidence relating to verification of transformation triggers

Transformation Trigger	Importance Ranking of Theoretical Evidence (Chapter 3)	**Strength of Theoretical Evidence (importance ranking)	**Strength of Operational Evidence (based on Fig. 4.1 to 4.12)	***Computed Difference (Theoretical & Operational)
1 Healthcare Management Focused	7	55	90	35
2 Fully Integrated Pharma Network*	3	80	80	0
3 Personalised Medicine*	1	100	100	0
4 Virtual R&D	12	20	45	25
5 Translational Research*	4	70	60	10
6 Adaptive Trials	13	10	50	40
7 Regulatory Harmonization	9	45	50	5
8 Science & Risk Based Regulations	6	60	55	5
9 Progressive/Live Licensing	11	30	0	30
10 Regulatory Enforcement	14	0	55	55
11 Biotechnology	8	50	60	10
12 Nanomedicine	10	35	50	15
13 Bioinformatics	5	65	65	0
14 Pervasive/Could Computing*	2	90	70	20

*Transformation triggers 2, 3, 5, and 14 with strong theoretical and operational evidence
**Strength scale: Very Strong$_1$ = 86-100; Very Strong$_2$ = 71-86; Strong = 57-71; Medium = 43-57; Weak = 29-43; Very Weak = 14-29, 30, None = 0-14 (see Section 7.2.1)
***Strength of theoretical evidence minus the operation evidence: Excellent 0 to 10; Good 10 to 20; Acceptable 20 to 30; Weak > 30 (see Section 7.2.2)

7.3.2 Relational data for the quality risk model

The relationship between the transformation triggers and the expert opinion were established by determining the correlation between the sum of respondent comments for the mapped survey questions and each of i) the transformation trigger ranks and ii) the strength of operational evidence. The results are listed in Table 7.4 and Table 7.5. Column 2 identifies the main survey questions that are mapped into a given transformation trigger. Columns 3, 4, and 5 contain the strength of theoretical evidence, operational evidence and expert opinion respectively. The strength of expert opinion is represented by the sum of respondent comments to mapped questions. Note that the strength values are in different units and hence Correlation and not Covariance was used to determine their relationship.

Table 7.4 Correlation between transformation trigger ranking, operational evidence and the main survey

Pharmaceutical Transformation Triggers	Transformation trigger and survey question mapping	Theoretical evidence strength (importance ranking)*	Operational evidence strength*	Sum of respondent comments*
1 - Healthcare Management Focused	8,22	6	90	7
2 - Fully Integrated Pharma Network	8, 9,10,18	3	80	9
3 - Personalised Medicine	8,9,10,11,13, 22,24	1	100	19
4 - Virtual R&D	8	11	45	3
5 - Translational Research	8,17	4	60	6
6 - Adaptive/In-life Trials		12	50	0
7 - Global Harmonization	7,17	9	50	5
8 - Science & Risk Based Regs.	15,16,17	7	55	8
9 - Live Licensing		13	0	0
10 - Enforcement	17	14	55	3
11 - Biotechnology	8,13,24	8	60	7
12 - Nanomedicine		10	50	0
13 - Bioinformatics		5	65	0
14 - Pervasive/Cloud Computing	8,9,12,14, 29	2	70	10

* Results from Chapters 3, 4 and 6

The result of the Correlation computation between the expert opinion and the theoretical and operational evidence is provided in Table 7.5.

Table 7.5 Correlation between theoretical and operational transformation evidence and the main survey variables

	Expert Opinion (sum of respondent comments for mapped questions)
Theoretical Evidence transformation trigger ranks (Table 7.4)	α = 0.7584
Operational Evidence operational evidence strength (Table 7.4)	α = 0.7182

The fundamental backbone of the quality risk model is determining the relationship between transformation-induced quality risks (independent variables) and the corresponding regulatory compliance outcomes (dependent variables). This was accomplished by computing the covariance between the respective means of the transformation-induced quality risks and the regulatory compliance outcomes (Table 7.6). This was performed by finding the covariance between the mean of the main survey questions that constitute the independent variables and mean of the main survey questions that comprise the dependent variables. Three correlation coefficients one for each of the dependent variables were computed and the results captured in Table 7.6.

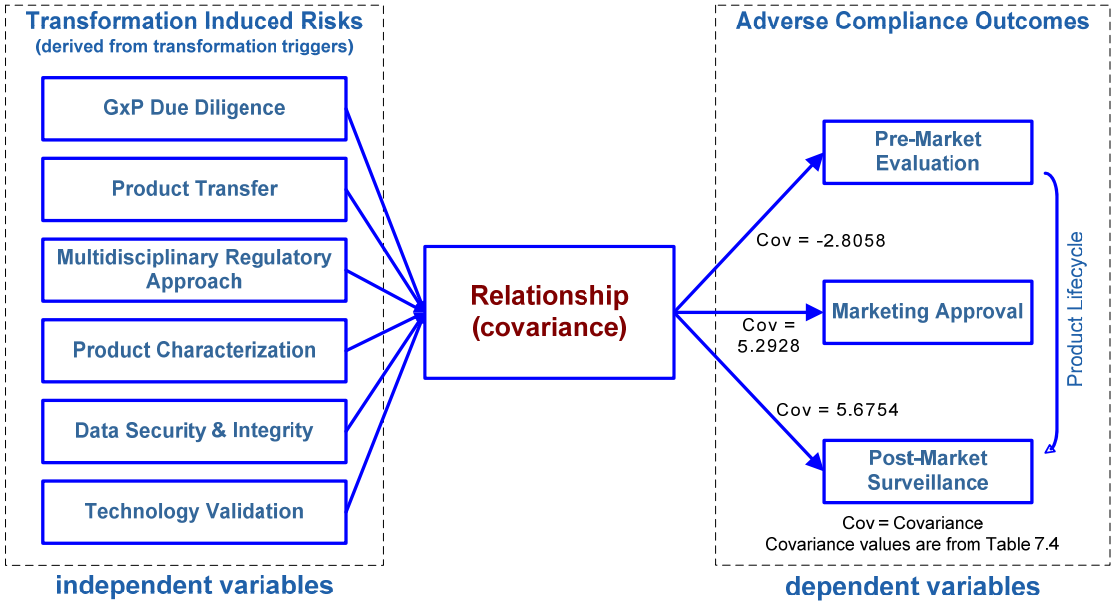
Table 7.6 Quality Risk Model - covariance between transformation-induced quality risks and compliance outcomes of the main survey

Independent Variables		Dependent Variables			
Quality Risk Questions	Quality Risk mean	Compliance Outcome Questions	Pre-market Evaluation mean	Marketing Approval mean	Post-market Surveillance mean
Q18	69.32	Q19	15.15	33.33	48.48
Q20	67.42	Q21	6.06	30.30	54.55
Q22	68.94	Q23	6.06	36.36	48.48
Q25	75.00	Q26	18.18	33.33	45.45
Q27	56.82	Q28	18.18	30.30	48.48
Q29	57.20	Q30	12.12	33.33	42.42
Covariance between independent & dependent variables			-2.8058	5.2928	5.6754

7.3.3 Development of the pharmaceutical quality risk model

Figure 7.1 is the conceptual depiction of the quality risk model showing the relationship between quality *Risks* and regulatory compliance *Outcomes* in terms of their covariance. The risk assessment was focused on assessing the likelihood of adverse compliance outcomes during product lifecycle due to the transformation induced risks if they are not properly integrated with and managed as part of the quality management system.

Figure 7.1 Conceptual depiction of the pharmaceutical transformation quality risk model



The covariance between transformation-induced quality risks and the corresponding regulatory compliance outcomes was computed and found to be negative for the pre-market evaluation and positive for the marketing approval and post-market surveillance phases of the product lifecycle (Table 7.6). The quality risk model indicates a firm relationship between the pharmaceutical

quality risks (independent variables) and regulatory compliance outcomes (dependent variables) during the marketing approval and post-marketing phases of the product lifecycle and a weaker relationship during the pre-market evaluation phase. This model can be used by the industry practitioners to develop appropriate risk mitigation strategies in product lifecycle activities that are impacted by the four main transformation triggers and the associated transformation-induced quality risks.

7.4 GENERAL DISCUSSION

The intent of the general discussion is to address the research questions that were asked in Chapter 1 and to provide a commentary on similar work that exists within and outside the pharmaceutical industry. The strength of relationship between the theoretical and operational evidence is also discussed.

7.4.1 Relationship between theoretical and operational evidence

The computed difference between strengths of theoretical and operational evidence, presented in Table 7.3, suggest an “excellent” correlation with respect to Trigger 2 (Fully Integrated Pharma Network), Trigger 3 (Personalised Medicine), Trigger 5 (Translational Research), Trigger 7 (Regulatory Harmonisation), Trigger 8 (Science and Risk Based Regulation), Trigger 11 (Biotechnology), and Trigger 13 (Bioinformatics). This means that there is a strong agreement between the theoretical and operational evidence for these triggers. However the areas of strong contrast where the computed difference is “weak” are Trigger 1 (Healthcare Management Focused), Trigger 6 (Adaptive Clinical Trials), Trigger 9 (Progressive/Live Licensing), and Trigger 10 (Regulatory Enforcement). The areas of moderate similarity between the theoretical and operation evidence, where the computed difference is “good/acceptable” include Trigger 12 (Nanomedicine), 14 (Pervasive/Cloud Computing), and Trigger 4 (Virtual R&D). See Section 8.1 for further commentary and conclusion.

The results of the “computed difference” provided in Table 7.3 are dependant on researcher’s interpretation of trends in Figures 4.1 to 4.12. Although these trends are based on solid operational data, however assignment of strength values to those trends is based on researcher’s visual observations. An area of improvement would be to improve the accuracy of the strength values assigned to the operational evidence. This can be done by requiring multiple researchers to perform the same visual observations and averaging results of strength values they assign to each observation.

7.4.2 Addressing research questions

The specific findings of this research study are discussed in detail in each Chapter. This section will synthesise these findings into unified form in order to answer the research study's three main questions:

Question 1: What are the key triggers impacting pharmaceutical transformation? The theoretical evidence established in Chapter 3 identified fourteen triggers influencing the ongoing pharmaceutical transformation. Four of these triggers: fully integrated Pharma network, personalised medicine, translational research, and pervasive computing were considered the most impactful on drug product lifecycle. The importance of the four triggers was further supported by the operational evidence established in Chapter 4.

Question 2: What will be the impact on regulatory science especially with respect to quality risk management? The impact on regulatory science was determined from the perspective of pharmaceutical quality. The opinion of expert practitioners in the field (Chapfer 6) confirmed the theoretical proposal that GxP due diligence, drug product transfer, product characterisation, multidisciplinary regulatory skills/knowledge, and data security/integrity - related to products and patients - are the main areas of quality risk that should be managed in practice within the framework of the pharmaceutical quality.

Question 3: What is a plausible model for pharmaceutical quality risk suitable for the transformed environment? The quality risk model (Section 7.3.3) was defined based on the data collected from the expert opinion study. The analysis of this data indicates that there is firm relationship between the proposed pharmaceutical quality risks and the compliance outcomes that take place during the marketing approval and post-market surveillance phases of the product lifecycle. The quality risk model indicates that the relationship between pharmaceutical quality risks and the compliance outcomes during pre-market evaluation (i.e. research and development) phase of the product lifecycle is significantly weaker. Although in practice the regulatory compliance issues are prominent in the marketing approval and post-marketing phases of the drug product lifecycle than the pre-market evaluation phase, based on Author's industrial experience, the compliance outcomes in the pre-marketing phase also exist. One explanation for the mismatch between this research finding and the operational experience is that the profile of the respondents in the main survey (Section 6.3.1) from a product lifecycle expertise standpoint included fewer experts with clinical and medical background, which would be necessary to accurately estimate the impact of the quality risks in the pre-market evaluation phase of the product lifecycle. From a product lifecycle expertise standpoint most of the respondents (55.4%) had a commercial manufacturing background and lesser percentage (8.9%) had clinical and medical background.

7.4.3 Comparison of this PhD research with similar work in the literature

In order to compare this PhD research with similar work in a wider context, the following three perspectives are discussed with respect to their treatment inside and outside the pharmaceutical industry.

i) General approaches to quality management
ii) Industry transformation
iii) Management of quality risks induced by industry transformation

The intent is to enrich the discourse by exploring main features/themes of other similar research and discuss how they relate to what has been presented in this thesis. Since the work in this thesis is essentially centred on the three key concepts of quality management, industry transformation and risk management, the comparative discussion below is aligned accordingly.

The examination of the literature presented below confirms that this PhD research is an original body of work that has not been performed before. Although there are areas of similarity between the literature and this research, however neither of the articles selected for comparison focused on quality risks induced by pharmaceutical industry transformation.

7.4.3.1 General approaches to quality management

In introducing this PhD research in Chapter 1 the study of quality management topic was explored in the literature and it was found that of the 38 most cited quality management articles (Section 1.3.5) published between 1989 and 2009 only two articles studied pharmaceutical industry (Rowley & Sneyd, 1996; Ahmad et al., 2009). The main themes in the 38 articles relate to theory and practice of Quality Management (Badri et al. 1995; Das et al. 2000; Dow et al. 1991; Flynn et al. 1994; Saraph et al. 1989; Zu et al. 2008), theory and practice of Total Quality Management (Bou-Llusar et al. 2009; Kaynak 2003; Samson & Terziovski 1999; Ahire et al. 1996; Antony et al. 2002; Black & Porter 1996; Choi & Eboch 1998; Cua et al. 2001; Douglas & Judge 2001; Forza & Flippini 1998; Grandzol & Gershon 1998; Ho et al. 2001; Joseph et al. 1999; Martinez-Lorente et al. 2000; Powell 1995; Tamimi 1998), and their study in some specialised situations such as quality awards, Deming method, role of top management, quality performance, continuous improvement, service quality, etc. (Curkovic et al. 2000; Ahire & Dreyfus 2000; Ahire & O'Shaughnessy 1998; Ahmad et al. 2009; Anderson et al. 1995; Kaye & Anderson 1999; Kontoghiorghes 2004; Lai 2003; Lau et al. 2004; Miyagawa & Yoshida 2005; Prajogo & Sohal 2003; Rowley & Sneyd 1996; Rungtusanatham et al. 1998; Sanchez- Rodriguez 2004; Sun 2000; Tan 2001).

Two of the specialised studies were set in the pharmaceutical industry, The first (Ahmad et al. 2009) conducted a narrow research studying service quality in pharmaceutical supply chain within Pakistan. They focused on measuring reliability of service quality within the pharmaceutical supply chain and did not address any new or emerging risks relating to regulatory science. Therefore no meaningful comparisons can be made between their study and this PhD research. The second study (Rowley & Sneyd 1996) on the other hand describes a questionnaire-based survey of the UK pharmaceutical industry, which investigated the implementation of total quality in research-based environments. They concluded that two central issues that may merit further investigation are the relationship between total quality and the research culture and the measurement of quality in R&D. This conclusion is compatible with the proposal in Section 8.3 of this thesis that additional research is needed to better characterise the transformation-induced quality risks within the pre-market evaluation (i.e. R&D) phase of the product lifecycle.

7.4.3.2 Industry transformation

The literature search for "Industry Transformation" revealed 180 articles of which 12 were deemed relevant and four were directly relevant to the pharmaceutical or healthcare industry. Of the four articles Ramaprasad & Johnson (2000) focused on use of e-technologies to fundamentally transform physician office visit impacting the operations within the *office* (the way appointments, patient records, and billing is handled), the nature of the *visit* (preparation for, interaction, and follow-up with the patient), and the *physician* (the concept of virtual physician – reducing barriers to getting second or multiple opinions via physician collaboration using online communication technology). The finding of this article is compatible with the findings of this PhD research in relation to pervasive computing and its importance to patient healthcare from the perspective of drug delivery and prescription compliance in an investigational or commercial-use setting. See Section 8.3 for recommendation for future research that could further enrich this field.

Arora et al. (2009) on the other hand focused on industry transformation in the context of Indian patent reform and its impact on R&D investment and innovation within the pharmaceutical industry. They observed that the patterns in data collected from 315 Indian drug procedures are consistent with the idea that at least some Indian firms have shifted to a more R&D-intensive business models in the wake of patent reform. They did not address industry transformation relating to regulatory science and hence there is no tangible similarity between work done by Arora et al. and this PhD research. Therefore no meaningful comparisons can be made between the two bodies of work.

Ugalde et al. (2009) analyzed the case of Merck pharmaceuticals and shows that this firm, considered during many decades to be the most innovative, highly scientific and profitable, has in the last years transformed itself into a commercial enterprise. The authors argue that firm's main objective is to increase the sales of drugs regardless of their therapeutic value. They point out that discovery of true innovative drugs that add new therapeutic value has decreased notably in recent years. The Authors present data indicating that Merck's case is not unique and that innovative pharmaceutical industry, known as "Big Pharma", has followed the same trend. There is no substantive similarity between work of Ugalde et al. and this PhD research except for Big Pharma diversification – which is due to an increase in pharmaceutical revenues from products or services other than from the traditionally strong prescription drug sales.

The research conducted by Lee (2012) in agricultural biotechnology, although not in a pharmaceutical setting, is relevant and close enough in approach to explore. The study used Delphi method to integrate views of experts from industry and academia regarding future direction of agricultural biotechnology in Taiwan in order to extract the critical success factors influencing industry transformation. The author treats transformation as two types i) *non-cross-domain* type in which "enterprises concentrate on the development of their existing product, but change the activities of production technology, marketing direction, market transformation, and the horizontal or vertical integration" and ii) *cross-domain* type in which "enterprises give up their original products and operate in the existing or new business areas; at the same time, they invest in or operate products of the new business area to decrease the operational risk". The study divides the critical parameters influencing the industry transformation into "primary activities" (product lifecycle activities) and "support activities" (enabling processes) and uses Fuzzy Delphi to assign importance level to each of the critical parameters.

Areas of similarity between the study conducted by Lee and this PhD research include:

- Use of literature review to determine factors influencing industry transformation
- Use of questionnaire based survey to elicit expert opinion
- Ranking of critical factors influencing the industry transformation
- Industry diversification – Author's description of cross-domain transformation approach is consistent with the concept of pharmaceutical industry diversification exemplified by Trigger 1 (Healthcare Management Focused) in Chapter 3 and 4.

Areas of contrast include:

- Agriculture biotechnology industry versus pharmaceutical industry
- Transformation from a supply chain perspective versus transformation from a science and quality risk management perspective
- Use of operational data as an intermediate control to back-up literature findings versus moving directly from literature findings to expert opinion elicitation

The main themes of the other relevant articles on industry transformation were management science centric with the following focus:

- The role of information technology in enabling or impeding industry transformation (Howard et al. 2001; Hanley 2003; Mortehan 2004; King and Lyytinen 2004, Pussep et al. 2012)
- The role of technological change in triggering industry transformation in automotive industry (Struben 2008; Bouza et al. 2009)
- The role of alliances, strategic partnerships and virtual organisations in industry transformation (Elliot 2006; Gersch et al. 2006; Karvonen 2008; Goeke et al. 2010)
- Industry transformation to lean enterprise model (Hallam 2003)

7.4.3.3 Quality Risk Management

The search resulted in 138 articles of which nine were directly relevant to quality risk management. None of the other articles was compatible with scope of this PhD research and they mainly focused on the operational process for how to conduct risk management, specialised tools used to perform risk assessment, and the theory and practice of quality by design.

The general theme of quality risk management topics that these articles covered were as follows:

- Application of Quality Risk Management in pharmaceutical industry. Mainly focusing on risk management practices and application of ICH Q9. (Claycamp, 2007; Ahmed et al., 2008; Hajela and Ali, 2011; Charoo and Ali, 2012; Vartak, 2012).
- The procedural aspect of how to implement a quality management system focusing on the key aspects such as risk identification, risk assessment, risk control and risk communication (BR, 2007; Claycamp, 2007; Charoo and Ali, 2012).
- Various tools used to conduct risk assessment (Dimeny and Popescu, 2006; Claycamp, 2007; Dahiya et al., 2009; Xu et al., 2010)

- Quality by design - focusing on full understanding of how product attributes and associated process relate to product performance (too numerous to list – 180 articles and books)

CHAPTER 8: *Conclusions and Recommendations for Future Research*

The aim of this Chapter is to synthesise the conclusions discussed in earlier chapters into a unified whole highlighting new knowledge that inform policy, practice and future research.

8.1 CONCLUSIONS

The regulatory environment described in Chapter 2 confirmed that regulatory science (of which pharmaceutical quality is a branch) has a substantial impact on drug product lifecycle with respect to innovation and productivity. Public health protection, public health promotion, crisis management, harmonisation, fostering innovation, and modernisation were identified as key topics defining mission of the regulatory authorities. Provision of science-based regulatory controls to ensure the safety and efficacy of pharmaceutical products were considered an important instrument in managing risk. From the perspective of science-based regulatory controls the regulatory actions to date indicate a move towards public health promotion, modernization and fostering innovation. Although this trend in regulatory thinking is likely to continue in the future it is also reasonable to posit that the industry transformation (those discussed in Chapter 3) will pose new regulatory challenges that require mitigation strategies to manage risks. Some of these challenges are identified as future research in Section 8.3.

In Chapter 3 pharmaceutical transformation was defined as the process by which the pharmaceutical industry intends to achieve and maintain advantage through changes in operational concepts, regulatory science, and technologies that will significantly improve its capability to innovate. Open innovation was identified as an important element of the transformation and was defined as leveraging external sources of innovation by collaborating with small biotechnology companies, universities, research partnerships, etc. The outcome of the systematic review of the literature, which is also referred to in thesis as “theoretical evidence” identified fourteen triggers impacting the ongoing transformation in the pharmaceutical industry. The importance-ranking of these triggers revealed that of the fourteen transformation triggers four, namely Fully Integrated Pharma Network, Personalised Medicine, Translational Research and Pervasive Computing are considered as the most impactful.

The assessment of the identified pharmaceutical triggers from an open innovation perspective suggested that the trends listed below will likely increase in the pharmaceutical industry and will have an impact on pharmaceutical quality from a risk management perspective.

- External research, commercial partnerships and in-licensing of products
- Research and Development on combination, biological and biotechnology products
- Smart implantable devices for product tracking, patient monitoring, drug delivery
- Outsourcing of information systems for management of clinical and product data (e.g. for clinical trials, drug safety surveillance, customer complaints, etc.)

The impact on pharmaceutical quality was further explored from a risk perspective and the following quality risk areas were proposed.

- GxP due diligence of external research/commercial partners
- Product transfer processes
- Multidisciplinary regulatory knowledge and skills
- Product characterisation
- Data security and integrity
- Technology validation to ensure fitness for intended use

The theoretical evidence relating to the transformation triggers were supported by the operational evidence and the proposed quality risks were examined during the expert opinion survey.

In order to confirm the existence or absence of theoretical evidence, operational evidence in Chapter 4 was established based on practical application of the transformation triggers. The trends in operational evidence and the associated theoretical evidence were compared to identify areas of similarity and contrast. In general there is a good correlation between the theoretical evidence derived from the literature review and the corresponding operational evidence. The strength of the operational evidence supports the literature findings that *Triggers 2 (fully integrated Pharma network), 3 (personalised medicine), 5 (translational research)* and *14 (pervasive computing)* are important drivers of pharmaceutical industry transformation (Table 7.3) and hence were used to determine their impact on pharmaceutical quality. Key areas of contrast however are *Trigger 1 (healthcare management focused), Trigger 6 (adaptive/in-life trials), and Trigger 10 (enforcement)* for which the operational evidence is stronger than the theoretical evidence (Table 7.3). A general explanation for this contrast could be attributed to the fact that there is a paucity of academic research in the field of pharmaceutical quality (see Section 7.4). This is particularly true for Trigger 10 and to a lesser extent to Trigger 1. The explanation for Trigger 6 is more nuanced and could be linked to the originator of the adaptive trial concept (i.e. led by industry hence lag in academic work).

Having established the theoretical evidence and the supporting operational evidence for the transformation triggers it was necessary to examine them from a reality-on-the-field perspective using an expert opinion survey described in Chapter 6. The survey results support the theoretical and operational evidence on the four main pharmaceutical transformation triggers. The correlation between strength of the opinion-based variable (i.e. survey respondent comments for the mapped questions) and strength of the evidence-based variables (i.e. theoretical and operational evidence) were computed and found to be within the acceptable range (Table 7.4, 7.5). This indicates that the expert opinion survey validate importance ranking of the transformation triggers.

As demonstrated in this thesis the pharmaceutical industry transformation is changing the way the drug products are developed, approved, manufactured and used. The traditional approaches to regulatory science will face challenges. The pharmaceutical industry should ensure that the pharmaceutical quality evolves/transforms in parallel with other aspects of the ongoing transformation focusing their attention more on science and risk based approaches to quality.

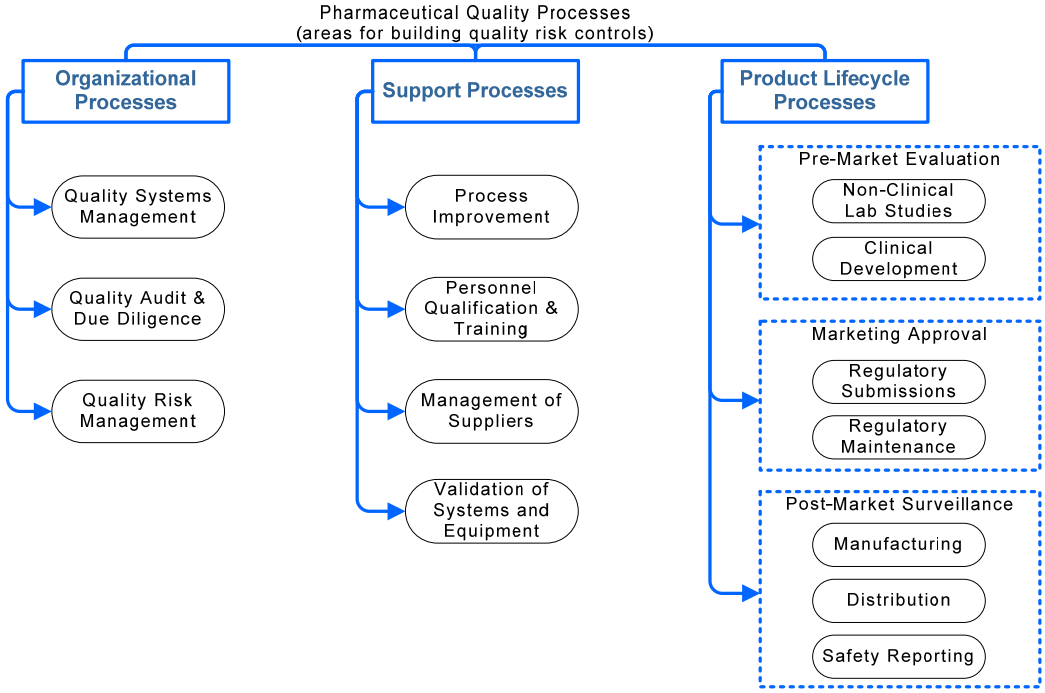
8.1.1 Policy and practice implications

As discussed in Chapter 1 and 2, in the pharmaceutical industry quality risks are expected to be managed within a quality risk management framework as recommended by ICH Q9 (2005) guidance. This global regulatory guidance defines the framework as “an effective quality risk management approach that can further ensure the high quality of the medicinal products to the patient by providing a proactive means to identify and control potential quality issues during development, manufacturing and post marketing use”. Another ICH guidance discussed in Chapter 1 and 2 was ICH Q10 (2007), which defines a model for a pharmaceutical quality system that can be used throughout the different stages of a product lifecycle and can provide an effective framework to implement quality risk management. This guidance describes pharmaceutical processes that govern management responsibility *(organization)*, continual improvement of the pharmaceutical quality systems *(support)*, and continual improvement of process performance and product quality *(product lifecycle).*

The findings of this research study would be a valuable input to implementation of the ICH quality risk management framework stated above. From a practical standpoint the mitigation strategies for the management of the quality risks should be built into the pharmaceutical processes that govern *organization*, *support*, and *product lifecycle* activities (conceptually illustrated in Figure 8.1 based on ICH Q10). The important *organisation* related processes that should be considered are the quality systems management, quality audit, and quality risk management processes. These processes are overarching in scope and will

cover all the proposed areas of quality risk. The *support* processes typically deal with transverse topics that apply across the product lifecycle. Activities that should be considered for this category include product and process improvement, personnel qualification and training, management of suppliers and subcontractors, and validation of systems/equipment to ensure fitness for intended use. The *product lifecycle* processes that govern post-marketing activities (i.e. manufacturing, distribution, and surveillance of commercial drug products), marketing approval activities (i.e. regulatory submission and maintenance), and pre-marketing activities (i.e. non-clinical laboratory studies and clinical development) should be considered. Application of the quality risk model described here would mean that the priority for implementation of risk mitigation controls should be given to the post-marketing and product approval activities that are significantly impacted by the proposed quality risks related to i) external partner due diligence and oversight, ii) product transfer, iii) characterization of biological/biotechnology products, and iv) outsourcing of GxP data management.

Figure 8.1 Pharmaceutical quality processes where quality risk controls should be built



8.2 RESEARCH LIMITATIONS

A key limitation of this research was lack of similar peer reviewed research for comparison purposes. This is a unique study and the researcher at the time of conducting this research did not find any published research with similar coverage. Another limitation was paucity of regulatory data in public domain. To the extent possible both US FDA and EMA databases were consulted for regulatory evidence. However in some cases (e.g. regulatory enforcement) due

to freedom of information act the only publicly available data was found in the US FDA databases. Regardless of country of origin since the US FDA has an extensive regulatory network and global oversight on drug products marketed in the US this limitation did not negatively impact the validity of the results.

8.3 RECOMMENDATIONS FOR FUTURE RESEARCH

The scale of this research study is large and there are many interesting areas for future research, some examples include:

A dedicated expert opinion survey focusing on pre-market evaluation phase is needed in order to more accurately characterise the relationship between the proposed quality risks and the regulatory compliance outcomes for this phase of the product lifecycle.

Section 8.1.1 discussed some areas within the product lifecycle that requires most attention from a science and risk based approaches to quality management. Assessment of how closely the proposed model (Figure 8.1) is applied across the pharmaceutical industry would be a good indicator if science and risk based approaches are being built into the quality risk management framework.

The pharmaceutical quality as a subset of regulatory science has a potential to significantly impact productivity in industry and as such science and risk based approaches to pharmaceutical quality should be encouraged through more academic research. As demonstrated in Chapter 1 the paucity of the academic research and peer reviewed papers on this topic is palpable.

Future research in the specialised branch of pharmaceutical quality is also needed, some examples include:

- Challenges posed by progressive/live licensing model of product approval to pharmaceutical quality.
- Impact of science and risk based approach to pharmaceutical quality on depth and frequency of regulatory inspections.
- Regulatory compliance in patients' home - use of smart drug delivery and monitoring systems – implications for the regulators and the pharmaceutical industry.
- Real time product release – move from traditional analytical chemistry (Quality Control concept) to real time product release using online smart analytical devices.
- Impact of embedding smart devices in primary product packaging on improving patient compliance. In clinical trials or during routine use efficacy of certain drug products is directly related to strict adherence to prescribed frequency of drug intake. Ensuring patient compliance is difficult and

building intelligence in primary packaging of the drug product may help. The aim of this proposed research is to investigate the effectiveness of such solutions

- Impact of embedding smart devices in primary product packaging on managing risks associated with counterfeiting.
- Regulatory compliance and intellectual property implication of cloud computing when applied to pre-clinical, clinical, safety reporting, and manufacturing data.
- Impact of the application of pervasive computing in GxP environments and characteristics of validation methodology needed to ensure fitness for intended use.

Postscript

When I started this research, I was confronted with a subject that was vast in scope and multidisciplinary in nature. At times, it seemed impossible to imagine building a path through the maze of topics connecting the beginning to the end. From today's vantage point I clearly see a shortcut, a straight line connecting then and now. But I guess this is the purpose of the PhD journey, during which my knowledge and learning behaviour has evolved in the following two key areas.

The first area was the application of the scientific method. As an industry practitioner one tends to be minimalistic when it comes to written communication and tend to rely on experience, instinct, some data, and often assumptions to formulate and test hypothesis. This PhD research has undone my 20 years of industrial approach to problem solving and enabled me to learn how to effectively apply rigorous methods to a scientific inquiry.

The second area was the progression of my thinking overtime on the ongoing pharmaceutical transformation and its impact on pharmaceutical quality. There were topics for which I had firm opinions and the research either confirmed or disproved my thinking (e.g. industry diversification, virtual R&D, personalised medicine, regulatory harmonisation, and regulatory enforcement). For some topics my thinking was not fully developed and the research findings improved my knowledge base (e.g. nanotechnology, bioinformatics and pervasive computing). Other topics such as translational research, live licensing and adaptive clinical trials were new knowledge for which I did not have any prior point of reference.

So how has this new knowledge been implemented in practice? The following are some of the programs that I have initiated or contributed to in the context of Sanofi. In some cases this involved establishment of working groups to explore the topics and propose practical solutions.

- Directives and guidelines on quality risk management
- Due-diligence practices relating to external partners
- Risk rating methodology for compliance ranking of manufacturing sites
- Risk rating methodology for compliance ranking of GxP data management systems
- Control measures for quality risks associated with pervasive and cloud computing
- Recruitment of quality experts with multidisciplinary regulatory knowledge (drugs, biologics, devices, etc.)
- Presentations to various R&D and manufacturing teams

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APPENDIX A: Raw Data for Operational Evidence

A1: Healthcare Management Focused
A2: Fully Integrated Pharma Network
A3: Personalised Medicine
A4: Virtual R&D
A5: Translational Research
A6: Adaptive Clinical Trials
A7: Regulatory Harmonisation
A8: Science and Risk Based Approach
A9: Progressive/Live Licensing
A10: Regulatory Enforcement
A11: Biotechnology
A12: Nanomedicine
A13: Bioinformatics
A14: Pervasive/Cloud Computing
A15: Ranking of Transformation Triggers

A1: HEALTHCARE MANAGEMENT FOCUSED

YEAR	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
ABT														
Rx Profits	7,614	8,962	11,719	13,990	12,756	14,632	16,708	16,486	20,087	20,603	21,124	21,646	21,202	20,365
Non-Rx Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other Profits	7,666	8,318	7,961	8,348	9,720	11,282	12,820	14,279	15,678	16,385	16,960	17,310	17,642	17,939
AZN														
Rx Profits	17,343	18,318	20,866	23,303	25,741	28,713	30,677	31,905	33,310	34,212	33,029	33,180	32,860	32,929
Non-Rx Profits	498	531	560	647	734	846	924	899	952	984	1,019	1,054	1,092	1,132
Other Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BAY														
Rx Profits	6,631	6,600	5,509	5,657	9,432	12,475	13,048	13,308	13,546	13,768	14,156	14,841	15,906	16,752
Non-Rx Profits	6,405	5,739	5,699	7,458	6,875	8,120	8,382	8,930	9,053	9,181	9,333	9,486	9,646	9,807
Other Profits	27,243	27,396	21,170	24,973	23,968	24,450	24,356	21,114	22,118	22,849	23,605	24,405	24,996	25,604
BMY														
Rx Profits	12,069	14,126	14,712	14,303	12,948	14,593	16,675	17,902	18,942	19,546	16,633	14,553	14,617	13,575
Non-Rx Profits	743	799	853	951	913	1,029	1,041	906	807	767	728	697	666	648
Other Profits	5,294	5,969	3,816	3,351	3,395	3,726	2,882	0	0	0	0	0	0	0
DAI														
Rx Profits	3,703	3,834	3,426	6,754	8,663	8,247	8,458	9,672	10,527	10,856	12,075	11,862	12,741	12,752
Non-Rx Profits	1,040	1,167	1,443	1,361	548	486	504	467	457	453	446	441	437	433
Other Profits	1,347	1,371	1,413	1,780	722	673	37	35	34	34	33	33	33	32
LLY														
Rx Profits	10,055	11,494	12,719	13,386	14,317	17,170	18,806	19,940	21,031	21,354	20,080	19,715	18,138	18,488
Non-Rx Profits	693	727	799	864	876	996	1,093	1,207	1,258	1,318	1,382	1,448	1,504	1,548
Other Profits	329	362	340	395	498	468	473	665	693	742	715	783	932	1,018

Appendix A1 Continued

YEAR	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
GILD														
Rx Profits	424	836	1,242	1,809	2,588	3,733	5,085	6,469	7,710	8,667	9,769	10,702	11,079	11,396
Non-Rx Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other Profits	43	31	82	219	438	497	251	542	560	302	286	346	330	343
GSK														
Rx Profits	28,077	28,263	26,680	29,116	31,327	29,899	31,800	37,000	35,218	36,887	37,777	39,166	40,772	41,410
Non-Rx Profits	5,019	4,612	4,503	4,679	4,910	5,544	6,196	7,261	7,569	8,059	8,524	8,965	9,404	9,759
Other Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
JNJ														
Rx Profits	17,275	19,517	22,128	22,322	23,267	24,866	24,567	22,520	22,232	22,014	22,268	23,073	23,724	24,455
Non-Rx Profits	19,023	22,345	25,220	28,192	30,057	36,229	39,180	39,377	41,278	43,370	45,313	46,915	48,422	49,046
Other Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MRK														
Rx Profits	19,637	20,310	21,226	20,093	20,241	22,253	22,049	25,192	40,706	41,109	41,345	40,572	40,489	41,299
Non-Rx Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other Profits	32,153	2,176	1,747	1,919	2,395	1,945	1,802	2,236	5,926	6,044	6,165	6,288	6,337	6,388
NVS														
Rx Profits	15,345	18,926	21,542	24,956	29,491	32,646	35,647	38,455	41,818	45,324	46,771	45,725	47,221	48,922
Non-Rx Profits	5,532	5,938	6,705	6,049	4,902	5,426	5,812	5,812	6,213	6,490	6,727	6,929	7,177	7,379
Other Profits	0	0	154	314	712	875	1,125	836	882	943	1,009	1,080	1,156	1,214
NOVO														
Rx Profits	4,644	4,886	5,422	6,306	7,236	7,813	8,508	9,540	10,376	11,144	12,079	12,831	13,623	14,310
Non-Rx Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PFE														
Rx Profits	28,275	39,425	46,121	44,269	45,083	44,424	44,174	45,448	57,354	55,439	51,651	52,991	52,846	54,136
Non-Rx Profits	3,581	4,547	1,953	2,206	2,311	2,639	2,825	3,449	8,651	9,216	9,771	10,316	10,883	11,469
Other Profits	438	764	914	930	977	1,355	1,297	1,112	1,085	1,020	958	913	870	832

Appendix A1 Continued

YEAR	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
ROG														
Rx Profits	15,936	18,227	19,991	25,126	30,679	33,894	33,136	35,933	36,605	38,928	40,805	42,677	44,362	45,778
Non-Rx Profits	1,454	1,631	0	0	0	0	0	0	0	0	0	0	0	0
Other Profits	9,750	8,910	7,212	7,596	8,060	8,616	8,898	9,265	9,735	10,218	10,696	11,185	11,657	12,040
SNY														
Rx Profits	9,842	10,634	19,650	36,088	37,491	37,067	36,377	38,773	38,552	38,427	37,592	36,735	36,503	36,519
Non-Rx Profits	518	560	2,233	1,899	1,973	1,951	1,968	1,989	2,387	2,627	2,797	2,970	3,112	3,338
Other Profits	0	0	0	1,672	1,552	1,607	1,737	2,007	2,003	2,075	1,401	857	835	838
TEVA														
Rx Profits	2,206	2,754	4,118	4,428	7,428	8,435	10,144	12,821	14,690	14,815	15,429	16,104	15,451	14,574
Non-Rx Profits	313	522	681	822	980	973	941	1,078	1,125	1,175	1,224	1,264	1,299	1,330
Other Profits	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rx Profits	199,075	227,112	257,072	291,907	318,688	340,859	355,858	381,366	422,703	433,092	432,583	436,372	441,532	447,659
Non-Rx Profits	44,819	49,118	50,648	55,128	55,079	64,239	68,866	71,375	79,750	83,642	87,265	90,485	93,642	95,890
Other Profits	84,263	55,297	44,809	51,495	52,439	55,492	55,677	52,091	58,714	60,611	61,829	63,200	64,787	66,248
Div. Profits	129,082	104,415	95,457	106,623	107,518	119,731	124,543	123,466	138,463	144,252	149,094	153,686	158,429	162,139

Div. Profits = Diversified Profits = Non-Rx Profits + Other Profits
Rx = Prescription Drug Products

A2: FULLY INTEGRATED PHARMA NETWORK

There are 2713 lines of raw data which is too large for this appendix. Summary information describing the raw data is provided in table below.

Product Source	>15 years	11 to 15 years	5 to 10 years	<5 years
Acquired product	6	3	10	8
Co-developed	7	8	14	67
In-licensed	38	52	67	115
Internal	149	78	96	133
M&A	126	84	132	168
Other external	5	14	41	59
n/a	0	0	0	0

	Very Old (>15)	Old (11-15)	Recent (5-10)	New (<5)
Internal	149	78	96	133
External	182	161	264	417
External / Internal	1.2	2.1	2.8	3.1
	332	241	363	553

A3: PERSONALISED MEDICINE

Orphan Drug Designation Year	Number of Orphan Drugs Designated by the FDA
1983	0
1984	5
1985	10
1986	11
1987	18
1988	20
1989	30
1990	43
1991	40
1992	27
1993	33
1994	35
1995	33
1996	29
1997	35
1998	45
1999	58

Orphan Drug Designation Year	Number of Orphan Drugs Designated by the FDA
2000	56
2001	62
2002	48
2003	75
2004	95
2005	104
2006	126
2007	107
2008	160
2009	157
2010	188
Total	1650
<2000	472
2000-2005	440
>=2006	738

A4: VIRTUAL R&D

There are 2713 lines of raw data which is too large for this appendix. Summary information describing the raw data is provided in table below.

Company Type	Internal	External	Co-developed	Externalization	Collaboration	Acquired product	In-licensed	Products from Merger & Acquisition	Other external	Not Applicable
Big Pharma	564	487	71	0.9	0.13	10	118	303	56	255
Mid Pharma	173	240	18	1.4	0.10	13	97	102	28	0
Japan Pharma	219	236	27	1.1	0.12	1	102	127	6	0
Biotech	96	74	3	0.8	0.03	6	31	27	10	7
Generics	72	160	2	2.2	0.03	0	6	50	104	0

External = Acquired products + In-licensed products + M&A products+ Other external products
Externalization = External / Internal
Collaboration = Co-developed / Internal

A5: TRANSLATIONAL RESEARCH

Biomarker	Drugs Associated with this Biomarker	Other Associated Drugs	Therapy Area	FDA Approval Year
Anaplastic Lymphoma Kinase (ALK)	Crisotinib		Oncology	2011
BRAF	Vemurafenib		Oncology	2011
CCR5 -Chemokine C-C motif receptor	Maraviroc		Infectious Diseases	2007
CD20 antigen	Tositumomab			2003
CD30	Brentuximab			2011
Cerebro spinal fluid related biomarkers for drugs affecting amyloid burden			Central Nervous System	2011
Cholinesterase gene	Mivacurium			1992
C-KIT expression	Imatinib mesylate		Oncology	2003
CYP2C19 Variants	Clopidogrel		Cardiovascular	2008
CYP2C19 Variants with alternate context	Diazepam	Diazepam	Central Nervous System	
CYP2C19 Variants with alternate context	Esomeprazole	Esomeprazole	Gastroenterology	
CYP2C19 Variants with alternate context	Nelfinavir	Nelfinavir	Infectious Diseases	
CYP2C19 Variants with alternate context	Omeprazole	Omeprazole	Gastroenterology	
CYP2C19 Variants with alternate context	Pantoprazole	Pantoprazole	Gastroenterology	
CYP2C19 Variants with alternate context	Rabeprazole	Rabeprazole	Gastroenterology	
CYP2C19 Variants with alternate context	Voriconazole		Infectious Diseases	2002
CYP2C19 Variants with alternate context (no effect of Variants)	Prasugrel		Cardiovascular	2007
CYP2C9 Variants	Celecoxib		Immunology & Inflammation	2003
CYP2C9 Variants with alternate context	Warfarin		Cardiovascular	2008
CYP2D6 (UM) with alternate context	Codeine Solfate		Central Nervous System	1991
CYP2D6 Variants	Atomoxetine		Central Nervous System	2005
CYP2D6 Variants	Risperidone	Risperidone	Central Nervous System	
CYP2D6 Variants	Tamoxifen	Tamoxifen	Oncology	

Appendix A5 Continued

Biomarker	Drugs Associated with this Biomarker	Other Associated Drugs	Therapy Area	FDA Approval Year
CYP2D6 Variants	Timolol maleate	Timolol maleate	Ophthalmology	
CYP2D6 Variants	Tiotropium bromide inhalation	Tiotropium bromide inhalation	Respiratory	
CYP2D6 Variants	Venlafaxine	Venlafaxine	Central Nervous System	
CYP2D6 with alternate context	Aripiprazol	Aripiprazol	Central Nervous System	
CYP2D6 with alternate context	Carvedilol	Carvedilol	Cardiovascular	
CYP2D6 with alternate context	Cevimeline Hydrochloride	Cevimeline Hydrochloride	Immunology & Inflammation	
CYP2D6 with alternate context	Clozapine	Clozapine	Central Nervous System	
CYP2D6 with alternate context	Fluoxetine HCL		Central Nervous System	1999
CYP2D6 with alternate context	Fluoxetine HCL & Olanzapine	Fluoxetine HCL & Olanzapine	Central Nervous System	
CYP2D6 with alternate context	Metoprolol	Metoprolol	Cardiovascular	
CYP2D6 with alternate context	Propafenone	Propafenone	Cardiovascular	
CYP2D6 with alternate context	Propranolol	Propranolol	Cardiovascular	
CYP2D6 with alternate context	Protriptyline	Protriptyline	Central Nervous System	
CYP2D6 with alternate context	Terabenazine	Terabenazine	Central Nervous System	
CYP2D6 with alternate context	Terbinafine	Terbinafine	Infectious Diseases	
CYP2D6 with alternate context	Thioridazine	Thioridazine	Central Nervous System	
CYP2D6 with alternate context	Tolterodine	Tolterodine	Genitourinary	
CYP2D6 with alternate context	Tramadol + Acetaminophen	Tramadol + Acetaminophen	Central Nervous System	
CYPA2				
Deletion of Chromosome 5q(del(5q))	Lenalidomide		Oncology	2006
DPD Deficiency	Capecitabine		Oncology	2004
DPD Deficiency	Fluorouracil Cream	Fluorouracil Cream	Dermatology	
DPD Deficiency	Fluorouracil Topical Solution & Cream	Fluorouracil Topical Solution & Cream	Dermatology	
EGFR expression	Erlotinib		Oncology	2005
EGFR expression with alternate Context	Cetuximab		Oncology	2004

Appendix A5 Continued

Biomarker	Drugs Associated with this Biomarker	Other Associated Drugs	Therapy Area	FDA Approval Year
EGFR expression with alternate Context	Gefitinib	Gefitinib	Oncology	
Estrogen Receptor			Oncology	
Familial Hypercholestremia	Atorvastatin		Cardiovascular	2002
G6PD Deficiency	Dapsone	Dapsone	Dermatology	
G6PD Deficiency	Rasburicase		Genitourinary	2002
G6PD Deficiency with alternate Context	Chloroquine	Chloroquine	Infectious Diseases	
G6PD Deficiency with alternate Context	Primaquine		Infectious Diseases	2003
Her2/neu Over-expression	Lapatinib	Lapatinib	Oncology	
Her2/neu Over-expression	Trastuzumab		Oncology	2004
HLA-B*1502 allele presence	Carbamazepine		Central Nervous System	2004
HLA-B*5701 allele presence	Abacavir		Infectious Diseases	2007
IL28B				2011
KRAS mutation	Cetuximab	Cetuximab	Oncology	
KRAS mutation	Panitumumab		Oncology	2008
NAT Variants	Isosorbide dinitrate and Hydralazine hydochloride	Isosorbide dinitrate and Hydralazine hydochloride	Cardiovascular	
NAT Variants	Rifampin, isoniazid, and pyrazinmide		Infectious Diseases	2001
Novel Renal Biomarkers for Toxicity			Nephrology	2010
Philadelphia Chromosome- positive responders with alternate context	Dasatinib		Oncology	2007
Philadelphia Chromosome- positive responders with alternate context	Nilotinib	Nilotinib	Oncology	
Philadelphia Chromosome-positive responders	Busulfan		Oncology	2002
PML/RAR alpha gene expression	Arsenic Trioxide	Arsenic Trioxide	Oncology	
PML/RAR alpha gene expression	Tretinoin		Oncology	2000
Protein C deficiencies	Warfarin		Cardiovascular	1996

Appendix A5 Continued

Biomarker	Drugs Associated with this Biomarker	Other Associated Drugs	Therapy Area	FDA Approval Year
TPMT Variants	Azathioprine		Immunology & Inflammation	1995
TPMT Variants	Mercaptopurine	Mercaptopurine	Oncology	
TPMT Variants	Thioguanine	Thioguanine	Oncology	
UGT1A1 Variants	Irinotecan		Oncology	2004
UGT1A1 variants with alternate context	Nilotinib		Oncology	2007
Urea Cycle Disorder (UCD) Deficiency	Valporic acid		Central Nervous System	1999
Vitamin K epoxide reductase (VKORC1) Variants	Warfarin		Cardiovascular	2008

A6: ADAPTIVE TRIALS

Year Received	Clinical Study Description (source: ClinicalTrials.gov)
2006	An Adaptive Design Trial Of GW274150 In The Treatment Of Acute Migraine Condition: Migraine
2009	Active, not recruiting Adaptive-design Dose Finding Study to Assess the Antiviral Efficacy and Safety of NIM811 Administered in Combination With Standard of Care (SOC) in Relapsed Hepatitis C Virus 1 (HCV-1) Infected Patients Condition: Chronic Hepatitis C Genotype-1 Relapse
2009	Recruiting Clinical Study to Test a New Drug to Treat Major Depression Condition: Major Depressive Disorder (MDD)
2007	Active, not recruiting Safety/Efficacy Study of Rexin-G to Treat Pancreatic Cancer Condition: Pancreatic Cancer
2007	Active, not recruiting Safety and Efficacy Study Using Rexin-G for Breast Cancer Condition: Breast Cancer
2007	Active, not recruiting Safety and Efficacy Study Using Rexin-G for Sarcoma Condition: Sarcoma
2007	Recruiting To Evaluate Antiviral Efficacy of Telbivudine in Hepatitis B Antigen Positive (HbeAg-positive) Compensated Chronic Hepatitis B (CHB) Condition: Hepatitis B, Chronic
2009	Suspended A Study of ALKS33 (RDC-0313) in Adults With Alcohol Dependence Condition: Alcohol Dependence
2008	Recruiting Study of Pegylated Human Recombinant Arginase for Liver Cancer Conditions: Neoplasm; Hepatocellular Carcinoma
2009	Recruiting A Study of the Pharmacokinetics of Albiglutide in Normal and Renally Impaired Subjects. Conditions: Diabetes Mellitus, Type 2; Renal Impairment
2009	Recruiting A Study in Cancer Patients to Evaluate the Bioequivalence of Alternative Formulations of Lapatinib Conditions: ErbB2 Overexpressing; Metastatic Breast Cancer; Solid Tumors
2008	Terminated A Dose-Ranging Study of ATI 7505 in Patients With Postprandial Distress Syndrome Condition: Post Prandial Distress Syndrome
2008	Terminated Has Results A Study Evaluating Desvenlafaxine Sustained Release (DVS SR) in Adult Female Outpatients With Fibromyalgia Condition: Fibromyalgia
2009	Recruiting Safety and Efficacy of CEM-102 Compared to Linezolid in Acute Bacterial Skin Infections Condition: Acute Bacterial Skin Structure Infections
2009	Completed Single Dose Study of N1539 in the Treatment of Pain Secondary to Dental Impaction Surgery Condition: Dental Pain
2007	Completed Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of QAU145 in Patients With Cystic Fibrosis Condition: Cystic Fibrosis
2006	Terminated Study Evaluating the Efficacy of DVS-233 in Fibromyalgia Condition: Fibromyalgia
2009	Recruiting EFFicacy Optimization Research of Telbivudine Therapy Condition: Compensated Chronic Hepatitis B
2007	Terminated Safety and Efficacy Study of ABT-089 in Adults With Mild to Moderate Alzheimer's Disease Condition: Alzheimer's Disease
2010	Recruiting Safety and Cognitive Function Study of EVP-6124 in Patients With Mild to Moderate Alzheimer's Disease Conditions: Alzheimer's Disease; Central Nervous System Diseases; Cognition
2009	Recruiting Safety, Tolerability, Efficacy and Optimal Dose Finding Study of BAF312 in Patients With Relapsing-remitting Multiple Sclerosis Start Date: March 2009
2007	Terminated Study Evaluating Vabicaserin in Subjects With Schizophrenia Start Date: December 2007

Appendix A6 Continued

Year Received	Clinical Study Description (source: ClinicalTrials.gov)
2009	Recruiting Long-Term Extension Study of the Effects of SCH 527123 in Subjects With Moderate to Severe COPD (P05575AM2) Start Date: October 2009
2006	Terminated Has Results Study Evaluating Desvenlafaxine Succinate Sustained-release (DVS SR) in Adult Outpatients With Pain Associated With Diabetic Peripheral Neuropathy Start Date: March 2006
2008	Recruiting Phase II Study Evaluating the Safety and Efficacy of GSK315234 in Patients With Rheumatoid Arthritis Start Date: April 2008
2008	Recruiting Safety and Efficacy of LibiGel® for Treatment of Hypoactive Sexual Desire Disorder in Postmenopausal Women Start Date: January 2008
2006	Recruiting Randomised Trial of Two Different Strategies to Treat Paroxysmal Atrial Fibrillation Start Date: February 2006
2009	Completed The Effect of a New Specific Enteral Formula Compared to a Standard Formula on the Tolerability of a Combined Radio- and Chemotherapy in Cancer Patients Start Date: September 2006
2005	Completed SB-773812 Administered In Adults With Schizophrenia Start Date: September 2005
2008	Terminated Safety and Efficacy of Cethrin® in Adult Subjects With Acute Cervical Spinal Cord Injury Start Date:
2010	Not yet recruiting Novel Approach to Stimulant Induced Weight Suppression and Its Impact on Growth Start Date: July 2010
2008	Active, not recruiting A Multiple Ascending Dose Study of RO4905417 in Healthy Volunteers and Patients With Peripheral Arterial Disease (PAD). Start Date: September 2008
2007	LMP1- and LMP2-Specific CTLs to Patients With EBV-Positive NPC (NATELLA) Start Date: August 2007
2009	Efficacy and Safety Study of the Misoprostol Vaginal Priming Insert (MVPI) Prior to Hysteroscopy Start Date: January 2010
2009	[11C]Carfentanil PET Study of GSK1521498 Start Date: June 2009
2008	Enhancing Fitness in Older Overweight Vets With Impaired Fasting Glucose Start Date: October 2008
2010	An Open Label Positron Emission Tomography Study in Healthy Male Subjects to Investigate Brain DAT and SERT Occupancy,Pharmacokinetics and Safety of Single Oral Doses of GSK1360707, Using 11C- PE2I and 11C-DASB as PET Ligands Start Date: April 2009
2010	Recruiting Safety and Pharmacokinetic Study of Oral ON 01910.Na in Patients With Myelodysplastic Syndrome
2010	Not yet recruiting A Study of MK-3415, MK-6072, and MK-3415A in Participants Receiving Antibiotic Therapy for Clostridium Difficile Infection (MK-3415A-001 AM2) Condition: Clostridium Difficile Infection
2010	Active, not recruiting A Study to Investigate the Impact of Dose and Dosing Frequency of AZD8848 on the Response on Biomarkers Condition: Healthy Volunteers
2010	Recruiting Comparing the Efficacy, Safety, and Tolerability of Combination Antivirals (Amantadine, Ribavirin, Oseltamivir) Versus Oseltamivir for the Treatment of Influenza in Adults at Risk for Complications Condition: Influenza
2010	Recruiting Novel Approach to Stimulant Induced Weight Suppression and Its Impact on Growth Conditions: ADHD; Growth
2010	Recruiting Study to Evaluate the Efficacy and Safety of Three Different Doses of SCV 07 in Attenuating Oral Mucositis in Subjects With Head and Neck Cancer Condition: Oral Mucositis

A7: GLOBAL HARMONIZATION

ICH Guideline	Topic	Sub-Topic	Publication Year	Status
Q1A(R2)	Quality	Stability	2003	Implementation
Q1B	Quality	Stability	1996	Implementation
Q1C	Quality	Stability	1996	Implementation
Q1D	Quality	Stability	2002	Implementation
Q1E	Quality	Stability	2003	Implementation
Q2(R1)	Quality	Analytical Validation	1994	Implementation
Q3A(R2)	Quality	Impurities	2006	Implementation
Q3B(R2)	Quality	Impurities	2006	Implementation
Q3C(R4)	Quality	Impurities	2009	Implementation
Q4B	Quality	Pharmacopoeias	2007	Implementation
Q4B Annex 1	Quality	Pharmacopoeias	2007	Implementation
Q4B Annex 2	Quality	Pharmacopoeias	2008	Implementation
Q4B Annex 3	Quality	Pharmacopoeias	2008	Implementation
Q4B Annex 4A	Quality	Pharmacopoeias	2008	Implementation
Q4B Annex 4B	Quality	Pharmacopoeias	2008	Implementation
Q4B Annex 4C	Quality	Pharmacopoeias	2008	Implementation
Q4B Annex 5	Quality	Pharmacopoeias	2009	Implementation
Q4B Annex 6	Quality	Pharmacopoeias	2008	Consultation
Q4B Annex 7	Quality	Pharmacopoeias	2009	Implementation
Q4B Annex 8	Quality	Pharmacopoeias	2009	Implementation
Q4B Annex 9	Quality	Pharmacopoeias	2009	Implementation
Q4B Annex 10	Quality	Pharmacopoeias	2009	Implementation
Q4B Annex 11	Quality	Pharmacopoeias	2010	Consultation
Q4B Annex 12	Quality	Pharmacopoeias	2010	Consultation
Q4B Annex 13	Quality	Pharmacopoeias	2010	Consultation
Q4B Annex 14	Quality	Pharmacopoeias	2010	Consultation
Q5A(R1)	Quality	Quality of Biotechnological Products	1997	Implementation

Appendix A7 Continued

ICH Guideline	Topic	Sub-Topic	Publication Year	Status
Q5B	Quality	Quality of Biotechnological Products	1995	Implementation
Q5C	Quality	Quality of Biotechnological Products	1995	Implementation
Q5D	Quality	Quality of Biotechnological Products	1997	Implementation
Q5E	Quality	Quality of Biotechnological Products	2004	Implementation
Q6A	Quality	Specifications	1999	Implementation
Q6B	Quality	Specifications	1999	Implementation
Q7	Quality	Good Manufacturing Practice	2000	Implementation
Q8(R2)	Quality	Pharmaceutical Development	2005	Implementation
Q9	Quality	Quality Risk Management	2005	Implementation
Q10	Quality	Pharmaceutical Quality System	2008	Implementation
S1A	Safety	Carcinogenicity Studies	1995	Implementation
S1B	Safety	Carcinogenicity Studies	1997	Implementation
S1C(R2)	Safety	Carcinogenicity Studies	2008	Implementation
S2(R1)	Safety	Genotoxicity Studies	2008	Consultation
S3A	Safety	Toxicokinetics and Pharmacokinetics	1994	Implementation
S3B	Safety	Toxicokinetics and Pharmacokinetics	1994	Implementation
S4	Safety	Toxicity Testing	1994	Implementation
S5(R2)	Safety	Reproductive Toxicology	1993	Implementation
S6	Safety	Biotechnological Products	1997	Implementation
S6(R1)	Safety	Biotechnological Products	2009	Implementation
S7A	Safety	Pharmacology Studies	2000	Implementation
S7B	Safety	Pharmacology Studies	2005	Implementation
S8	Safety	Immunotoxicology Studies	2005	Implementation
S9	Safety	Immunotoxicology Studies	2009	Consultation
E1	Efficacy	Clinical Safety	1994	Implementation
E2A	Efficacy	Clinical Safety	1994	Implementation
E2B(R3)	Efficacy	Clinical Safety	2000	Implementation
E2C(R1)	Efficacy	Clinical Safety	1996	Implementation
E2D	Efficacy	Clinical Safety	2003	Implementation

Appendix A7 Continued

ICH Guideline	Topic	Sub-Topic	Publication Year	Status
E2E	Efficacy	Clinical Safety	2004	Implementation
E2F	Efficacy	Clinical Safety	2008	Consultation
E3	Efficacy	Clinical Study Reports	1995	Implementation
E4	Efficacy	Dose-Response Studies	1994	Implementation
E5(R1)	Efficacy	Ethnic Factors	1998	Implementation
E6(R1)	Efficacy	Good Clinical Practice	1996	Implementation
E7	Efficacy	Clinical Trials	1993	Implementation
E8	Efficacy	Clinical Trials	1997	Implementation
E9	Efficacy	Clinical Trials	1998	Implementation
E10	Efficacy	Clinical Trials	2000	Implementation
E11	Efficacy	Clinical Trials	2000	Implementation
E12	Efficacy	Guidelines for Clinical Evaluation by Therapeutic Category	2001	Implementation
E14	Efficacy	Clinical Evaluation	2008	Implementation
E15	Efficacy	Pharmacogenomics	2007	Implementation
E16	Efficacy	Pharmacogenomics	2009	Consultation
M1	Multidisciplinary	MedDRA	Draft stage in 2011	Draft
M2	Multidisciplinary	MSTRI	Draft stage in 2011	Draft
M3	Multidisciplinary	Nonclinical Safety Studies	2009	Implementation
M4	Multidisciplinary	CTD	2003	Implementation
M5	Multidisciplinary	Data Elements and Standards for Drug Dictionaries	??	Consultation

A8: SCIENCE AND RISK BASED REGULATIONS

FDA Centre	Collaborator(s)	Title of FDA Cooperative Research and Development Agreements (CRADA)	Research Focus
CBER	Alliance Biosecure Research Foundation	Infectivity Titrations of Blood Components from Chimpanzees Infected with the Agent of Gerstmann-Sträussler-Scheinker Syndrome in Mice and Comparison of Sensitivity of Mouse Bioassays	-
CBER	PATH Vaccine Solutions	Development of Conjugation Technology for Pneumococcal Conjugate Vaccines	Biotechnology
CBER	Muscular Dystrophy Association	Remote Therapeutic Delivery for Spinal Muscular Atrophy	Pervasive Computing
CBER	Nanosphere, Inc.	Development of a Nano-Particle Influenza Assay	Nanotechnology
CDRH	Fraunhofer USA, Inc. - CESE	Software Re-engineering and Forensic Analysis	Bioinformatics
CDRH	Cytel, Inc.	Software for Bayesian Clinical Trials	Bioinformatics
OC, OCPP	GlobalSubmit, Inc.	Study Design Software	Bioinformatics
CDER	Eli Lilly and Company	Development of Standards, Data Integration, and Applications for Analyzing and Visualizing Heterogeneous Datasets	Bioinformatics
CDER	Mosaiques Diagnostics	Identification and Validation for Urinary Biomarkers for Drug Toxicity	Personalised Medicine
CDRH	Ginzton Technology Centre--Varian Medical Systems, Inc.	X-ray Detector Models for Imaging Breast Cancer	-
CDER	Adaptive Pharmacogenomics, LLC, and GlaxoSmithKline R&D	Development of a General Purpose Software Tool that Optimises Clinical Study Design with Biomarkers	Bioinformatics
CBER	Program for Appropriate Technology in Health	Bioassays to Predict the Biological Activity, Safety, and Virulence of Live Attenuated *Plasmodium Falciparum* Sporozoite	-
CDRH	Eyelight Diagnostics, Inc.	Non-Invasive Assessment of Individuals at Risk for Diabetes	Pervasive Computing
CBER	Protox Therapeutics, Inc.	Development and Characterization of Novel Protein Toxin Therapeutics Targeting IL-4 Receptor	-
CDER	American Association of Pharmaceutical Scientists (AAPS)	Enhancing IND/NDA Review Quality via Quantifying Prior Knowledge	Bioinformatics
CDER	Ingenuity, Inc.	Reference Database Exploration Tool for Regulatory Review of Biomarker, Pharacogenomic, and Toxicogenomic Data	Bioinformatics

Appendix A8 Continued

FDA Centre	Collaborator(s)	Title of FDA Cooperative Research and Development Agreements (CRADA)	Research Focus
CDER	Infrastructures for Information, Inc. (i4i)	FACTS@FDA Label and Listing Collaboration System	Critical Path
CDER	Eli Lilly and Company	An Integrated Approach to Evaluation of Viral Clearance for Monoclonal Antibodies	Biotechnology
CDER	Entelos, Inc.	Development of Drug-Induced Liver Injury (DILI) PhysioLab Platform	-
CDRH	Raydiance, Inc.	Medical Applications of a High Energy Femtosecond Laser	-
CDRH	Epicor/St. Jude Medical	Optical Techniques for the Non-Invasive 3D Characterization of Biomedical Ultrasound Beams	Pervasive Computing
CDER	Affymetrix, Inc.	Toxigenomic Signature Analysis of Drug-Induced Phospholipidosis	-
CBER	Novartis	Env-Gp41 Oligomeric Immunogen	-
CDER	Pfizer, Inc.	Evaluation of Biomarkers of Drug-Induced Vascular Injury	Personalised Medicine
CDRH	FIMI/Phillips, Inc.	High-Dynamic-Range Display of Medical Images	-
CBER	National Hemophilia Foundation	Genetics of Inhibitor Antibody Response	-
CDER	ChemImage	Raman Chemical Imaging of Pharmaceutical Solids	Process Analytical Technology (PAT)
CDER	Lhasa Limited	Development of FDA Toxicology Databases Suitable for Human Expert Rule Development and Mechanistic Understanding of Chemical-Induced Toxicity	Bioinformatics
CDER, CDRH	Novartis	Co-Development of Drugs and Pharmacogenomic Tests	Personalised Medicine
CBER	US Civilian Research & Development Foundation	Test Kit for Quantitative Genotyping of Subtypes of HCV	Personalised Medicine
CDER	Pharsight Corporation	Enhancing IND/NDA Study Data Review Process	Bioinformatics
CDER	US Pharmacopeia	Substance Registration Project	Critical Path
CDRH	Biophan Laboratories	Measurement and Computer Modeling to Evaluate the Safety of Medical Implants in the Presence of Electromagnetic Fields from Magnetic Resonance Imaging	-
CDER	LightPharma, Inc.	Understanding manufaturing Science to Caprture Opportunities on the Critical Path for Chemistry, Manufacturing, and Controls (CMC)	Critical Path
CBER	Albert Einstein College of Medicine	Characterization of Novel Live Attenuated TB Vaccine Strains	Biotechnology
CDER	Leadscope, Inc.	Development of Toxicology and Clinical Effects Databases	Bioinformatics

Appendix A8 Continued

FDA Centre	Collaborator(s)	Title of FDA Cooperative Research and Development Agreements (CRADA)	Research Focus
CBER	American Type Culture Collection (ATCC)	Oligonucleotide Microarrays for Identification and Genotyping of Mycoplasma	-
CDER	Novartis Institutes for Biomedical Research, Novartis, Inc.	Criteria for Drug Evaluation of Genomic Biomarkers of Safety	Personalised Medicine
CBER	Meriture, Inc.	Development of Analysis or Peptides for Antiviral Effect on Ebola Virus Infection	-
CDRH	The Foundation for Research on Information Technologies in Society--IT'IS	Numerical Models and Tools	Bioinformatics
CDER	Texas A&M University, Kingsville	Creation of "Design Space" for Novel Targeted Dosage Forms	QbD
CDER	Novartis, Inc.	Application of PAT Tools During Manufacturing	PAT
CDER	Conformia, Inc.	Survey of Pharmaceutical Needs	Critical Path
CBER	Aeras Global TB Vaccine Foundation	Development of Preclinical Assays for Safe Use of TB Vaccines	-
CBER	Technion Research and Development Foundation	Use of Microarray Technology to Identify New Genes	-
CBER	University Michigan Medical School	IL-13 Fusion Cytotoxin as a Targeted Therapeutic	-
CDRH	NanoSonic, Inc.	Optical Fiber-Based Instrumentation for Monitoring Breath Biomarkers	Personalised Medicine
CDRH	Univ. of Pennsylvania	Biomechanics and Genomics of Vascular Dysfunction and Healing	Personalised Medicine
CBER	Alpha-1 Foundation	Investigation of Alpha-1-PI Polymer Structure	-
CBER	Program for Appropriate Technology in Heath (PATH)	High Yield Group A Meningococcal Polysaccharide-Tetanus Toxoid Conjugates	-
CDER	MultiCASE	Enhancement of the Performance of the MultiCASE (Q)SAR Software and FDA Toxicology Prediction Models	Bioinformatics
CDER	Parenteral Drug Assn.	Large Virus Filter Nomenclature Standardization	Bioinformatics
CDER	Mortara Instrument	Design and Development of a Customised ECG Warehouse	-
CBER	NeoPharm, Inc. and NIH/NINDS	Convection-enhanced Delivery of IL13-PE38QQR for Treatment of Diffuse Brainstem Gliomas	-

Appendix A8 Continued

FDA Centre	Collaborator(s)	Title of FDA Cooperative Research and Development Agreements (CRADA)	Research Focus
CBER	HemaTech, LLC	Analysis of Anthrax Antibody Production in Conventional and Transchromosomal Cows	-
CBER	Scripps Research Institute	Expression and Function of the Human PERV A Receptor	-
CBER	University of Illinois	Rational Design of Anti-Meningococcal Polysaccharide Conjugate Vaccine	Biotechnology
CDRH	LifeSpan, Inc.	Explant Pathology Studies of Small Intestinal Submucosa Fabricated Pulmonary and Mitral Valve Replacements Implanted in Sheep	-
CBER	American Type Culture Collection (ATCC)	Analysis of Gene Expression by Microarray on Various Cell Lines	-
CBER	Holland Laboratory, American Red Cross	Transgenic Mouse Model for the Study of Variant Creutzfeldt-Jakob Disease	-
CDER	Pfizer, Inc.	Assessment of On-line or At-line Vibrational Spectroscopy and Chemical Imaging Techniques in Pharmaceutical Manufacturing for Controlling Critical Quality Attributes	PAT
CDER	MDL, Inc.	Development of Toxicology Prediction Modeling Modules	Bioinformatics
CDER	IBM	Development of a Physical Database for Study Data for Clinical and Non-Clinical Data at FDA	Bioinformatics
CBER	Johns Hopkins University	Development of Biochip-Based Technologies for Detection of Pathogenic Bacteria and Viral Agents and Establishment of a Secure Central Repository for Microarray Data	Pervasive Computing
CBER	Research Triangle Institute	Porin Gene Variable Region Typing of *Neisseria gonorrhoeae*	-
CDRH	Mobile Manufacturers Forum	Medical Device Electromagnetic Interference. (EMI) from Wireless Data Devices and Interlaboratory Comparison of Radiofrequency (RF) Dosimetry Data from Handheld Transmitters	-
CDER	Lincoln Technologies	Advanced Analytical Tools for Drug Safety Risk Assessment	PAT
CDER	OxfordGlycoSciences, Inc.	Development of Improved Biomarkers for Early Detection of Mycocardial Injury, Vascular Injury,and Liver Injury	Personalised Medicine
CDER	DataPharm Foundation	Electronic Collection, Processing and Distribution of Drug Product Infomation	Critical Path
CDER	Lincoln Technologies, Inc.	Design and Development of a Prototype Integrated Submissions Data Repository and Data Validation and Transformation Tool for eSubmission CRT Data	Critical Path
CDER	Schering Plough	Identification and Evaluation of Vasculitis Induced by SCH351591	-
CDER	PharmQuest, Inc.	Development of Carcinogenicity and Toxicology Data Management System	Bioinformatics

Appendix A8 Continued

FDA Centre	Collaborator(s)	Title of FDA Cooperative Research and Development Agreements (CRADA)	Research Focus
CBER	NIH/National Cancer Institute and Correlogic Systems, Inc.	Use of Pattern Discovery Technology to Identify Patterns of Protein Expression Associated with Specific Disease States	Bioinformatics
CDER	PPD Informatics/PPD Development, Inc.	Automation of Patient Profiles for Use with Submission Data Interface and Automated Import Screening	Critical Path
CBER	Agilent Technologies, Inc.	Synthesis of Oligonucleotides on Planar Glass Surfaces	-
CDER, CBER, CVM	Pharsight Corp.	Enhanced Clinical Drug Trial Simulation and Population PK Analysis Software	Bioinformatics
CBER	Coley Pharmaceuticals Group, Inc.	CpG Oligonucleotides Optimised for Activity in Humans	-
CDER	US Pharmacopeia (USP)	Collaboration Regarding USP Reference Standards	-
CDRH	Cellular Telecommunications Industry Assn. (CTIA)	Health Effects of RF Emissions from Wireless Phones	-
CDER	Boehringer Ingelheim Pharmaceuticals, Inc.	Immune Biomarkers for Monitoring Drug-Induced Vasculitis	Personalised Medicine
CDRH	Program for Appropriate Technology in Health (PATH)	Effects of Storage, Materials and Stress on Latex Glove Integrity	-
CBER	Neurocrine Biosciences, Inc.	A Circular Permuted IL-4 Pseudomona Exotoxin as an Anti-Cancer Agent	-
CDER	Boehringer Ingelheim Pharmaceuticals, Inc.	Transgenic Mouse Model as a Short-term Alternative to Predicting the Carcinogenecity of Pharmaceuticals	-
CDRH	Safeskin Corporation	Frequent Use of C Latex Products that may Play a Role in the Rate of Sensitization and the Intensity of Reaction to Latex Products	-
CDRH	Institute of Electrical and CDP Electronics Engineers (IEEE)	Improvement in the Quality of Software that is Used in Medical Devices to Increase Their Safety and Effectiveness	-
CDER	Multi/CASE	Multi/CASE Software Program Database Modules to Enhance Their Application for Predicting and Characterizing Toxicity of Pharmaceuticals	Bioinformatics
CBER	NeoPharm, Inc.	Interleukin-13 Pseudomonas Exotoxin as Anticancer Agent	-
CDRH, CBER, ORA	Diagnostic Products Corporation	Testing Human Sera for Total IgE and Specific IgE for Detection and Survey of Allergenic Disease	Personalised Medicine
CDRH	Organ, Inc.	Rapid and Uniform Heating of Vitrified Organs Under 1000 Atmoshperes of Pressure	-

Appendix A8 Continued

FDA Centre	Collaborator(s)	Title of FDA Cooperative Research and Development Agreements (CRADA)	Research Focus
CDER	Medifacts, Inc.	Ambulatory Blood Pressure Monitoring	Pervasive Computing
CBER	Tulane University	Development of Non-Human Primate Model for Krebbe's Disease	-
CBER	SNS, Inc.	Auto On-Line Hydrolysis System	PAT

A9: PROGRESSIVE/LIVE LICENSING

No operational evidence was found in support of this trigger.

A10: REGULATORY ENFORCEMENT

Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Austrade Inc.	Energy Drinks/Failure to Hold an Entry Intact	8/10/2000
Appalachina Medical Equipment Co. Inc.	Medical Oxygen / CGMP	8/30/2000
Ayundantes Inc.	Narcotic Treatment Program Standards	9/21/2000
Brigham Radiology Group	Mammography Standards	10/4/2000
Abkit Inc.	Alpha Betic Multi-Vitamin Supplement with Alpha Lipoic Acid/Labeling/Lacks NDA/Misbranded	10/30/2000
Batshaw Mark L. M.D.	Clinical Investigator	11/30/2000
Chemrich Holdings Inc.	Manufacturing Facility/Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	12/11/2000
Holy Cross Hospital	Mammography Standards	12/11/2000
Everett Clinic	Mammography Standards	12/13/2000
Airgas Norpac	Medical Gas/Adulterated	12/14/2000
Genentech Inc.	Good Manufacturing Practices for Finished Pharmaceuticals/Biological Products General Provisions	12/14/2000
Intercoastal Medical Group	Mammography Standards	12/14/2000
ADI Corporation	Television/Computer Monitor Factories/Automatic Detention	12/18/2000
Blue Light Inc.	New Drug/Misbranded/Adulterated	12/18/2000
Coram Healthcare	Liquid Medical Oxygen/Adulterated	12/18/2000
E.A. Conway Medical Centre	Mammography Standards	12/19/2000
Alexander Community Hospital	Mammography Standards	12/20/2000
Banco de Sangre Humacao Inc.	Good Manufacting Practices for Blood and Components	12/20/2000
Elcat Company	Methamphetamine Hydrochloride/Active Pharmaceutcal Ingredients/Adulterated	12/20/2000
Advanced Health Care	Mammography Standards	12/22/2000
Beverly Hills Diagnostic Breast Centre	Mammography Standards	12/22/2000
East Palestine Family Medical Clinic Inc.	Mammography Standards	12/22/2000
American Bio Medica Corporation	Rapid Drug Screen/Adulterated/Lacks Premarket Approval/Misbranded	12/26/2000
Fox Chase Cancer Centre	Mammography Standards	12/28/2000
Fox Chase Cancer Centre	Mammography Standards	12/28/2000
Haribo of America Inc.	Jellied Candy/Lacks	12/28/2000

Appendix A10 Continued

Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Leiner Health Products Inc.	Good Manufacturing Practice for Finished Pharmaceuticals/Adulterated	12/11/2000
Radiology Clinics of Laredo	Mammography Standards	12/11/2000
Scholzen Products Company Inc.	GMP for Finished Pharmaceuticals/Gas & Liquid Medical Oxygen/Adulterated	12/12/2000
University OB-GYN Specialties Inc.	Mammography Standards	12/12/2000
San Dimas Community Hospital	Mammography Standards	12/14/2000
Tianjin Xin Xin Pharmaceutical Corporation	Active Pharmaceutical Ingredient/Adulterated/FMP's Manufacturing Processing Packing etc.	12/14/2000
Murex Diagnostics Inc.	Quality System Regulation	12/15/2000
Ultralite Enterprises Inc.	Quality System Regulation/Phototherapy Units/Adulterated	12/15/2000
Ultralite Enterprises Inc.	Quality System Regulation/Phototherapy Units/Misbranded/MDR Reporting/Adulterated	12/15/2000
Xinjiang Pharmaceutical Factory	Active Pharmaceutical Ingredient Mfr Facility/Adulterated/Manufactu ring Processing Packaging etc.	12/18/2000
Organon Teknika BV	Postmarketing Adverse Drug Experience Reporting Requirements	12/20/2000
St. Mary's Gateway Health Centre	Mammography Standards	12/20/2000
St. Mary's Centre for Women's Health	Mammography Standards	12/21/2000
Westerly Hospital	Mammography Standards	12/21/2000
Spectrum Health Betty Ford Breast Care Services	Mammography Standards	12/22/2000
Allina Medical Group	Mammography Standards	01/05/2001
AJ Slenders Dairy	New Animal Drug/Held Under Insanitary Conditions/Adulterated	01/10/2001
Allison Breast Centre at Monument Radiology	Mammography Standards	01/19/2001
Barnes Health Care Services	Medical Oxygen/Adulterated	03/07/2001
Biogen Inc.	Labeling/False & Misleading/Avonex	03/29/2001
Albert Lea Medical Centre	Mammography Standards	03/30/2001
Aventis Pasteur Inc.	GMP for Mfr Processing Packing Holding Drugs/Biological Products	04/09/2001
Albermarle Hospital	Mammography Quality Standards	04/24/2001
Colgate Palmolive Company	CGMP for Finished Pharmaceutical/Adulterated	05/04/2001
Alta District Hospital	Mammography Quality Standards	05/18/2001
Adventist Health Walla Walla General Hospital	GMP for Blood & Blood Components/General Biological Standards	07/13/2001
Aventis Bio-Sciences	Good Manufacturing Practice Regulations for Blood and Blood Components	07/13/2001

Appendix A10 Continued

Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Allergan, Inc.	Violative Promotion Advertising/Lacking Fair Balance/Misleading	08/22/2001
Bourbon County Hospital	Mammography Quality Standards	09/10/2001
AirTran Airways	Interstate Conveyance Sanitation Regulations	09/18/2001
ADAC Laboratories	CGMP requirements for the Quality System Regulation/Medical Device Reporting / Adulterated/ Misbranded	10/25/2001
Gorman, John F., M.D.	Mammography Quality Standards	11/01/2001
All Care Medical Group, Inc.	Mammography Quality Standards	11/19/2001
Dallas County Hospital District	Mammography Quality Standards	12/13/2001
Dextrum Laboratories Inc	CGMP for Drugs/Manufacture Processing Packing Holding/Adulterated	12/13/2001
Biorem s.r.l.	Medical Device/Lacks Premarket Approval/Adulterated/Misbranded	12/14/2001
Bollinger Quick Repair, Inc.	Interstate Conveyance Sanitation Regulations	12/14/2001
Atlantic General Hospital	Mammography Quality Standards Act	12/18/2001
Community Radiology Inc.	Mammography Quality Standards	12/18/2001
Diagnostic Medical Imaging Associates	Mammography Quality Standards	12/19/2001
Breast Cancer Detection Centre of Alaska	Mammography Quality Standards	12/20/2001
Feldman Mark H. D.P.M.	Clinical Investigator	12/21/2001
Forever Young Products, Inc.	Current Good Manufacturing Practice Regulation for Finished Pharmaceuticals	12/21/2001
2-2-0 Laboratories	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	12/27/2001
Island Kinetics Inc	CGMP for Finished Pharmaceutical/Adulterated	12/27/2001
Green Gold Wholesale Produce Inc.	Avocados/Lacks	12/28/2001
Hen-Lin Dairy	Animal Drug/Adulterated	12/28/2001
Merck & Co. Inc.	GMP for Finished Pharmaceuticals/Biologics Licensing	02/09/2001
Medical Device Services, Inc.	Quality System/Good Manufacturing Practice for Medical Devices/Adulterated	12/13/2001
Providence Milwaukie Hospital	Mammography Quality Standards	12/13/2001
Wise Regional Health	Mammography Quality Standards	12/13/2001
Natural Technology, Inc.	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	12/14/2001
Rowan Animal Clinic	Illegal Drug Residue/Adulterated	12/14/2001
Shelly Smith Farm	Illegal Drug Residue/Adulterated	12/14/2001

Appendix A10 Continued

Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Trusted Care	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	12/14/2001
Van Haitsma Dairy Farm	Illegal Drug Tissue Residue/Adulterated	12/14/2001
Sibley Medical Associates	Mammography Quality Standards	12/17/2001
Women's Diagnostic Imaging Centre	Mammography Quality Standards	12/17/2001
Multidata Systems International Corporation	Electronic Product Radiation Control/Premarket Notification Requirements/Adulterated/Misbranded	12/18/2001
The Medical Group	Mammography Quality Standards	12/19/2001
Wayzata Bay Products Inc	Good Manufacturing Practice for Finished Pharmaceuticals/Adulterated	12/19/2001
Medical Centre at Lancaster	Mammography Quality Standards	12/20/2001
Misonix, Inc.	GMP Requirements for the Quality System Regulation/Adulterated	12/20/2001
NCOIC	Mammography Quality Standards	12/20/2001
Norton Suburban Hospital	Mammography Quality Standards	12/20/2001
Van de Graaf Racnhes, Inc.	Current Good Manufacturing Practice for Medicated Feeds/Adulterated	12/20/2001
West Agro, Inc.	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	12/21/2001
N TECH Instrument Repair, Inc.	Quality System Regulation for Medical Devices/Adulterated	12/27/2001
Trotters Importers	Dried Fig Spread/Lacks	12/28/2001
Matthews, Dana C., M.D.	Sponsor/Clinical Investigator	12/31/2001
Aspen Medical Group	Mammography Quality Standards	01/14/2002
Berlex Laboratories, Inc.	Quinaglute Dura-Tabs/CGMP for Finished Pharmaceuticals/Adulterated	03/11/2002
Americaloe, Inc.	Seasilver/New Drug/Labeling/Misbranded	04/03/2002
Ashland Drug	Nicotine Lollipops/New Drug/Misbranded	04/09/2002
Arizona Institue of Medicine & Surgery	Mammography Quality Standards	04/30/2002
America West Airlines, Inc.	Control of Communicable Diseases and Interstate Conveyance Sanitation	05/08/2002
Allosource, Inc.	Human Issue Intended for Transplantation	07/02/2002
BCS Farms	Drug Residue in Animal Tissue/Adulterated	08/08/2002
Automatic Liquid Packaging, Inc.	GMP for Finished Pharmaceuticals/Adulterated	09/23/2002
Allscripts Healthcare Solutions	Certain Drugs Accord New Drug Status through Rulemaking Procedures/Guaifenesin	10/11/2002
Alphagen Laboratories Inc.	Certain Drugs Accord New Drug Status through Rulemaking Procedures/Guaifenesin	10/11/2002
Ambi Pharmaceuticals	Certain Drugs Accord New Drug Status through Rulemaking Procedures/Guaifenesin	10/11/2002

Appendix A10 Continued

Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
ChemSource Corporation	Current Good Manufacturing Practice of Active Pharmaceutical Ingredients /Adulterated	11/15/2002
Blond, Scott, D.V.M	Illegal Tissue Residue/Extra-label Use/Adulterated	12/02/2002
Charles L. Earsing Dairy Farm	Illegal Tissue Residue/Extra-label Use/Adulterated	12/02/2002
Hoogendam Dairy	Illegal Drug Tissue Residue/Adulterated	12/02/2002
Classic Medical, Inc.	Medical Oxygen/CGMP for Finished Pharmaceuticals/Adulterated/Mi sbranded	12/03/2002
Desert Advanced Imaging Centre	Mammography Quality Standards	12/05/2002
Hobart Laboratories, Inc.	CGMP in Manufacturing, Processing, Packing or Holding/CGMP for Finished Pharmaceuticals/Adulterated	12/06/2002
E.M. Adams Co., Inc.	Quality System Reguation/Adulterated	12/09/2002
Beaumont Products, Inc.	Unapproved New Drug/GMP for Finished Pharmaceuticals/Misbranded	12/11/2002
Gulf Medical Services	CGMP for Finished Pharmaceuticals/CGMP in Manufacturing, Processing, Packing, or Holding/Adulterated	12/16/2002
Eastern Medical Equipment Distributors, Inc.	CGMP for Finished Pharmaceuticals/CGMP in Manufacturing, Processing, Packing, or Holding/ Adulterated	12/17/2002
Gateway Blood Association	Blood Products/Lacks Approved License for Interstate Commerce	12/18/2002
Costa View Farms	Illegal Edible Tissue Residue/Adulterated	12/19/2002
Coulter Corporation	GMP for Blood and Blood Products/Quality System Regulation	12/19/2002
Edward W. McCready Memorial Hospital	Mammography Quality Standards	12/20/2002
DBA Zacharias Holsteins	Drug in Edible Tissue/Extra label Use/Adulterated	12/23/2002
Hoover Feed Service, Inc.	New Drug/Adulterated	12/24/2002
Boersma #2 Dairy	Illegal Edible Tissue Residue/Adulterated	12/26/2002
Fischer Imaging Corporation	Quality System Regulation/Good Manufacturing Practice for Medical Devices/Adulterated	12/27/2002
Diamond Pacific	CGMP for Licensed Medicated Feeds/Adulterated	12/28/2002
Medina General Hospital	Mammography Quality Standards	09/17/2002
Softchrome, Inc.	Listing Color Additives Exempt from Certification/Lacks Premarket Application/Adulterated/Misbra nded	09/26/2002
Riverside Medical Clinic, Inc.	Mammography Quality Standards	11/06/2002
Navajo Manufacturing Company, Inc.	CGMP in Manufacturing, Processing, Packing or Holding/CGMP for Finished Pharmaceuticals/Adulterated	12/02/2002
Medical Diagnostic Centre (Southside)	Mammography Quality Standards	12/03/2002

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Walk, William M.	Edible Tissue/Adulterated	12/06/2002
Serv-A-Pure Company	Quality System Regulation/Water Purification Systems/Adulterated	12/10/2002
Superior Uniform Group, Inc.	QSR/Lack Premarket Approval/Registration Listing/Adulterated/Misbranded	12/10/2002
Metropolitan Hospital Centre	Mammography Quality Standards	12/11/2002
VISX Inc	Premarket Approval/Misbranded/Adulterate d	12/11/2002
Land O'Lakes	Extra label Drug Use in Animals/Adulterated	12/12/2002
Primary Care Plus	Mammography Quality Standards	12/12/2002
Southern Herb Acquisition Co., LLC	New Drug/Misbranded	12/12/2002
VBM Medizintechnik GMBH	Quality System Regulation/Adulterated	12/13/2002
Minneapolis Radiology Associates, Ltd.	Mammography Quality Standards	12/17/2002
Paul Ramer Construction	New Drug/Adulterated	12/17/2002
Vet Pharm, Inc.	Extra label Drug Use in Animals/Adulterated	12/18/2002
Southwest Pharmacy / DBA Anchor	CGMP/Oxygen Compressed/Adulterated	12/19/2002
McAnally Enterprises LLC	CGMP for Licensed Medicated Feeds/Adulterated	12/20/2002
Wallach Surgical Devices, Inc.	CGMP for Finished Pharmaceuticals/CGMP in Manufacturing, Processing, Packing, or Holding/Adulterated	12/20/2002
William M. Vargulick Dairy Farm	Illegal Drug Residue/Adulterated	12/24/2002
Searle, Ltd.	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	12/27/2002
Reyncrest Farms, Inc.	Extra label Drug Use in Animals/Adulterated	12/30/2002
Vukman, Gerald R., D.V.M.	Illegal Tissue Residue/Extra label Drug Use in Animals/Adulterated	12/30/2002
1-Supplements.net	Dietary Supplement/Labeling/Misbranded	02/28/2003
Crown Laboratories, Inc.	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	02/28/2003
Alvieira Dairy	Illegal Drug Tissue Residue/Adulterated	03/14/2003
Baltimore Imaging Centres	Mammography Quality Standards	03/20/2003
Hoffman-La Roche Inc	Misleading Promotional Materials	05/29/2003
Criado, Frank J. M.D.	Clinical Investigator	06/19/2003
Astro Instrumentation LLC	Quality System Regulation/Adulterated	08/21/2003
Applied Laboratories, Inc.	Quality System Regulation/Adulterated	11/19/2003
American Medical Devices, Inc.	Quality System Regulation	11/24/2003

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Dairyland Milk Company	Illegal Drug Residue/Adulterated	12/04/2003
Caldwell, Stephen H., M.D.	Clinical Investigator	12/11/2003
Absolute Packaging Inc	CGMP for Drugs/Manufacture, Processing, Packing, Holding/Adulterated	12/15/2003
Central Missouri Agri-Service LLC	Medicated Feeds/Adulterated	12/15/2003
Joharra Dairy Farms	Illegal Drug Residue Animal Tissue/Adulterated	12/17/2003
Joe M. Simoes Family Dairy	Illegal Drug Residue in Animal Tissue/Extralabel Drug Use/Adulterated	12/18/2003
Custom Compounding Centres	Pharmacy Compounding/GMP for Finished Pharmaceuticals	12/23/2003
Eldon Biologicals A/S	CGMP Requirements of the Quality System Regulations/Adulterated	12/23/2003
H.B. Williams, Inc.	Illegal Drug Residue/Adulterated	12/23/2003
IND Diagnostic, Inc.	CGMP Requirements of the Quality System Regulations/Adulterated	12/23/2003
Kos Pharmaceuticals, Inc.	Good Manufacturing Processing, Packing, Holding/Finished Pharmaceuticals/Adulterated	12/29/2003
Aqua Micron LLC	CGMP/Finished Pharmaceuticals/Adulterated	12/31/2003
Shiro and Associates	FD&C Yellow No. 5/Undeclared Color Additive/Adulterated/Misbrande d	01/30/2003
Skaggs, David, M.D.	Institutional Review Board	02/14/2003
Mary's Malasadas, Inc.	Color Additive Undeclared/Misbranded	03/18/2003
Kral X-Ray, Inc	Performance Standard for Ionizing Radiation Emitting Products	12/03/2003
Medron, Inc.	Quality System Reguation/Adulterated	12/03/2003
Odyssey Medical Inc.	Quality System Regulation for Medical Devices/Adulterated	12/04/2003
Sun Valley Jerseys	Illegal Drug Residue Animal Tissue/Extralabel Use/Adulterated	12/04/2003
Western Missouri Medical Centre	Blood Bank/GMP for Blood & Blood Components	12/08/2003
Southside Community Hospital	Blood & Blood Products/Adulterated	12/09/2003
New York Eye & Ear Infirmary	Institutional Review Board	12/11/2003
Smith Sterling Dental Laboratory, Inc.	Quality System Regulation/Adulterated	12/11/2003
Nutralife Laboratories	New Drug/Nutrition Labeling Dietary Supplements/Misbranded	12/16/2003
Schell's Pine Grove Dairy	Illegal Drug Residue in Animal Tissue/Extralabel Drug Use/Adulterated	12/18/2003
Prescript Pharmaceuticals, Inc.	CGMP for Drugs/Manufacture, Processing, Packing, Holding/Adulterated	12/22/2003
Staar Surgical Company	Current Good Manufacturing Practice Requirements for Medical Devices/Quality System Regulation	12/22/2003
Rusk County Memorial Hospital	GMP for Blood & Blood Components/Adulterated	12/23/2003

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Turner County Dairy, LLP	Illegal Drug Residue in Animal Tissue/Extralabel Drug Use/Adulterated	12/23/2003
Lordex Inc	Current Good Manufacturing Practice Requirements for Medical Devices/Quality System Regulation	12/29/2003
Orleans Poverty Hill Farm	Illegal Drug Residue in Animal Tissue/Extralabel Drug Use/Adulterated	12/29/2003
TJ Candy Corporation	Import/Lacks	12/29/2003
Xttrium Laboratories, Inc.	Post-marketing Reporting of Adverse Drug Experience	12/30/2003
Acuderm Inc	QSR for Medical Devices/Medical Device Reporting/Adulterated	01/08/2004
Electro Therapeutic Devices, Inc.	QSR for Medical Devices/Medical Device Reporting/Misbranded/Adulterated	04/05/2004
American Sports Nutrition	Unapproved New Drug/Adulterated	06/24/2004
Higher Power, Inc.	Unapproved New Drug/Adulterated	06/25/2004
Affordable Supplements	Unapproved New Drug/Adulterated	06/28/2004
Amstutz, Harlan C., M.D.	Clinical Investigator	07/19/2004
E. Franco & Co.	Labeling/Adulterated/Misbrande d	09/14/2004
3TP LLC	Premarket Approval/Misbranded	10/05/2004
Alveolus, Inc.	CGMP Requirements for Medical Devices/Quality System Regulations/Adulterated	11/10/2004
Colloids for Life, LLC	Labeling/Promotional Claims False & Misleading/New Drug	12/02/2004
Chiron Corporation	CGMP for Finished Pharmaceuticals/CGMP in Manufacturing, Processing, Packing, or Holding/ Adulterated	12/09/2004
Danlee Medical Products, Inc.	Quality System Regulation for Medical Devices/Adulterated/Misbranded	12/09/2004
Collins, Tyrone J., M.D.	Clinical Investigator	12/10/2004
Jean's Greens	Labeling/Promotional Claims False & Misleading/Misbranded	12/10/2004
Can-x Products	Lacks New Drug Approval /Misbranded	12/14/2004
Kling, Mitchel A., M.D.	Clinical Investigator	12/15/2004
Borawski, Lawrence A.	Labeling/False & Misleading Claims/Misbranded	12/21/2004
Denver Tofu Company, Inc.	Labeling/Promotional Claims False & Misleading/Misbranded	12/21/2004
Advanced Sterilization Products	Good Manufacturing Practice Requirement for the Quality System Regulation/Adulterated	12/22/2004
Cyberonics, Inc.	CGMP Requirement of the Quality System Regulation for Medical Devices/Adulterated	12/22/2004
Huebner Farm	Extralabel Drug Use in Animals/Adulterated	12/22/2004
Best Veterinary Solutions, Inc.	Labeling/Adulterated	12/23/2004

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
BioHorizons Implant Systems, Inc.	CGMP Requirements for Medical Devices/Quality System Regulations/Adulterated	12/27/2004
Pyng Medical Corporation	Medical Device Reporting/Misbranded	04/09/2004
Old Hickory Medicine Company, Inc.	Current Good Manufacturing Practice for Finished Pharmaceuticals/Misbranded/Adu lterated	04/21/2004
Sunder Biomedical Tech Co.	Quality System Regulation/Adulterated	04/23/2004
Our Lady of the Lake Hospital, Inc.	GMP for Blood & Blood Components/Adulterated	05/07/2004
Scientific Botanicals Co., Inc.	Dietary Supplement Regulations/Misbranded	05/21/2004
Prime Nutrition	Unapproved New Drug/Adulterated	06/28/2004
SmartBodyz Nutrition	Unapproved New Drug/Adulterated	06/28/2004
RPM Total Vitality	Unapproved New Drug/Adulterated	06/29/2004
World Class Nutrition	Unapproved New Drug/Adulterated	06/29/2004
OST Medical, Inc.	Lacks Premarket Approval/Adulterated/Misbrande d	07/19/2004
Ortho-McNeil Pharmaceutical, Inc.	Promotional Claims/False & Misleading	09/15/2004
Lifecore Biomedical, Inc.	Medical Device Reporting/Misbranded	10/08/2004
Pharmachem Laboratories, Inc.	Dietary Supplement/Labeling/False & Misleading Claims/Misbranded	11/19/2004
Purest Colloids, Inc.	Promotional Claims/False & Misleading/Misbranded	12/02/2004
Lex, Inc.	CGMP for Drugs/Manufacture, Processing, Packing, Holding/Adulterated/Misbranded	12/07/2004
Veterinary Enterprises of Tomorrow, Inc.	Active Pharmaceutical Ingredient/Adulterated	12/08/2004
Lincare, Inc.	Pharmacy Compounding/Misbranded	12/09/2004
Sunshine Mills, Inc.	Animal Proteins Prohibited in Ruminant Feed/Misbranded	12/09/2004
The Sanapac Co., Inc.	Dietary Supplement/Promotional Claims False & Misleading/Adulterated/Misbran ded	12/10/2004
Nolan Livestock	Extralabel Drug Use in Animals/Adulterated	12/15/2004
Precision Piece Parts, Inc.	CGMP Requirement of the Quality System Regulation for Medical Devices/Adulterated	12/15/2004
Prime Veal Feed, Ltd.	Extralabel Drug Use in Animals/Misbranded	12/15/2004
White Egret Farm	Control of Communicable Disease	12/15/2004
Red River Pharmacy Services, Inc.	Active Pharmaceutical Ingredient/Adulterated	12/17/2004
U R Farms	Extralabel Drug Use in Animals/Adulterated	12/17/2004
Respi Care Group of Puerto Rico	Unapproved New Drug/Adulterated/Misbranded	12/20/2004
N64 Neutraceutica	Labeling/False & Misleading Claims/Misbranded	12/21/2004
Nelson Laboratories, Inc.	Good Laboratory Practices	12/21/2004

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Medefil, Inc.	Quality System Regulation for Medical Devices/Adulterated	12/29/2004
Basic Research, LLC	Labeling/Promotional Claims False & Misleading/New Drug	01/14/2005
GlaxoSmithKline	Labeling/Promotional Claims False & Misleading/Misbranded	01/31/2005
Amgen Inc.	Labeling/Promotional Claims False & Misleading/Misbranded	02/18/2005
Animas Corporation	CGMP Requirements for Medical Devices/Quality System Regulations/Adulterated	02/24/2005
Assistive Technology, Inc.	Quality System Regulation/Adulterated/Misbran ded	03/21/2005
Bar-B-R Farm	Extralabel Drug Use in Animals/Adulterated	04/15/2005
Boston Scientific Corporation	Current Good Manufacturing Practice Regulation/Adulterated	05/18/2005
Allergan, Inc.	Labeling/Promotional Claims False & Misleading/Misbranded	09/06/2005
Houchin Blood Services	Current Good Manufacturing Practices Regulations for Blood & Blood Components/Adulterated	09/21/2005
BioHarmonics Research and Consulting	Lacks Premarket Approval Application Misbranded	10/14/2005
Amon Orchards	Labeling and Promotional Violations	10/17/2005
Corin USA	Lacks Premarket Approval Application Adulterated	11/22/2005
G&S Instrument Company	CGMP Requirements for Medical Devices/Quality System Regulations/Adulterated	11/22/2005
BODeSTORE.com	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/29/2005
Chozyn, LLC	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/29/2005
Healthworks 2000	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/30/2005
Iceland Health, Inc	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/30/2005
Carrington Laboratories, Inc	Insanitary Conditions/Adulterated/Misbran ded	12/05/2005
IIT Research Institute	GLP Regulations	12/05/2005
Ise Newberry, Inc.	Control of Communicable Diseases/Adulterated	12/13/2005
Baltimore City Health Department	Institutional Review Board (IRB)	12/15/2005
Clarkdale Fruit Farms Inc.	Juice HACCP	12/21/2005
Dore, David D., M.D.	Clinical Investigator	12/21/2005
Gold Eagle Cooperative	Animal Proteins Prohibited in Ruminant Feed/Misbranded	12/21/2005
Guidant Corporation	CGMP for Medical Devices/QS/Adulterated	12/22/2005
Edgar Martin Dairy	Illegal Drug Residue /Adulterated	12/29/2005
Nichols, Trent M.D.	Clinical Investigator	02/24/2005
Rapid Recovery Health Services Inc.	Lacks Premarket Approval/Adulterated/Misbrande d	03/07/2005

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
RealPure Beverage Group, LLC	Juice HACCP/Adulterated	03/10/2005
Lydall, Inc.	CGMP/Adulterated	05/27/2005
Panbio, Inc.	Lacks Premarket Approval Application/Misbranded	10/05/2005
Professional Hair Institute, Inc.	Lacks Approved New Drug Application/Misbranded	10/13/2005
Weese-Mayer, Debra E., M.D.	Clinical Investigator	10/14/2005
Normed Medizin-Technik GmbH	CGMP for Medical Devices/QSR/Adulterated/Misbra nded	11/18/2005
Revival Animal Health, Inc.	Promotional Claims False & Misleading/Adulterated/Misbran ded	11/21/2005
Kramer Laboratories Inc.	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/22/2005
Milbank Mills Inc	CGMP for Medicated Feeds/Adulterated	11/22/2005
NativeRemedies.com	Promotional Claims False & Misleading/Misbranded	11/22/2005
PRB Pharmaceuticals	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/23/2005
PolyCil Health Inc	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/23/2005
The Electrode Store, Inc.	Current Good Manufacturing Practices Requirements for Medical Devices/Adulterated	11/23/2005
Sacred Mountain Management Inc	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/28/2005
Spectrum Chemicals & Laboratory Products	Active Pharmaceutical Ingredients/Misbranded	11/28/2005
Vitacost.com	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	11/30/2005
YSIS, Incorporated	Current Good Manufacturing Practice for Medical Devices/Adulterated/Misbranded	11/30/2005
Samson Medical Technologies, Inc.	Labeling/New Drug/Misbranded	12/01/2005
Restorative Products, Inc.	Medical Device Reporting Regulations/Quality System Regulation/Adulterated/Misbranded	12/02/2005
Rite-Dent Manufacturing Corp.	Medical Device Reporting Regulations/Quality System Regulation/Adulterated/Misbranded	12/02/2005
WaJa Farms, Inc	New Animal Drugs/Extra label Drug Use in Animals/Adulterated/Misbranded	12/06/2005
LifeScan, Inc.	CGMP requirements for the Quality System Regulation/Medical Device Reporting/Adulterated/Misbrand ed	12/07/2005
Michael Mumbulo	New Animal Drugs/Extra label Drug Use in Animals/Adulterated/Misbranded	12/08/2005
MCT Medical Products	Current Good Manufacturing Practice for Medical Devices/Adulterated	12/09/2005
Milk Flow Dairy	Illegal Drug Residue /Adulterated	12/09/2005
Morrell Farm	New Animal Drugs/Extra label Drug Use in Animals/Adulterated/Misbranded	12/12/2005
Shelhigh, Inc.	CGMP Requirement for Medical Devices/Lacks Premarket Approval Application/Adulterated	12/14/2005
Seecor, Inc.	CGMP Requirements for Medical Devices/Quality System Regulations/Adulterated	12/16/2005

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Tidman, Raymond E., M.D.	Clinical Investigator	12/19/2005
Lawsons Farm	Illegal Drug Residue /Adulterated	12/21/2005
Paradise Farm Corporation	Juice HACCP/Adulterated	12/22/2005
Siouxland Community Blood Bank	Current Good Manufacturing Practices Regulations for Blood & Blood Components/Adulterated	12/23/2005
Wellness Resources, Inc.	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	12/27/2005
Cache Commodities, Inc.	CGMP Requirements For Medicated Feeds/Adulterated	01/13/2006
Del-Immune V	Labeling/Promotional Claims False & Misleading/New Drug	01/26/2006
Community Blood Centre of Greater Kansas	Current Good Manufacturing Practices Regulations for Blood & Blood Components/Adulterated	03/09/2006
Chocolate Cottage, Inc.	Labeling/Misbranded	04/25/2006
Bioesl Packing Company, Inc.	Lacks New Animal Drug Application/Adulterated	06/14/2006
Guilin Pharmaceutical Corporation, Limited	Current Good Manufacturing Practices/Active Pharmaceuticals Ingredient/Adulterated	06/23/2006
Hohmann, Elizabeth L., M.D.	Clinical Investigator	07/10/2006
Concord Laboratories, Inc	Current Good Manufacturing Practices for Finished Pharmaceuticals/Adulterated	07/11/2006
Boulder Natural Labs, LLC	Labeling/Promotional Claims False & Misleading Claims/New Drug/Misbranded	07/19/2006
Black Henna Ink, Inc.	Color Additive/Adulterated	08/14/2006
ALK-Abello, Inc.	Promotional Claims False & Misleading/Misbranded	09/06/2006
Banner Pharmacaps, Inc.	Drug Manufacturing Operations/CGMP deviations	09/28/2006
Benchmark Medical, Inc.	Labeling/OTC Human Use/New Drug/Misbranded	11/03/2006
Conti, Ralph M., M.D.	Clinical Investigator	11/22/2006
Craftmatic Organization, Inc.	CGMP Requirements for Medical Devices/Quality System Regulation	11/27/2006
Health Dimensions, Inc.	Pharmacy Compounding/New Drug/Misbranded	11/27/2006
HemoSense, Inc.	CGMP for Medical Devices/QS/Adulterated	11/29/2006
Customs Scripts Pharmacy	Pharmacy Compounding/New Drug/Misbranded	12/04/2006
Feenstra, John	Extra label Drug Use/Adulterated	12/04/2006
Hal's Compounding Pharmacy, Inc	Pharmacy Compounding/New Drug/Misbranded	12/04/2006
INCELL Corporation, LLC	GLP/Bioresearch Monitoring Program/Investigational drugs	12/06/2006
Biotecx Laboratories, Inc.	CGMP/QSR/Medical Device Reporting/Adulterated	12/08/2006
Ganeden Biotech Inc.	Misbranded/Labeling/Unauthorised Health Claims	12/08/2006
GSCM Ventures Inc.	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	12/12/2006

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Biora AB	CGMP/QSR/Medical Devices/Adulterated	12/18/2006
Colusa Regional Medical Centre	Mammography Quality Standards	12/21/2006
Abraxis Bioscience, Inc.	Deviations from CGMP for Finished Pharmaceuticals	12/26/2006
Applied Water Engineering, Inc.	CGMP/QSR/Medical Device Reporting/Adulterated	12/27/2006
Southern Meds Joint Venture, LLC	CGMP for Finished Pharmaceuticals/Misbranded/Adulterated	02/15/2006
PrimaPharm Inc	Labeling/False & Misleading Claims/Misbranded	06/29/2006
Nardi, Claudia	Lacks Premarket Approval Application	11/21/2006
Natren Inc.	Labeling/Promotional Claims False & Misleading/Misbranded/Adulterated	11/21/2006
Trionix Research Laboratory, Inc.	CGMP Requirements of the Quality System Regulations/Adulterated	11/21/2006
Meyer Farm	Illegal Drug Residue /Adulterated	11/22/2006
Nestle S.A.	Infant Formula/Labeling/Misbranded	11/27/2006
Skytron	Current Good Manufacturing Requirements for Medical Devices/Adulterated	11/29/2006
Steris Corporation	Medical Device Reporting (MDR) Regulation Misbranded/Adulterated	11/29/2006
Spoonamore Drug Co., Inc.	Pharmacy Compounding/New Drug/Adulterated/Misbranded	12/01/2006
Lamb Farms, Inc.	Extralabel Drug Use/Adulterated	12/04/2006
New England Compounding Centre	Pharmacy Compounding/New Drug/Misbranded	12/04/2006
Ritch, Robert M.D.	Clinical Investigator	12/04/2006
Ritch, Robert MD	Clinical Investigator	12/04/2006
Triangle Compounding Pharmacy	Pharmacy Compounding/New Drug/Misbranded	12/04/2006
University Pharmacy	Pharmacy Compounding/New Drug/Misbranded	12/04/2006
MRL Inc.	CGMP For Medical Device Report/Adulterated	12/08/2006
Nasiff Associates, Inc.	CGMP/Adulterated	12/08/2006
Quick-Fill Mobile Oxygen, Inc.	CGMP for Finished Pharmaceuticals/Adulterated	12/08/2006
Ratcliff, David C, M.D.	Institutional Review Board (IRB)	12/08/2006
Schumacher's	Extralabel Drug Use/Adulterated	12/08/2006
Viasys Healthcare	CGMP/Requirements for Medical Devices/QSR/Adulterated	12/12/2006
Sharma, Baljit K., M.D.	Clinical Investigator	12/20/2006
TMJ Implants, Inc.	Lacks Premarket Approval Application/Adulterated/Misbranded	12/20/2006
Williams Farms Inc.	Animals for sale for slaughter/Adulterated	12/20/2006

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Palmer Farms	Animals for sale for slaughter/Adulterated	12/21/2006
Lee Laboratories, Inc.	CGMP Requirements of the Quality System Regulations/Adulterated	12/26/2006
Rickland Farms, LLC	Animals for sale for slaughter/Adulterated	12/27/2006
Advanced Reproductive Laboratory	Deviations/CFR/Regulations for Human Cells, Tissues & Cellular Products	01/09/2007
Forest Grove Dairy	PHS Act/Violation	02/08/2007
Beehive Botanicals, Inc.	Dietary Supplements	03/02/2007
Abbott Laboratories, Inc.	QSR/Medical Devices/Adulterated/Misbranded	03/13/2007
Fusion Brands International SRL	Drug Products/Labeling	04/24/2007
Cytosol Laboratories, Inc.	CGMP/Deviations/Adulterated	10/30/2007
International Technidyne Corporation	CGMP/QSR/Medical Device Reporting/Adulterated	10/30/2007
Fisheries Research Laboratory- SIU-C	GLP/Bioresearch Monitoring Program	11/02/2007
Amerifit Brands, Inc	CGMP for Drugs/Manufacture, Processing, Packing, Holding/Adulterated/Misbranded	11/07/2007
Ben Venue Laboratories, Inc.	CGMP/Deviations/Adulterated	11/16/2007
Custom Assemblies, Inc.	CGMP/QSR/Medical Devices/Adulterated/Misbranded	11/16/2007
GE Healthcare/General Electric Company	Devices/X-ray Equipment	11/16/2007
GlaxoSmithKline	Drug Labeling/Promotional Claims/Misbranded	11/21/2007
E-Med Future, Inc.	Devices/Quality System Regulation	11/29/2007
Avicenna Laser Technology Inc	CGMP/QSR/Manufacture/Packing/Storage/Installation/Adulterated	11/30/2007
G. Dundas Company Inc	CGMP/QSR/Medical Devices/Adulterated/Misbranded	12/13/2007
Abbott Vascular, Inc.	Medical Devices/Adulterated/Misbranded	12/19/2007
Schering-Plough Animal Health Corporation	Promotional Claims/False & Misleading/Misbranded	07/11/2007
Leiner Health Products, LLC	CGMP for Finished Pharmaceuticals/Deviations/Adulterated	08/28/2007
SCM True Air Technologies LLC	CGMP/QSR/Medical Devices/Adulterated	09/24/2007
Northeast General Pharmaceutical Factory	Current Good Manufacturing Practice Regulation/Adulterated	10/31/2007
Troy Innovative Instruments, Inc.	CGMP for Medical Devices/QS/Adulterated	11/01/2007
Nurse Assist, Inc.	CGMP/QSR/Medical Devices/Adulterated	11/09/2007
Venosan North America	Medical Device Reporting	11/21/2007
Precision Biometrics, Inc.	Device/Lacks Premarket Approval Application/Adulterated/Misbranded	11/28/2007
Stryker Orthopaedics Corp.	CGMP/QSR/Manufacture/Packing/Storage/Installation/Adulterate d	11/28/2007

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Pacific Consolidated Industries LLC	CGMP For Manufacturing, Packing, Storage or Installation/Adulterated	12/03/2007
Wheatley, Susan J., M.D.	Clinical Investigator	12/05/2007
Polychrome Medical, Inc	CGMP/QSR/Manufacture/Packing/Storage/Installation/Adulterate d	12/07/2007
Spinal, USA	CGMP For Manufacturing, Packing, Storage or Installation/Adulterated/Misbranded	12/07/2007
Wyeth Pharmaceuticals Inc.	DDMAC/Promotional Claims False & Misleading/Misbranded	12/10/2007
Morton Grove Pharmaceuticals, Inc.	DDMAC/Promotional Claims False & Misleading/Misbranded	12/13/2007
Siemens Medical Solutions	Premarket Approval/Misbranded/Adulterate d	12/17/2007
P-Ryton Corporation	CGMP/QSR/Manufacture/Packing/Storage/Installation/Adulterate d	12/18/2007
Universal Enterprises Inc.	Interstate Conveyance Sanitation Regulations/Provisional	12/20/2007
Medical Device Resource Corporation	Premarket Approval/Misbranded/Adulterate d	12/21/2007
Northwest Medical Physics Equipment, Inc.	CGMP/QSR/Manufacture/Packing/Storage/Installation/Adulterate d	12/21/2007
Adams, Mark M.D.	Investigational Device Exemptions	01/23/2008
Atlantic Southeast Airlines	Interstate Conveyance Sanitation Regulations/Provisional	05/02/2008
Allez Spine, LLC	CGMP/QSR/Medical Devices/Adulterated	08/08/2008
Caraco Pharmaceutical Laboratories, Ltd	CGMP Deviations	10/31/2008
Deltex Pharmaceuticals Inc	CGMP/OTC Drug Products/Adulterated	10/31/2008
Innovative Neurotronic, Inc.	CGMP/QSR/Medical Devices/Adulterated	11/04/2008
American Association of Acupuncture	Institutional Review Board (IRB)	11/13/2008
Eagle Parts and Products	CGMP/QSR/Medical Devices/Adulterated	11/14/2008
Jeffrey Steinberg MD Inc.	Human Cells, Tissues & Cellular Products	11/18/2008
Goosefoot Acres, Inc.	Labeling/False & Misleading Claims/New Drug/Misbranded	11/19/2008
Contract Medical Manufacturing	CGMP/QSR/Medical Devices/Adulterated	11/20/2008
Actelion Pharmaceuticals US, Inc.	DDMAC/Promotional Claims False & Misleading/Misbranded	11/24/2008
Kids Company Ltd Yugengaisha Kids	Device/Lacks Approved Premarket Application/Adulterated/Misbranded	12/03/2008
Carib Supply of St. Croix, Inc.	CGMP Manufacture, Processing, Packing or Holding of Human Drugs/Adulterated	12/04/2008
Haemonetics Corporation	CGMP/QSR/Medical Devices/Adulterated	12/04/2008
Craig General Hospital	Deviation from Good Manufacturing Practice	12/15/2008
Civic Centre Pharmacy	New Drug, Unapproved	12/16/2008
Columbia Presbyterian Medical Centre	Deviation/Adulterated	12/22/2008

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
I-Flow Corporation	CGMP/QSR/Medical Devices/Adulterated	12/22/2008
Dongkuk Techco Rubber Ind. Sdn Bhd	CGMP/QSR/Adulterated	12/30/2008
Pacifica Pharmacy	New Drug/False Misleading/Labeling/Misbranded	01/07/2008
Reed's Compounding Pharmacy	New Drug/False Misleading/Labeling/Misbranded	01/07/2008
Village Compounding Pharmacy	New Drug/False Misleading/Labeling/Misbranded	01/07/2008
Michael S. Miller, D.O.	Investigational Device Exemptions (Clinical Investigator)	02/12/2008
Midland Pharmaceutical LLC	CGMP for Finished Pharmaceutical/Adulterated	03/03/2008
Merck & Company, Inc.	CGMP Manufacture of Licensed Biological Vaccine Products/Bulk Drug Substances/Components	04/28/2008
Steris Corporation	Premarket Approval/Adulterated	05/15/2008
Safer Sleep, LLC	CGMP/QSR/Medical Devices/Adulterated	05/27/2008
Laboratory Corporation of America	Device Lacks Marketing Clearance Approval/Adulterated/Misbranded	09/29/2008
PrimaPharm Inc.	Unapproved New Drug/Adulterated/Misbranded	10/31/2008
Spacelabs Healthcare Incorporated	CGMP/QSR/Medical Devices/Adulterated	11/03/2008
Steven's Pharmacy	New Drug/Labeling/False & Misleading Claims	11/12/2008
Lam, Fred M.D.	Institutional Review Board (IRB)	11/13/2008
Rezai, Ali R, M.D	Clinical Investigator	11/13/2008
Saudek, Christopher D. MD	Clinical Investigator	11/13/2008
Saudek, Christopher D., M.D.	Clinical Investigator	11/13/2008
Shinogi USA, Inc.	DDMAC/Promotional Claims False & Misleading/Misbranded	11/14/2008
RHG & Company, Inc., dba Vital Nutrients	New Drug/Labeling/False & Misleading Claims/Misbranded	11/18/2008
Surgical Implant Generation Network	CGMP for Medical Devices/QS/Adulterated	11/18/2008
PDS Manufacturing, Inc.	CGMP/QSR/Medical Devices/Adulterated	11/24/2008
Perich, Larry M	Clinical Investigator	12/01/2008
Vital Signs, Inc.	Premarket Approval/Misbranded/Adulterate d	12/01/2008
Pneumex, Incorporated	Premarket Approval/Misbranded/Adulterate d	12/05/2008
RGI Medical Manufacturing, Inc.	CGMP/QSR/Manufacture/Packing/S torage/Installation/Adulterate d	12/08/2008
Savec Health Systems	Premarket Approval/Misbranded/Adulterate d	12/10/2008
Virbac Inc.	CGMP For Manufacturing, Packing, Storage or Installation/Adulterated/Misbr anded	12/10/2008

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Biomed Devices Corporation (AKA: Medlens Innovations, Inc.)	CGMP/Quality System/Adulterated	02/02/2009
BestLife International, Inc.	New Drug/Labeling/False & Misleading Claims	02/04/2009
American Mammographics Inc	CGMP/QSR/Medical Devices/Adulterated	03/16/2009
Cargill Flavor Systems Puerto Rico Inc.	Juice HACCP/Adulterated	03/30/2009
Amrex-Zetron, Inc.	CGMP/QSR/Medical Devices/Adulterated	04/14/2009
Amrita Aromatherapy, Inc	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	05/28/2009
Americell-labs.com VMG Global Inc	Dietary Supplements/Adulterated/Misbra nded	07/27/2009
ANIP Acquisition Company	CGMP for Drugs/Manufacture, Processing, Packing, Holding/Adulterated/Misbranded	08/21/2009
Customed, Inc 9/11/09	CGMP/QSR/Medical Devices/Adulterated	09/11/2009
East Wind Community, Inc	Manufacturing Facility/Adulterated/Insanitar y conditions	10/05/2009
Han, Jeffrey	Tobacco Products/Adulterated	11/02/2009
Chavez, Inc.	Tobacco Products/Adulterated/Misbrande d	11/03/2009
Durango Smoke Shop, Inc.	Tobacco Products/Adulterated/Misbrande d	11/03/2009
Gibson Laboratories Inc	CGMP for Medical Devices/QS/Adulterated	11/03/2009
H.J. Bailey Co.	Tobacco Products/Adulterated	11/03/2009
Centra Health Inc Irb	Investigational Device Exemptions	11/20/2009
Buettner, Craig M., MD	Clinical Investigator	11/24/2009
Gazda, Thomas M.D.	Clinical Investigator	11/24/2009
GDMI, Inc	CGMP for Finished Pharmaceuticals/Adulterated/Mi sbranded	11/27/2009
ICON Clinical Research, Inc.	Bioresearch Monitoring Program	11/27/2009
Aluwe, LLC	Unapproved New Drug/Misbranded	11/30/2009
Aregenius Worldwide LLC	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	11/30/2009
Kenshin Trading Corporation	Premarket Approval/Misbranded/Adulterate d	12/08/2009
Freeman Manufacturing Company	Medical Devices/Adulterated/Misbranded	12/09/2009
Heartsine Technologies Inc	Device/Misbranded	12/10/2009
Interacoustics A/S	CGMP/QSR/Adulterated/Misbrande d	12/10/2009
Indonesia Clove Cigarettes	Tobacco Products/Adulterated/Misbrande d	12/14/2009
Florida Atlantic University IRB	Institutional Review Board (IRB)	12/17/2009

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Balchem Corporation	Current Good Manufacturing Practice Regulation for Finished Pharmaceuticals	12/22/2009
Arteriocyte Medical Systems Inc	Device/Lacks Approved Premarket Application/Adulterated/Misbra nded	12/23/2009
Genetics & IVF Institute IRB	Institutional Review Board (IRB)	12/23/2009
Branan Medical Corp. Inc.	Premarket Approval/Misbranded/Adulterate d	12/28/2009
Crothall Healthcare, Inc.	CGMP/QSR/Medical Devices/Adulterated/Misbranded	12/29/2009
Prodesse, Inc	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	05/11/2009
Nozin LLC	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	05/22/2009
Matrixx Initiatives, Inc. AKA Zicam LLC	OTC Drug Labeling/New Drug/Misbranded	06/16/2009
Mgs Soapopular	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	07/15/2009
Q-Based Solutions	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	07/22/2009
Platinum Strategies, Inc.	Labeling/Promotional Claims False & Misleading/New Drug/Misbranded	09/23/2009
Tampa Peanut Distributors	CGMP for Deviations/Adulterated	10/08/2009
www.novalistintegra.com	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	10/08/2009
Li Ning	Tobacco Products/Adulterated/Misbrande d	11/02/2009
Smoke Shop USA Ltd	Tobacco Products/Adulterated/Misbrande d	11/02/2009
Texas Wholesale	Tobacco Products/Adulterated/Misbrande d	11/03/2009
Silver Soft for Skin	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	11/04/2009
www.bestswinefluvaccine.com	Unapproved/Uncleared/Unauthori zed Products Related to the H1N1 Flu Virus	11/30/2009
Tetracore, Inc.	CGMP/QSR/Medical Devices/Adulterated	12/01/2009
www.secretsofbetterhealth.com	Unapproved/Unauthorised Products Related to the H1N1 Flu Virus	12/01/2009
P.M.T. Corp	CGMP/QSR/Medical Devices/Adulterated	12/03/2009
Ward, John A., M.D.	Clinical Investigator	12/03/2009
Z-Medica, LLC	CGMP/QSR/Medical Devices/Adulterated	12/03/2009
MyKretek.com	Flavored cigarettes/Misbranded/Adulterated	12/07/2009
M W Laboratories Inc	OTC Drug Labeling/New Drug/Misbranded	12/09/2009
www.sharco.tv	Biological Products Standards	12/09/2009
LSG SkyChefs DEN 235	PHS Act & Control of Communicable Diseases & Interstate Conveyance Sanitation Violations	12/10/2009
Teva Parenterals Medicines, Inc.	CGMP for Finished Pharmaceuticals/Adulterated	12/11/2009
Langit Bali	Tobacco Products/Adulterated/Misbranded	12/14/2009

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Micromed Technology, Inc	Medical Device Reporting/Misbranded	12/15/2009
Sibley Memorial Hospital	CGMP for Blood & Blood Products/Adulterated	12/15/2009
Ohm Laboratories, Inc.	CGMP for Finished Pharmaceuticals/Adulterated	12/21/2009
Victus, Inc.	Medical Device/CGMP Requirements of Quality System Regulation	12/21/2009
Micro Current Technology, Inc.	Device Lacks Marketing Clearance Approval/Adulterated/Misbranded	12/24/2009
Penumbra, Inc.	CGMP/QSR/Medical Devices/Adulterated/Misbranded	12/31/2009
Ewin Soft and Trade SRL	Tobacco Products/Adulterated/Misbranded	01/05/2010
Baxter Biosciences	CGMP Deviations	01/15/2010
Home Remedies Solutions	Premarket Approval/Misbranded/Adulterate d	02/17/2010
Actavis Elizabeth LLC	Labeling/Promotional Claims False & Misleading/Misbranded	02/18/2010
HMI Industries, Inc.	CGMP/QSR/Adulterated/Misbranded	02/23/2010
Karl Storz	CGMP/QSR/Medical Devices/Adulterated	02/23/2010
Centrix Pharmaceutical Inc	New Drug/Adulterated	02/24/2010
Guidewire Technologies, Inc.	CGMP/QSR/Medical Devices/Adulterated	02/26/2010
Edwards Lifesciences, LLC	Device/Misbranded	03/01/2010
Clearwater Products, LLC	Medical Devices/Adulterated/Misbranded	03/10/2010
ISTA Pharmaceuticals Inc	Labeling/Promotional Claims False & Misleading/Misbranded	03/10/2010
Advanced Sterilization Products	CGMP/QSR/Medical Devices/Adulterated	03/12/2010
BTL Industries, Inc.	Premarket Approval/Misbranded/Adulterate d	03/12/2010
Endogastric Solutions Inc	Medical Device Reporting (MDR) Regulation Misbranded/Adulterated	03/12/2010
Intervet International Gmbh	New Animal Drug Application	03/12/2010
Healthy Body Forero	New Drug/Labeling/False & Misleading Claims/Misbranded	03/15/2010
Amerilab Technologies, Inc	Labeling/New Drug/Misbranded	03/16/2010
Glenmark Pharmaceuticals Inc. 3/16/10	Unapproved New Drug/Misbranded	03/16/2010
Konec Inc. 3/16/10	Unapproved New Drug/Misbranded	03/16/2010
Chawla, Sant P., M.D.	Clinical Investigator	03/17/2010
James P. Johnston, CO,	Device/Misbranded,	03/17/2010
KHL Inc	Device/Misbranded	03/17/2010
3CPM Company Inc	CGMP/QSR/Medical Devices/Adulterated	03/25/2010

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Apotex Inc.	CGMP for Finished Pharmaceuticals/Adulterated	03/29/2010
IVF Phoenix	Human Cells, Tissues & Cellular Products	03/29/2010
Coats International Holdings, Inc	CGMP Manufacture, Processing, Packing or Holding/Adulterated	03/30/2010
Deitz, Robert, M.D.	Clinical Investigator	04/01/2010
7Seas LLC	Dietary Supplement Regulations/Misbranded	04/05/2010
All About You Medspa, LLC	Lipodissolve/False & Misleading Claims/Misbranded	04/05/2010
Innovative Directions in Health	Lipdissolve/False & Misleading Claims/Misbranded	04/05/2010
Aloha Medicinals Inc.	New Animal Drug/Labeling/Misbranded/Adulterated	04/06/2010
Bryant Ranch Prepack Inc.	New Drug/Labeling/Misbranded/Adulterated	04/08/2010
Children's Hospital Assoc.	CGMP for Blood & Blood Products/Adulterated	04/08/2010
E-holistic Health /Hanna Cooper	Unapproved/Unauthorised Products Related to the H1N1 Flu Virus	04/12/2010
Hospira, Inc.	CGMP for Finished Pharmaceuticals/Deviations/Adulterated	04/12/2010
GlaxoSmithKline	Labeling/Promotional Claims False & Misleading/Misbranded	04/19/2010
Brookwood Medical Centre	Institutional Review Board (IRB)	04/22/2010
Accurate Set Inc.	CGMP/QSR/Adulterated/Misbranded	04/26/2010
Ephraim McDowell Regional Medical Centre	Institutional Review Board (IRB)	04/26/2010
Darr Feedlot Inc	CGMP for Medicated Feeds/Adulterated	04/30/2010
Braintree Laboratories Inc	CGMP For Manufacturing, Processing, Packing, Storage & Holding/Adulterated	05/10/2010
Healthy World Distributing	Promotional Claims/Misbranded	05/11/2010
CMC Commodity Transport Inc.	Animal Feed/Adulterated with shredded tire chips	05/12/2010
Cogent Solutions Group LLC	New Drug/Labeling/Misbranded	05/12/2010
Endocare	CGMP for Medical Devices/Adulterated	05/17/2010
Hyperbaric for Life LLC	Medical Device Reporting Regulation/Misbranded	05/20/2010
AVEVA Drug Delivery Systems, Inc.	CGMP for Finished Pharmaceuticals/Adulterated	05/21/2010
Dexcom Inc	Medical Device Reporting/Misbranded	05/21/2010
Feel Good Natural Health	Unapproved/Unauthorised Products Related to the H1N1 Flu Virus	05/21/2010
K. C. Pharmaceuticals Inc.	CGMP/QSR/Medical Devices/Finished Pharmaceuticals/Adulterated	05/21/2010
Flexcin International, Inc.	New Drug/Labeling/False & Misleading Claims	05/25/2010
Encompass Group, LLC	Medical Device Reporting (MDR) Regulation Misbranded	06/02/2010

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Baxter Healthcare Corporation	Medical Device Reporting (MDR) Regulation/Adulterated	06/03/2010
Atlas Operations, Inc.	CGMP for Drugs/Manufacture, Processing, Packing, Holding/Adulterated	06/04/2010
Arizant Inc	CGMP/QSR/Medical Device Reporting/Misbranded	06/07/2010
Homeopathy For Health	Unapproved/Unauthorised Products Related to the H1N1 Flu Virus	06/08/2010
Adamis Pharmaceuticals	Unapproved New Drug/Misbranded	06/09/2010
Artegraft, Inc.	CGMP/QSR/Medical Devices/Adulterated	06/11/2010
Beckman Coulter Inc.	Premarket Approval/Misbranded	06/21/2010
Cornerstone Therapeutics, Inc.	False & Misleading Claims/Misbranded	06/22/2010
AMPAC Fine Chemicals, LLC	CGMP For Manufacturing, Processing, Packing, Storage & Holding/Adulterated	06/25/2010
Arasys Perfector Inc	Medical Device Reporting (MDR) Regulation Misbranded/Adulterated	06/28/2010
Hi-Tech Pharmacal Co., Inc.	CGMP for Finished Pharmaceuticals/Adulterated/Misbranded	06/28/2010
Abbott Diabetes Care, Inc.	CGMP for Medical Devices/QS/Adulterated	07/02/2010
Country Road Veterinary Services LLC	New Animal Drug/Adulterated/Labeling/Misbranded	07/06/2010
Jazz Pharmaceuticals	Promotional Claims False & Misleading/Misbranded	07/06/2010
Florida Bottling, Inc.	New Drug/Drug Labeling/Misbranded	07/08/2010
AXCAN Scandipharm Inc	DDMAC/Promotional Claims False & Misleading/Misbranded	07/13/2010
Cincinnati Sub-Zero Products Inc	CGMP For Manufacturing, Processing, Packing, Storage & Holding/Adulterated	07/13/2010
ARJ Medical, Inc.	CGMP for Medical Devices/QS/Adulterated	07/16/2010
Independent Review Consulting, Inc	Institutional Review Board (IRB)	07/19/2010
Haw Par Healthcare Limited	CGMP for Finished Pharmaceuticals/OTC Drug Manufacturing/Adulterated/Misbranded	07/20/2010
Biomet, Inc.	Premarket Approval/Misbranded/Adulterate d	07/27/2010
Eaton Manufacturing Corporation	Medical Device Reporting/Misbranded	07/27/2010
Cosmed Labs, Inc.	CGMP for Finished Pharmaceuticals/Adulterated/Misbranded	08/03/2010
Juice Pac Inc	Juice/HACCP/Adulterated	08/13/2010
Providence Hospital IRB	Clinical Investigator	01/06/2010
Xian Libang Pharmaceutical Co., Ltd.	CGMP/Manufacturing Facility/Active Pharmaceutical Ingredient	01/28/2010
Punjwani, Sohail S., M.D.	Bioresearch Monitoring Program	02/04/2010
Summers, Timothy, MD	Clinical Investigator	02/04/2010
LASIK Vision Institute LLC	Medical Device Reporting Regulation/Misbranded	02/12/2010

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Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Nature'S Gift Inc	Unapproved//Unauthorised Products Related to the H1N1 Flu Virus	02/16/2010
Unisource, Inc.	Unapproved New Drug/Misbranded	02/17/2010
Lucky Farm Inc	Adulterated	02/18/2010
Rx Development Resources, LLC	Labeling/Promotional Claims False & Misleading/Misbranded	02/18/2010
Vertical Pharmaceuticals, Inc.	Premarket Approval/Misbranded/Adulterate d	02/18/2010
Tri-Med Laboratories Inc	Current Good Manufacturing Practice Regulation for Finished Pharmaceuticals	02/23/2010
Mueller Water Conditioning, Inc	CGMP/QSR/Medical Devices/Adulterated	02/24/2010
Olympus Temmo Biomaterials Corporation	CGMP/QSR/Medical Devices/Adulterated	02/25/2010
Paddock Laboratories, Inc.	New Drugs	03/01/2010
Perez-Cruet, Miguelangelo J., M.D., M.S.	Investigational Device Exemptions (Clinical Investigator)	03/02/2010
Sun Technologies, Inc.	Tanning Facility/Federal Performance Standard for Sunlamp Products/Misbranded	03/04/2010
Otologics LLC	Investigational Device Exemptions (Sponsor)	03/05/2010
Lin, Henry, M.D.	Clinical Investigator	03/08/2010
Toledo, Charles H., M.D.	Bioresearch Monitoring Program/IRB	03/11/2010
Medispec, Ltd.	Device/Lacks Premarket Approval Application/Adulterated/Misbranded	03/12/2010
Medline Industries Inc.	Medical Devices/Adulterated/Misbranded	03/12/2010
Orthotic & Prosthetic Lab Inc.	Device/Misbranded	03/17/2010
Orthotic & Prosthetic Lab, Inc.	Device/Lacks Annual Registration/Misbranded	03/17/2010
Tinnitus Control, Inc.	Device/Misbranded	03/17/2010
Tinnitus Control, Inc.	Device/Lacks Annual Registration/Misbranded	03/17/2010
Vulcon Technologies Inc	Device/Misbranded	03/17/2010
Paragon Dx, LLC	Premarket Approval/Misbranded/Adulterate d	03/18/2010
Salix Pharmaceuticals, Inc.	Labeling/Promotional Claims False & Misleading/Misbranded	03/19/2010
Slate Pharmaceuticals	DDMAC/Promotional Claims False & Misleading/Misbranded	03/24/2010
Pierre Fabre Medicament Production	CGMP for Finished Pharmaceuticals/Adulterated	03/26/2010
Wisconsin Brother's Bakery, Inc	Labeling/False & Misleading Claims/Misbranded	03/30/2010
Medical Cosmetic Enhancements	Lipodissolve/False & Misleading Claims/Misbranded	04/05/2010
Monarch Med Spa	Lipodissolve/False & Misleading Claims/Misbranded	04/05/2010
Spa 35	Lipodissolve/False & Misleading Claims/Misbranded	04/05/2010

Appendix A10 Continued

Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Pure Med Spa	Lipodissolve/False & Misleading Claims/Misbranded	04/06/2010
Wake Forest University Medical Centre	Device/Adulterated	04/07/2010
Physician Therapeutics, LLC	New Drug/Labeling/Misbranded/Adulterated	04/08/2010
Shamrock Medical Solutions Group LLC	CGMP for Finished Pharmaceuticals/Misbranded/Adulterated	04/08/2010
Storz Medical, AG	Premarket Approval/Misbranded/Adulterate d	04/08/2010
Pfizer Inc.	Sponsor	04/09/2010
Mid South Produce Distributors, LLC	CGMP/Adulterated	04/13/2010
Shreeji Homeo Clinic	Unapproved/Unauthorised Products Related to the H1N1 Flu Virus	04/13/2010
Super Body Care	Unapproved/Unauthorised Products Related to the H1N1 Flu Virus	04/13/2010
Templeton Feed & Grain Inc.	CGMP for Medicated Feeds/Adulterated	04/13/2010
Wayne State University IRB	Institutional Review Board (IRB)	04/15/2010
Lasik Vision Institute (Boca Raton, FL)	Medical Device Reporting Regulation/Misbranded	04/20/2010
Milky Way Farm	PHS Act Violation	04/20/2010
Rainbow Acres Farm	PHS Act Violation	04/20/2010
TLC Vision Corporation	Medical Device Reporting/Misbranded	04/20/2010
Uv Flu Technologies, Inc.	Unapproved//Unauthorised Products Related to the 2009 H1N1 Flu Virus	04/20/2010
Vision Care Holdings, LLC	Medical Device Reporting/Misbranded	04/20/2010
Novartis Oncology	False & Misleading Claims/Unapproved Use/Misbranded	04/21/2010
L. Perrigo Company	CGMP for Finished Pharmaceuticals/Adulterated	04/29/2010
Vision Pharm, LLC	Lacks Approved New Drug Application/Adulterated/Misbranded	04/29/2010
Medtronic Navigation, Inc	Medical Device/Lacks Premarket Approval/Adulterated/Misbranded	05/07/2010
Midstate Veterinary Services, PLLC	Extra label Drug Use in Animals/Adulterated	05/10/2010
River's Edge Pharmaceuticals, LLC	CGMP for Finished Pharmaceuticals/Adulterated/Misbranded	05/20/2010
Syntron Bioresearch Inc.	CGMP/QSR/Medical Device Reporting/Adulterated	05/24/2010
Toby's Nose Filters, Inc.	Premarket Approval/Adulterated	05/25/2010
Pfizer, Inc.	Post-marketing Adverse Drug Experience Reporting Requirements	05/26/2010
Ribbon SRL	CGMP Regulation for Finished Pharmaceuticals/Adulterated	05/27/2010
Yancey, Samuel DVM	Extra label Drug Use in Animals/Adulterated	05/28/2010
Piezosurgery Inc.	CGMP for Medical Devices/QS/Adulterated	06/08/2010

Appendix A10 Continued

Company Name	FDA Warning Letter (WL) Subject	WL Issue Date
Libido Edge Labs, Llc	Unapproved New Drug Promotional Claims/Misbranded	06/10/2010
Medefil Incorporated	CGMP/QSR/Medical Devices/Adulterated	06/10/2010
Optovue Inc.	CGMP/QSR/Medical Devices/Adulterated/Misbranded	06/11/2010
Pozner, Jason M.D.	Investigational Device Exemptions (Clinical Investigator)	06/25/2010
Nemechek Do Pa, Patrick	Institutional Review Board (IRB)	06/28/2010
Regancrest Holsteins, Inc.	Extra label Drug Use in Animals/Adulterated	07/02/2010
Replication Medical Inc	Medical Device/Lacks Premarket Approval/Adulterated/Misbranded	07/02/2010
Western Milling Company	CGMP for Medicated Feeds/Adulterated/Misbranded	07/06/2010
Med Prep Consulting, Inc	Failure to Register and List/Misbranded	07/09/2010
Stuart Harlin, Md	Clinical Investigator	07/21/2010
Nitrox, Inc.	CGMP for Finished Pharmaceuticals/Adulterated/Misbranded	07/26/2010
Life Recovery Systems HD, LLC	Medical Device/Lacks Premarket Approval/Adulterated/Misbranded	07/28/2010
Scully, Sean M.D.	Investigational Device Exemptions (Clinical Investigator)	07/30/2010
MP Biomedicals LLC	CGMP/QSR/Manufacture/Packing/Storage/Installation/Adulterate d/Misbranded	08/02/2010
Pioneer Surgical Technology	Sponsor/Clinical Investigator	08/03/2010
Starion Instruments	Device/Adulterated	8/10/2010

A11: BIOTECHNOLOGY

There are 2713 lines of raw data which is too large for this appendix. Summary information describing the raw data is provided in table below

	Cardiovascular	Central nervous system	Endocrine, metabolic & genetic disorders	Gastroenterology	Genitourinary	Hematology	Immunology & inflammation	Infectious diseases	Musculoskeletal	Oncology	Respiratory	Total
Small Molecule (SM) Product Launch												
2002	40	33	7	15	24	2	16	39	8	9	12	205
2003	18	14	10	4	23	0	6	18	3	16	7	119
2004	13	37	5	10	26	4	13	28	12	14	9	171
2005	16	43	11	7	14	4	8	41	7	12	9	172
2006	32	35	8	4	30	0	7	22	1	30	4	173
2007	33	21	12	11	9	6	16	31	7	23	21	190
2008	26	32	6	9	6	0	1	12	7	19	13	131
2009	42	56	11	7	16	2	7	15	4	24	11	195
2010	29	60	9	6	22	0	5	17	3	32	14	197
2011	56	62	17	4	19	3	7	31	7	41	9	256
2012	14	21	22	5	19	0	10	20	0	49	18	178
2013	26	24	18	3	2	0	2	6	0	29	9	119
2014	9	9	7	3	2	3	0	11	4	17	7	72
<2002	424	359	81	104	188	44	123	317	19	129	161	
>2015	88	224	117	13	22	31	66	109	3	203	155	

Appendix A11 Continued

	Cardiovascular	Central nervous system	Endocrine, metabolic & genetic disorders	Gastroenterology	Genitourinary	Hematology	Immunology & inflammation	Infectious diseases	Musculoskeletal	Oncology	Respiratory	Total	
Large Molecule (LM) Product Launch													
2002	1	1	4	0	0	0	5	5	0	6	0	22	
2003	0	0	7	0	0	0	10	3	0	0	2	22	
2004	0	2	7	0	2	2	3	1	0	15	0	32	
2005	0	1	8	0	1	0	5	8	0	2	3	28	
2006	0	3	14	0	3	0	3	17	0	2	0	42	
2007	0	0	8	0	0	4	1	3	0	1	0	17	
2008	0	0	0	0	1	7	8	2	0	5	0	23	
2009	0	0	5	0	0	2	17	7	0	10	1	42	
2010	4	0	7	0	4	0	7	17	4	8	0	51	
2011	3	2	2	0	0	5	8	9	0	7	2	38	
2012	1	12	6	0	0	4	10	2	0	27	0	62	
2013	0	9	9	0	0	4	7	0	0	10	0	39	
2014	0	17	7	0	0	1	10	5	0	13	0	53	
<2002	19	15	72	7	10	35	32	103	0	50	4		
>2015	14	32	35	0	3	0	70	59	9	122	24		
Launch Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
SM Launch (ALL markets)	205	119	171	172	173	190	131	195	197	256	178	119	72
LM Launch (ALL markets)	22	22	32	28	42	17	23	42	51	38	62	39	53

A12: NANOMEDICINE

Therapy Area	Marketed Nanomedicine Products
Cardiology	3
Central Nervous System	2
Genitourinary	2
Immunology & Inflammation	3
Infectious Diseases	10
Metabolic Disorders	3
Musculoskeletal	3
Oncology	8
Ophthalmology	2
Total	36

A13: BIOINFORMATICS

Patent Number	Title	Country	Year
EP1607898 (A2)	A bioinformatics system for functional proteomics modeling	EP	2005
WO2008000186 (A1)	A method for identifying novel gene And the resulting novel genes	WO	2008
CN101234113 (A)	Anti-tumor small molecular compound targeting to phosphatidylethanolamine conjugated protein 4 of human	CN	2008
7062076	Artificial intelligence system for genetic analysis	US	2006
6876930	Automated pathway recognition system	US	2005
US2009048125 (A1)	Biochip micro-system for bioinformatics recognition and analysis	US	2009
US2004236516 (A1)	Bioinformatics based system for assessing a condition of a performance animal by analyzing nucleic acid expression	US	2004
US2008133474 (A1)	Bioinformatics computation using a map-reduce-configured computing system	US	2008
US2009138251 (A1)	Bioinformatics research and analysis system and methods associated therewith	US	2009
US2008033999 (A1)	Bioinformatics system architecture with data and process integration	US	2008
US2003176976 (A1)	Bioinformatics system architecture with data and process integration for overall portfolio management	US	2003
US2003149595 (A1)	Clinical bioinformatics database driven pharmaceutical system	US	2003
7294487	Combinatorial oligonucleotide PCR: a method for rapid, global expression analysis	US	2007
7332282	Compositions and methods for detecting and treating neurological conditions	US	2008
7527930	Compositions and methods of use of standardised mixtures for determining an amount of a nucleic acid	US	2009
US2004224345 (A1)	Computational method and system for modeling, analyzing, and optimizing DNA amplification and synthesis	US	2004
CN101320404 (A)	Computer automatic sorting method of biological virus	CN	2008
US2009018809 (A1)	Computer gene	US	2009
7031843	Computer methods and systems for displaying information relating to gene expression data	US	2006
US2008097939 (A1)	Data mining platform for bioinformatics and other knowledge discovery	US	2008
US2004003132 (A1)	Data pool architecture, system, and method for intelligent object data in heterogeneous data environments	US	2004
US6631331 (B1)	Database system for predictive cellular bioinformatics	US	2003
US2007005263 (A1)	Database system including computer code for predictive cellular bioinformatics	US	2007
7392199	Diagnosing unapparent diseases from common clinical tests using Bayesian analysis	US	2008
7472121	Document comparison using multiple similarity measures	US	2008
7603304	Domain specific return on investment model system and method of use	US	2009
US2003099973 (A1)	E-GeneChip online web service for data mining bioinformatics	US	2003

Appendix A13 Continued

Patent Number	Title	Country	Year
JP2008117363 (A)	Execution method of bioinformatics analysis and bioinformatics analysis platform	JP	2008
7542959	Feature selection method using support vector machine classifier	US	2009
7049072	Gene expression analysis of pluri-differentiated mesenchymal progenitor cells and methods for diagnosing a leukemic disease state	US	2006
6912470	Genes and proteins involved in the biosynthesis of enediyne ring structures	US	2005
7625699	Genetic polymorphisms associated with coronary stenosis, methods of detection and uses thereof	US	2009
7321830	Identifying drugs for and diagnosis of benign prostatic hyperplasia using gene expression profiles	US	2008
7604955	Immunoglobulin E vaccines and methods of use thereof	US	2009
US2009063259 (A1)	Information system for biological and life sciences research	US	2009
7493265	Integrated biomedical information portal system and method	US	2009
7617163	Kernels and kernel methods for spectral data	US	2009
7370021	Medical applications of adaptive learning systems using gene expression data	US	2008
6970790	Method and apparatus for analysis of molecular combination based on computational estimation of electrostatic affinity using basis expansions	US	2005
US2006045348 (A1)	Method and apparatus for automated cellular bioinformatics	US	2006
6141657	Method and apparatus for identifying classifying or quantifying DNA sequences in a sample without sequencing	US	2000
6453245	Method and apparatus for identifying, classifying, or quantifying protein sequences in a sample without sequencing	US	2002
US2004229210 (A1)	Method and apparatus for predictive cellular bioinformatics	US	2004
US2002012456 (A1)	Method and apparatus for providing a bioinformatics database	US	2002
7356416	Method and system for automated inference creation of physico-chemical interaction knowledge from databases of co-occurrence data	US	2008
6768982	Method and system for creating and using knowledge patterns	US	2004
7467153	Method and system for efficient collection and storage of experimental data	US	2008
6813615	Method and system for interpreting and validating experimental data with automated reasoning	US	2004
6516288	Method and system to construct action coordination profiles	US	2003
6853952	Method and systems of enhancing the effectiveness and success of research and development	US	2005
7565247	Method for acquisition, storage, and retrieval of cell screening data on a computer system	US	2009
6721663	Method for manipulating protein or DNA sequence data in order to generate complementary peptide ligands	US	2004
6996473	Method for screening and producing compound libraries	US	2006

Appendix A13 Continued

Patent Number	Title	Country	Year
US2004068381 (A1)	Method of handling database for bioinformatics	US	2004
US2010030719 (A1)	Method and apparatus related to bioinformatics data analysis	US	2010
6855554	Methods and compositions for detection of breast cancer	US	2005
6355423	Methods and devices for measuring differential gene expression	US	2002
6873914	Methods and systems for analyzing complex biological systems	US	2005
7415359	Methods and systems for the identification of components of mammalian biochemical networks as targets for therapeutic agents	US	2008
6511808	Methods for designing exogenous regulatory molecules	US	2003
7620502	Methods for identifying sets of oligonucleotides for use in an in vitro recombination procedure	US	2009
7058515	Methods for making character strings, polynucleotides and polypeptides having desired characteristics	US	2006
7206699	Methods for measuring therapy resistance	US	2007
7089121	Methods for monitoring the expression of alternatively spliced genes	US	2006
7217510	Methods for providing bacterial bioagent characterizing information	US	2007
7599799	Methods for using co-regulated genesets to enhance detection and classification of gene expression patterns	US	2009
6882990	Methods of identifying biological patterns using multiple data sets	US	2005
7117188	Methods of identifying patterns in biological systems and uses thereof	US	2006
US2003177143 (A1)	Modular bioinformatics platform	US	2003
EP1466289 (A2)	Nonlinear system identification for class prediction in bioinformatics and related applications	EP	2004
CN101627989 (A)	Novel anti-tumor application of organic small-molecular compound JFD-03169	CN	2010
CN101627994 (A)	Novel anti-tumor application of organic small-molecular compound JFD-03554	CN	2010
6647358	Pharmacokinetic-based drug design tool and method	US	2003
US6677114 (B1)	Polypeptide fingerprinting methods and bioinformatics database system	US	2004
7475048	Pre-processed feature ranking for a support vector machine	US	2009
7379822	Protein design automation for protein libraries	US	2008
7177766	Selection of sites for targeting by zinc finger proteins and methods of designing zinc finger proteins to bind to preselected sites	US	2007
6389428	System and method for a precompiled database for biomolecular sequence information	US	2008
7356521	System and method for automatic molecular diagnosis of ALS based on boosting classification	US	2008
US2004249847 (A1)	System and method for identifying coherent objects with applications to bioinformatics and E-commerce	US	2004

Appendix A13 Continued

Patent Number	Title	Country	Year
US2010094889 (A1)	System, method and computer program for non-binary sequence comparison	US	2010
US2010130371 (A1)	System, method, device, and computer program product for extraction, gathering, manipulation, and analysis of peak data from an automated sequencer	US	2010
7425700	Systems and methods for discovery and analysis of markers	US	2008
US2003176929 (A1)	User interface for a bioinformatics system	US	2003
JP2010249831 (A)			2010
CN101812500 (A)		CN	2010
JP2010142230 (A)		JP	2010
CN101810608 (A)		CN	2010
US2008270438 (A1)		US	2010
CN101320404 (B)		CN	2010
US7711491 (B2)		US	2010
7546210	Visual-serving optical microscopy	US	2009

A14: PERVASIVE/CLOUD COMPUTING

Patent Number	Title	Issue Year
7520611	system for vision examination utilizing telemedicine	2009
7500795	apparatuses, systems and methods for enhancing telemedicine, video-conferencing, and video-based sales	2009
7232220	system for vision examination utilizing telemedicine	2007
6949073	dyspnea monitor, and telemedicine system and method	2005
6820057	telemedicine system	2004
6610010	portable telemedicine device	2003
6575900	meter with integrated database and simplified telemedicine capability	2003
6409660	portable telemedicine device	2002
6038465	telemedicine patient platform	2000
6033076	visual field testing via telemedicine	2000
6027217	automated visual function testing via telemedicine	2000
7742811	implantable device and method for the electrical treatment of cancer	2010
7582080	implantable, tissue conforming drug delivery device	2009
7526335	communications system for an implantable device and a drug dispenser	2009
7519409	implantable cell/tissue-based biosensing device	2009
7505869	non-conformance monitoring and control techniques for an implantable medical device	2009
7415384	therapy management techniques for an implantable medical device	2008
7285304	fluid treatment of a polymeric coating on an implantable medical device	2007
7072802	therapy management techniques for an implantable medical device	2006
7054782	non-conformance monitoring and control techniques for an implantable medical device	2006
7052488	implantable drug delivery device	2006
6799149	therapy management techniques for an implantable medical device	2004
6738663	implantable device and method for the electrical treatment of cancer	2004
6615083	implantable medical device system with sensor for hemodynamic stability and method of use	2003
6512949	implantable medical device for measuring time varying physiologic conditions especially edema and for responding thereto	2003
7632234	implantable biosensor devices for monitoring cardiac marker molecules	2009
7433727	implantable biosensor	2008

Appendix A14 Continued

Patent Number	Title	Issue Year
7223237	implantable biosensor and methods for monitoring cardiac health	2007
7146203	implantable biosensor and methods of use thereof	2006
6965791	implantable biosensor system, apparatus and method	2005
6699186	methods and apparatus for deploying and implantable biosensor	2004
7676263	minimally invasive system for selecting patient-specific therapy parameters	2010
7630986	secure data interchange	2009
7616117	reconciliation mechanism using rfid and sensors	2009
7593952	enhanced medical treatment system	2009
7587368	information record infrastructure, system and method	2009
7587259	items dispenser	2009
7575770	continuous production and packaging of perishable goods in low oxygen environments	2009
7502664	system and method for interactive items dispenser	2009
7502643	method and apparatus for measuring heart related parameters	2009
7436311	adaptive communication methods and systems for facilitating the gathering, distribution and delivery of information related to medical care	2008
7415428	processing meat products responsive to customer orders	2008
7205016	packages and methods for processing food products	2007
7181017	system and method for secure three-party communications	2007
7155306	medication administration system	2006
7107155	methods for the identification of genetic features for complex genetics classifiers	2006
7061831	product labeling method and apparatus	2006
7043415	interactive graphical environment for drug model generation	2006
7034691	adaptive communication methods and systems for facilitating the gathering, distribution and delivery of information related to medical care	2006
6986739	architecture tool and methods of use	2006
6965816	pfn/trac system faa upgrades for accountable remote and robotics control to stop the unauthorised use of aircraft and to improve equipment management and public safety in transportation	2005
6889165	application specific intelligent microsensors	2005
6842877	contextual responses based on automated learning techniques	2005

Appendix A14 Continued

Patent Number	Title	Issue Year
6817980	automated diagnostic system and method including disease timeline	2004
6767325	automated diagnostic system and method including synergies	2004
6764447	automated diagnostic system and method including alternative symptoms	2004
6746399	automated diagnostic system and method including encoding patient data	2004
6730027	automated diagnostic system and method including multiple diagnostic modes	2004
6569093	automated diagnostic system and method including disease timeline	2003
6527713	automated diagnostic system and method including alternative symptoms	2003
6524241	automated diagnostic system and method including multiple diagnostic modes	2003
6522945	customer specific packaging line	2003
6519601	relational database compiled/stored on a memory structure providing improved access through use of redundant representation of data	2003
6475143	automated diagnostic system and method including encoding patient data	2002
6468210	automated diagnostic system and method including synergies	2002
6401085	mobile communication and computing system and method	2002
6373786	cap for a hermetically sealed container	2002
6356905	system, method and article of manufacture for mobile communication utilizing an interface support framework	2002
6317648	customer specific packaging line having containers with tag means containing medication order information	2001
6199099	system, method and article of manufacture for a mobile communication network utilizing a distributed communication network	2001
6132724	allelic polygene diagnosis of reward deficiency syndrome and treatment	2000
6051249	dressing having a three-dimensional part and processes for the preparation of such a dressing	2000
7594889	integrated data collection and analysis for clinical study	2009
7177699	lifestyle management system	2007
7087027	device and method for monitoring respiration	2006
6917829	method and system for a distributed analytical and diagnostic software over the intranet and internet environment	2005
6805667	information remote monitor (irm) medical device	2004
6735479	lifestyle management system	2004
6454708	portable remote patient telemonitoring system using a memory card or smart card	2002

Appendix A14 Continued

Patent Number	Title	Issue Year
6416471	portable remote patient telemonitoring system	2002
6334778	remote psychological diagnosis and monitoring system	2002
US2010331711 (A1)	-	2010
US2010318380 (A1)	-	2010
US2010279718 (A1)	-	2010
EP2238552 (A1)	-	2010
KR20100107266 (A)	-	2010
EP2207479 (A1)	telemedicine care	2010
KR20100055261 (A)	total telemedicine system for hospital using a docking station and ultra mobile personal computer and management method threrof	2010
AU2008322641 (A1)	a telemedicine application for remote monitoring, viewing and updating of patient records	2009
KR20100005880 (A)	telemedicine device and core body predictor by telemedicine device	2010
US2010063395 (A1)	telemedicine platform for standardised interpretation of vascular data using vascular analysis	2010
EA008266 (B1)	telemedicine system	2007
WO2009138968 (A2)	improved devices and method for safe remote healthcare delivery through telemedicine	2009
WO2009126399 (A1)	telemedicine system and method	2009
US2009167842 (A1)	apparatuses, systems and methods for enhancing telemedicine	2009
WO2009095021 (A1)	telemedicine unit	2009
US2009112070 (A1)	telemedicine device and system	2009
CN101569521 (A)	telemedicine monitoring system	2009
US2009167838 (A1)	method and apparatus for cleaning a telemedicine station	2009
WO2008043341 (A1)	telemedicine system, especially for chronic diseases	2008
US2009083066 (A1)	method for routing user service requests from a telemedicine station	2009
WO2008031067 (A2)	mobile telemedicine vehicle	2008
WO2008028912 (A2)	method and device for deriving and evaluating cardiovascular information from curves of the cardiac current, in particular for applications in telemedicine	2008
WO2008022423 (A2)	telemedicine system for remote monitoring of patients	2008
KR20090003459 (A)	system and method for controlling telemedicine	2009

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Patent Number	Title	Issue Year
US2007195267 (A1)	system for vision examination utilizing telemedicine	2007
CN101239004 (A)	telemedicine image digital acquisition device and method thereof	2008
WO2007056601 (A2)	methods and apparatus for context-sensitive telemedicine	2007
JP2007073065 (A)	telemedicine system and terminal used for the same	2007
KR20080029391 (A)	system for telemedicine with wireless transmission, method for telemedicine using this system and recording medium thereof	2008
JP2007293499 (A)	telemedicine system using multifunctional video telephone	2007
KR100763757 (B1)	system for telemedicine by load balancing and method service providing thereof	2007
US2006167346 (A1)	telemedicine system	2006
WO2006088574 (A2)	multifunction telemedicine software with integrated electronic medical record	2006
DE102005048752 (A1)	method for interactive picture and sound transmission in telemedicine, involves picture presentation and bi-directional audio connection which are enabled by means of standard browser software of computer attached to computer network	2007
US2006122466 (A1)	telemedicine system comprising a modular universal adapter	2006
JP2006021031 (A)	telemedicine system and artificial pancreas system	2006
KR20050049448 (A)	residential district Centre of telemedicine system by internet and its method	2005
US2005149364 (A1)	multifunction telemedicine software with integrated electronic medical record	2005
DE102004059713 (A1)	road accident telemedicine initiation system has network connected portable modular emergency box for cars with communications and data interfaces to call centre and regional emergency centre	2005
KR20060044054 (A)	method and system for providing telemedicine service by using mobile communication terminal	2006
US2005043969 (A1)	telemedicine system, and method for communication with remotely located patients	2005
US2006064319 (A1)	method for telemedicine services	2006
JP2005352969 (A)	telemedicine support system	2005
JP2005346552 (A)	telemedicine audit system and telemedicine audit method	2005
KR20050115510 (A)	telemedicine system for heart disease	2005
KR100439442 (B1)	method for reserving telemedicine depending on patient condition using communication network	2004
US2004153340 (A1)	method for monitoring telemedicine healthcare services	2004
DE10342823 (A1)	implanted prosthesis seat check has two axis acceleration sensor with wireless data transmission to telemedicine centre to determine movement relative to bone	2005
US2005049898 (A1)	telemedicine system using the internet	2005

Appendix A14 Continued

Patent Number	Title	Issue Year
US2004039606 (A1)	telemedicine system	2004
WO03101289 (A1)	deployable telemedicine system	2003
US2004054760 (A1)	deployable telemedicine system	2004
KR20040098982 (A)	system for automatically paging telemedicine by using wireless sub terminal, and automatic telemedicine method using the same	2004
FR2853100 (A1)	interlocutor emotional state transmission device for e.g. telemedicine, has sensors obtaining sensory information e.g. heart beat, of interlocutor, and coding circuit transforming information to emotional state code	2004
WO03085508 (A1)	electronic needle mouse and telemedicine service system using it	2003
WO03073922 (A1)	system for vision examination utilizing telemedicine	2003
RU2251965 (C2)	data analysis system in the field of telemedicine	2005
DE10303665 (A1)	telemedicine system for remote collection of patient data whereby system access is controlled so that it can be ensured medical measurement data is collected in a correct manner	2004
KR20040057317 (A)	system for telemedicine service based on high quality multimedia using mpeg method	2004
WO03053232 (A1)	telemedicine system, use thereof and telemedicine patient care	2003
DE10254939 (A1)	telemedicine system for providing online disease diagnosis by a certificated or authenticated grader of medical images or signals, whereby images are entered at one point and a previously authorised person accesses them remotely	2004
DE10247440 (A1)	computer and network based telemedicine therapy system in which a control data packet is sent at the beginning of each therapy session to a patient computer that includes instructions relating to any changes in therapy	2003
KR20040017579 (A)	method for telemedicine serive using digital set-top box	2004
KR20040017031 (A)	pda based mobile telemedicine system	2004
AU2002300622 (B2)	telemedicine system	2004
EP1282062 (A2)	method for mediating for a telemedicine healthcare service provider	2003
JP2004054489 (A)	remote medical information system, information processing method, computer program, recording medium for computer program, and telemedicine system	2004
KR20040007003 (A)	telemedicine system and controlling method thereof	2004
JP2004041472 (A)	telemedicine information system	2004
WO03003912 (A1)	telemedicine system	2003
EP1267297 (A2)	method for controlling and monitoring the process flow to determine the performance of a telemedicine healthcareservice	2002
US2002115916 (A1)	portable telemedicin device	2002

Appendix A14 Continued

Patent Number	Title	Issue Year
US2003184649 (A1)	telemedicine booking station for mass casualty intake facility, relocation Centre, or the like, arising from bioterror hostage standoff, civil disobedience, or the like	2003
WO02073829 (A1)	maritime telemedicine system using satellite communication network	2002
KR20030060273 (A)	method and system for telemedicine using local area wireless interface	2003
DE10154908 (A1)	telemedicine system comprising doctor-side consultation Centre and mobile patient-side telemedicine devices that have a number of functional modules for recording medical data that can be linked to a base and communications module	2003
US2001056226 (A1)	integrated telemedicine computer system	2001
CA2343497 (A1)	virtual cosmetic autosurgery via telemedicine	2001
KR20020047586 (A)	method for operating telemedicine service using wireless communication terminal	2002
CA2323685 (A1)	autointerpretation of medical diagnostic tests via telemedicine	2001
KR20020016289 (A)	method and system for telemedicine using internet	2002
KR20020013311 (A)	method for real time telemedicine using data communication service of mobile communication network	2002
KR20020009302 (A)	telemedicine method and system	2002
KR20020005884 (A)	telemedicine method using internet	2002
US6575900 (B1)	meter with integrated database and simplified telemedicine capability	2003
WO0057774 (A1)	meter with integrated database and simplified telemedicine capability	2000
WO0022388 (A1)	telemedicine patient platform	2000
US6820057 (B1)	telemedicine system	2004
US6409660 (B1)	portable telemedicine device	2002
US6033076 (A)	visual field testing via telemedicine	2000
US6027217 (A)	automated visual function testing via telemedicine	2000
TW400503 (B)	a packet-based telemedicine system for communicating information between central monitoring stations and remote patient monitoring stations	2000
EP1027459 (A1)	telemedicine	2000
AU747299 (B2)	telemedicine system	2002
SE513506 (C2)	portable telemedicine apparatus used in preliminary diagnostic procedures	2000
US2010023071 (A1)	systems and devices for neural stimulation and controlled drug delivery	2010
US2008228133 (A1)	delivery of a sympatholytic cardiovascular agent to the central nervous system	2008
US2008058772 (A1)	personal paramedic	2008

Appendix A14 Continued

Patent Number	Title	Issue Year
WO2007035445 (A1)	implantable co-fired electrical feedthroughs	2007
WO2007035443 (A1)	miniaturised co-fired electrical interconnects for implantable medical devices	2007
WO2007035332 (A1)	implantable co-fired electrical interconnect systems and devices and methods of fabrication therefor	2007
US2007265662 (A1)	implantable electromagnetic interference tolerant, wired sensors and methods for implementing same	2007
US2007060974 (A1)	cognitive function within a human brain	2007
US2008168921 (A1)	method for making device for controlled reservoir opening by electrothermal ablation	2008
WO2005041767 (A2)	medical device for sensing glucose	2005
US2005096587 (A1)	medical device for sensing glucose	2005
WO2004033034 (A1)	medical device for neural stimulation and controlled drug delivery	2004
US2002013545 (A1)	synthetic muscle based diaphragm pump apparatuses	2002
US2010128104 (A1)	communication system for remote patient visits and clinical status monitoring	2010
US2010106046 (A1)	device and method for predicting and preventing pulmonary edema and management of treatment thereof	2010
US2008281633 (A1)	periodic evaluation and telerehabilitation systems and methods	2008
US2008249801 (A1)	distributed system for monitoring patient video, audio and medical parameter data	2008
CN101099666 (A)	method and system for clinical interpretation and review of patient data	2008
GB2440019 (A)	clinical interpretation and review of patient data	2008
US2007203415 (A1)	system and method for determining edema through remote patient monitoring	2007
US2008255874 (A1)	system and method for delivering clinical notifications	2008
WO2006104843 (A1)	integrated data collection and analysis for clinical study	2006
CN1788676 (A)	radio remote monitoring system for cardiogram	2006
WO2006033927 (A1)	clinic dashboard monitor	2006
US2006224421 (A1)	integrated data collection and analysis for clinical study	2006
JP2005253981 (A)	patient monitoring apparatus	2005
US2005200486 (A1)	patient visual monitoring system	2005
US2004199221 (A1)	lifestyle management system	2004
CN1524489 (A)	long range real-time monitoring system of a clinical monitoring equipment	2004
WO03020127 (A1)	lifestyle management system	2003

Appendix A14 Continued

Patent Number	Title	Issue Year
US2004006265 (A1)	wireless transmission-st-segment preserved of the standard 12 leads ekg apparatus for the remote administration of thrrombolytic therapy under severe cellular channel impairment	2004
US2003199780 (A1)	device and method for monitoring respiration	2003
JP2002245578 (A)	hazardous event automatic notifying system and method	2002
WO0212981 (A2)	method and system for a distributed analytical and diagnostic software over the intranet and internet environment	2002
US2002107452 (A1)	method and system for a distributed analytical and diagnostic software over the intranet and internet environment	2002
WO0193756 (A2)	portable remote patient telemonitoring system using a memory card or smart card	2001
US2003036683 (A1)	method, system and computer program product for internet-enabled, patient monitoring system	2003
US2001048077 (A1)	apparatus and method for spectroscopic analysis of human or animal tissue or body fluids	2001
KR20010095353 (A)	maritime remote medical system using satellite communication network	2001
WO0156467 (A1)	information remote monitor (irm) medical device	2001
US2002045804 (A1)	information remote monitor (irm) medical device	2002
JP2001222445 (A)	device and method for operating failure diagnosis, maintenance and upgrade work from remote site of device system for implantation	2001
US6454708 (B1)	portable remote patient telemonitoring system using a memory card or smart card	2002
US6334778 (B1)	remote psychological diagnosis and monitoring system	2002
WO2010107243 (A3)	-	2010
US2010274101 (A1)	-	2010
US2010228110 (A1)	-	2010
CA2701006 (A1)	implantable biosensor and methods of use thereof	2008
WO2010056624 (A2)	long-term implantable biosensor	2010
US2010056885 (A1)	implantable biosensor devices for monitoring cardiac marker molecules	2010
US2010056888 (A1)	implantable biosensor and sensor arrangement	2010
WO2009008932 (A2)	implantable wireless cmos biosensor	2009
US2009221882 (A1)	implantable biosensor assembly and health monitoring system and method including same	2009
US2006241365 (A1)	implantable biosensor and methods of use thereof	2006
WO2006113352 (A2)	implantable biosensor	2006
WO2006062668 (A2)	catheter-free implantable needle biosensor	2006

Appendix A14 Continued

Patent Number	Title	Issue Year
US2005183954 (A1)	implantable biosensor system, apparatus and method	2005
EP1588737 (A1)	implantable biosensor and methods for monitoring cardiac health	2005
US2005107677 (A1)	implantable biosensor	2005
GB2441078 (A)	systems biology based therapeutic modeling and implantable devices	2008
WO2005011490 (A1)	implantable biosensor	2005
US2005123680 (A1)	micro reference electrode of implantable continuous biosensor using iridium oxide, manufacturing method thereof, and implantable continuous biosensor	2005
WO03091701 (A2)	implantable biosensor from stratified nanostructured membranes	2003
US2004023317 (A1)	implantable biosensor from stratified nanostructured membranes	2004
US6699186 (B1)	methods and apparatus for deploying and implantable biosensor	2004
JP2010279707 (A)		2010
WO2010138875 (A1)		2010
WO2010126535 (A1)		2010
WO2010124137 (A1)		2010
US2010274587 (A1)		2010
US2010179820 (A1)	automated analysis of data collected by in-vivo devices	2010
US2010179828 (A1)	presenting related results during medication administration documentation	2010
WO2010054205 (A2)	smart medicine container	2010
WO2010042444 (A1)	devices and methods for determining a patient's propensity to adhere to a medication prescription	2010
US2010070304 (A1)	system and method for recognizing medication side effects in patients	2010
JP2009273502 (A)	medication monitoring apparatus	2009
US7630908 (B1)	wireless electronic prescription scanning and management system	2009
US2009276243 (A1)	healthcare notification method and system including a healthcare website	2009
JP2009142674 (A)	medication delivery system	2009
US2009265189 (A1)	medication therapy review methods	2009
JP2009009609 (A)	medical examination support device	2009
US2009012822 (A1)	medical records, documentation, tracking and order entry system	2009
US2008306768 (A1)	healthcare notification method and system including a healthcare website	2008

Appendix A14 Continued

Patent Number	Title	Issue Year
US2008275425 (A1)	method of controlling a medication delivery system with a removable label containing instructions for setting medication delivery rate overlying a second label with patient instructions	2008
WO2009009149 (A1)	electronic patient compliance device	2009
US2008215374 (A1)	clinical management system and methods	2008
US2008183091 (A1)	cardiac event categorization system	2008
US2008154646 (A1)	system and program for electronically maintaining medical information between patients and physicians	2008
US2008208914 (A1)	centralised mining of remote medical records databases	2008
JP2009146367 (A)	system for protecting member personal information with limited leak of individual non-specification information even in database information leak by writing information for treatment, contraindicated drug or individual specification into electronic information storage area of ic chip type member card in easily browsable, confirmable and changeable manner at medical institution and by storing only individual non-specification information in external disclosure database	2009
US2009144087 (A1)	medication identifying and organizing system	2009
US2009106313 (A1)	interactive prescription processing and managing system	2009
US2008059528 (A1)	patient care order and scanned document processing system	2008
US2008053040 (A1)	assembly, production and quality assurance processes respecting electronic compliance monitor (ecm) tags	2008
US2008015897 (A1)	method and system for delivering prescription medicine	2008
US2008312965 (A1)	medical compliance software based system and computer writeable medium	2008
US2009151721 (A1)	dispensing device	2009
US2008255874 (A1)	system and method for delivering clinical notifications	2008
WO2007106458 (A2)	methods and systems for using practice management data	2007
JP2007073074 (A)	medical information processing system, medical information processing method, information processor and information processing method	2007
WO2008016319 (A1)	a portable patient control system with storage box	2008
WO2007013952 (A2)	medication compliance system and associated methods	2007
US2007123772 (A1)	medication compliance system and associated methods	2007
KR20070117166 (A)	electonic medical record system	2007
US2007033073 (A1)	system and user interface for monitoring patient treatment orders	2007
WO2006094288 (A2)	method and apparatus for mobile health and wellness management incorporating real-time coaching and feedback, community and rewards	2006

Appendix A14 Continued

Patent Number	Title	Issue Year
WO2006069268 (A1)	system and method for analysis of neurological condition	2006
US2006136806 (A1)	system and method for analysis of neurological condition	2006
US2006080145 (A1)	method for reviewing electronic patient medical records to assess and improve the quality and cost effectiveness of medical care	2006
JP2007074068 (A)	video apparatus, system of supervised administration of medication, method of supervised administration of medication with video apparatus, and program thereof	2007
WO2006056002 (A1)	patient medication management system	2006
US2005119604 (A1)	medicament dispenser	2005
CA2565210 (A1)	installation for filling packaging units with medicaments for patients according to the prescribed weekly requirements	2005
US2006136261 (A1)	system and method for maintaining the association of healthcare orders from a healthcare plan in a computerised medical administration record	2006
JP2006149797 (A)	patient information network system	2006
JP2006146820 (A)	information display method in electronic medical chart system and electronic medical chart	2006
US2005182656 (A1)	on-line prescription service system and method	2005
JP2006051244 (A)	system for supporting infusion of medicine or the like in home	2006
US2004143171 (A1)	method for generating patient medication treatment recommendations	2004
US2004081587 (A1)	marker detection method and apparatus to monitor drug compliance	2004
EP1422649 (A2)	method for monitoring the taking of medicines	2004
US2005086077 (A1)	physician workstation computer software program: system and method for making prescription writing and other medical tasks simple and easy	2005
US2005027560 (A1)	interactive multi-user medication and medical history management method	2005
WO2004006062 (A2)	prescription data exchange system	2004
JP2004348271 (A)	clinical trial data outputting device, clinical trial data outputting method, and clinical trial data outputting program	2004
US2004010204 (A1)	electronic/fiberoptic tissue differentiation instrumentation	2004
JP2004252535 (A)	method and system of electronic pharmacy	2004
US2004162740 (A1)	digitised prescription system	2004
JP2003248722 (A)	method and system for managing medical care register	2003
JP2004212504 (A)	prescription using electronic paper with ic	2004
US2003154104 (A1)	method of operating a savings plan for health care services	2003

Appendix A14 Continued

Patent Number	Title	Issue Year
US2003208382 (A1)	electronic medical record system and method	2003
EP1389476 (A1)	programming device for a pump for injecting medicaments	2004
US2003089733 (A1)	medication monitoring device	2003
MXPA02004618 (A)	marker detection method and apparatus to monitor drug compliance.	2002
US2003139778 (A1)	rapid response system for the detection and treatment of cardiac events	2003
WO0241825 (A2)	medication monitoring device	2002
US2002046346 (A1)	electronic medical records system	2002
JP2003099536 (A)	mobile electronic medication history management system	2003
JP2003099533 (A)	electronic medication history system	2003
JP2003036312 (A)	electronic medical record-processing device and program for electronic medical record processing	2003
WO0203298 (A1)	electronic medical record system and method	2002
US6468263 (B1)	implantable responsive system for sensing and treating acute myocardial infarction and for treating stroke	2002
US2002004729 (A1)	electronic data gathering for emergency medical services	2002
US2002147526 (A1)	web-enabled medication dispenser	2002
DE10111113 (A1)	recording and transferring medical data from electronic patient care systems involves linking of systems with data transfer units, and provision of an overall automated control system	2002
WO0167345 (A1)	automated electronic encrypted prescription filling and record keeping and retrieval system	2001
US6347329 (B1)	electronic medical records system	2002
JP2002024391 (A)	system and method for medication management	2002
JP2001344342 (A)	storage and display method for electronic medical record	2001
WO0064517 (A1)	electronic monitoring medication apparatus and method	2000
US6680999 (B1)	interactive telephony system	2004
FR2803210 (A3)	extra-corporal apparatus uses heat treatment to destroy infectious pathogenic germs in patient's blood before cooling and reintroduction	2001
US6305377 (B1)	system and method for improving compliance of a medical regimen	2001
JP2000342638 (A)	patient identification system	2000
US6314384 (B1)	medication management apparatus	2001
US6167302 (A)	device for transcutaneous administration of medications using iontophoresis	2000

Appendix A14 Continued

Patent Number	Title	Issue Year
US6158613 (A)	voice based pharmaceutical container apparatus and method for programming	2000
US6088429 (A)	interactive telephony system	2000
US6075755 (A)	medical reminder system and messaging watch	2000

A15: RANKING OF TRANSFORMATION TRIGGERS

The pervasiveness and relative ranking of the transformation triggers in the primary and derived articles.

Reference	Source	Year	No. of Citations	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8	Trigger 9	Trigger 10	Trigger 11	Trigger 12	Trigger 13	Trigger 14
1	Acd	2006	8					116									
2	Acd	2004	4		42	82	40						37				
3	Con	2005	2	33				27	24								
4	Org	2007	3	13				12	11								
5	Con	2009	0	58	55												
6	Acd	2008	0		80												
7	Gov	2004	30			14					127		126			125	
8	Gov	2005	2							63	62						
9	Gov	2009	0			108		97		94				88	86		
10	Gov	2007	0			121					92		89			85	
11	Acd	2008	47		146	142		138		137						133	
12	Acd	2006	4			53		74		72							64
13	Acd	2009	18		145	39											
14	Acd	2003	490		122	141											
15	Acd	2009	3		81	119											
16	Acd	2010	4														36
22	Con	2007	3	60	57				48								
23	Con	2002	1		56											43	
24	Acd	2009	7		123		117										
25	Ind	2009	1		30			26									
26	Org	2005	15	31	29			25									

Appendix A15 Continued

Reference	Source	Year	No. of Citations	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8	Trigger 9	Trigger 10	Trigger 11	Trigger 12	Trigger 13	Trigger 14
27	Acd	2007	10		124	99											
28	Ind	2004	0			2											
30	Acd	2009	2			54		76								68	
31	Ind	2007	50	111		143											
32	Acd	2009	8			98											
33	Con	2006	4			144											
34	Con	2008	0	59		78	50	49									
35	Ind	2001	112			79		75									
36	Ind	2006	11					107									
37	Acd	2007	21			77											
38	Ind	2006	7					73									
40	Acd	2006	14					139									
41	Con	2003	343														102
42	Ind	2001	19											105			
43	Acd	2004	4														35
44	Acd	2005	10														101
45	Acd	2008	4														66
46	Acd	2003	21														113
47	Acd	2008	16														128
48	Acd	2005	24														110
49	Acd	2009	1														65
50	Acd	2008	9														112

Appendix A15 Continued

Reference	Source	Year	No. of Citations	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8	Trigger 9	Trigger 10	Trigger 11	Trigger 12	Trigger 13	Trigger 14
51	Acd	2009	64														131
52	Con	2009	0														41
53	Acd	2009	1														67
54	Ind	2009	0	32												15	
55	Ind	2008	0	34							20	18					
56	Acd	2007	37				140										130
57	Con	2008	2	61			51					46				44	
58	Org	1998	3				1										
59	Acd	2008	4			120											
60	Con	2006	0						47								
61	Acd	2005	42													114	
62	Con	2002	5						106								
63	Con	2004	0						22		19						
64	Acd	2009	1		83												
65	Ind	2009	1							21							
66	Org	2009	0							10							
67	Org	2006	6		28				23								
68	Gov	2006	0		100	118		96	95	93	91			87		84	
69	Acd	2008	16								136						
70	Ind	2008	5								71						
71	Con	2008	0									45					
72	Gov	2007	3									90					

Appendix A15 Continued

Reference	Source	Year	No. of Citations	Trigger 1	Trigger 2	Trigger 3	Trigger 4	Trigger 5	Trigger 6	Trigger 7	Trigger 8	Trigger 9	Trigger 10	Trigger 11	Trigger 12	Trigger 13	Trigger 14
73	Acd	2007	3									69					
74	Acd	2007	1									38					
75	Acd	2008	0									70					
76	Org	2009	0										9				
77	Org	2009	0										8				
78	Con	2001	21											104			
79	Org	2000	35											17			
80	Ind	2009	0											16			
81	Acd	2001	83											115			
82	Acd	2006	153												134		
83	Org	2006	0												7		5
84	Acd	2007	36												135		
85	Org	2009	1												6		
86	Org	2005	0			129										4	
87	Acd	2006	33													132	
88	Org	2003	3														3
N	146		n	11	16	22	6	15	8	7	8	7	5	7	6	11	17
sample size = 82		# of triggers K=14	Rank	7	**3**	**1**	12	**4**	13	9	6	11	14	8	10	5	**2**

APPENDIX B: Survey Material

B1 Participant Information Leaflet
B2 Pilot Questionnaire
B3 Summary of Completed Pilot Survey Questionnaires
B4 Study Protocol for Expert Opinion Survey
B5 Pilot Participant Comments during the Cognitive Interviews

PARTICIPANT INFORMATION LEAFLET

A Survey of expert opinion on Pharmaceutical Quality Risks

We would like to invite you to take part in research to better understand the quality risks in the pharmaceutical industry due to business, technology and regulatory transformation currently underway. This leaflet gives you more information about the study – please read it carefully before deciding whether to take part or not. If you would like to take part in the study:

- You will received an e-mail asking to complete a questionnaire
- You will be required to attend a 30 minutes teleconference to learn about the study and the questionnaire
- Your return of the completed questionnaire to the investigator will indicate your consent
- You will receive the anonymised version of the survey results

What is the purpose of the study?
The ongoing transformational and disruptive changes in Pharma business, technology and regulations are having significant impact on pharmaceutical quality. Open innovation is a key characteristic of the ongoing industry transformation and it will pose new challenges to Pharmaceutical Quality. The aim of this research is to identify transformation-induced quality risks and develop a *Theoretical Quality Risk Model* to characterise the relationship between transformation-induced quality risks and the regulatory compliance outcomes. The aim of this survey is to support the outlined research by determining the opinions of experts in the field of pharmaceutical innovation regarding transformation-induced quality risks and its impact / influence on regulatory compliance.

Why have I been invited?
You are invited to contribute to this original research because you are a recognised expert in the field of pharmaceutical quality and your opinion will greatly benefit the outcome of this research.

Do I have to take part?
No. It is up to you to decide whether to take part. Before you decide, we ask you to read this information leaflet. If there is anything that is not clear or if you would like more information, please contact the principal investigator using the details given at the end of this leaflet. You can withdraw from the study at any time.

What are the possible benefits of taking part?
As a pharmaceutical quality expert you will contribute to and shape needed research in the field of pharmaceutical quality by sharing your expert opinion via this survey. You will receive a summary of the anonymised findings and conclusions of the survey.

What are potential risks?
Since the study involves a Questionnaire completed at participant' convenience it is unlikely that any adverse effects, risks or hazards are involved.

Will my taking part in the study be kept confidential?
Yes, in order to conceal your identity the questionnaires will be anonymised. Safeguards are in place to prevent other participants from connecting your responses to you. No information you provide will be attributable or provided to other individual participants.

What will happen to the results of the study? The anonymised results will be used in the development of a PhD thesis and research papers, which will be submitted to international journals.

For further information on any aspect of the study contact:
Nader Shafiei Tel: +1 (908) 391-1206 e-mail:
(N.Shafiei@2009.ljmu.ac.uk)

In case of complaints contact Director of studies:
Professor James L. Ford Tel: +44 (151) 231-2096 e-mail: (J.L.Ford@ljmu.ac.uk)

Thank you: we hope that you will take part in this study.

This study is sponsored by the Liverpool John Moores University and has been given a Favourable ethical opinion by LJMU Research Ethics Committee (11/PBS/004). Ref: NS_PhD_LJMU_PIL_1.1

B2 - PILOT QUESTIONNAIRE

A survey of expert opinion on *Pharmaceutical Quality Risks*

This survey is the empirical component of the research being conducted by Nader Shafiei, a PhD student in the School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University.

The aim of this survey research is to determine the opinions of experts in the field of pharmaceutical innovation regarding transformation-induced quality risks and its impact / influence on regulatory compliance.

Completing the questionnaire should take no longer than 60 minutes.

Participation in this study is voluntary and completion of this questionnaire implies consent. The questionnaire and data are anonymised. Publication of study results will be managed using the anonymised data. This study has received unconditional ethical approval from Liverpool John Moores Research Ethics Committee – Ref: 11/PBS/004.

Thank you for completing this questionnaire. Ref: NS_PhD_LJMU_QAR_1.0

Appendix B2 Continued

SECTION A – Definitions and Instructions

This first section of the questionnaire provides you with definition of some key terms used throughout this document plus instructions on how to complete the questionnaire.

Definitions / Acronyms	Source
GxP – Good Laboratory, Clinical, Manufacturing Practices	
ICH – International Conference on Harmonization	
Innovation – the introduction of new technologies or methodologies	ICH Q10
Open Innovation - the practice of leveraging the discovery of others and not rely exclusively on own R&D for innovation	Chesbrough H, Kardon Crowther A. (2006). "Beyond high tech: early adopters of open innovation in other industries"
Pervasive Technologies – smart implantable devices used for product tracking, remote patient monitoring or drug delivery	Blended definition
Pharma Transformation - is concerned with ongoing disruptive changes currently shaping the operational concepts, organization, and technologies impacting pharmaceutical innovation and the ability to meet the demands of a changing healthcare environment	Blended definition
Post-market Surveillance – Regulatory agency risk assessment activities that take place after approval of the drug product	FDA
Pre-market Assessment – Regulatory agency risk assessment activities that take place prior to approval of the drug product	FDA
Product Lifecycle - all phases in the life of the product from the initial development through marketing until the product's discontinuation	ICH Q9
Quality – the degree to which a set of inherent properties of a product, system or process fulfils requirements	ICH Q9
Quality Risk – a GxP activity that if not performed properly may have the potential to result in adverse events impacting product quality, data integrity or patient safety	Blended definition

Appendix B2 Continued

Instructions:

This questionnaire has been designed to be filled electronically in MSWord or manually by hand written means. Specific instructions are provided in each section. Here we provide some guidance on how to complete the questionnaire and its subsequent transmission to the principal investigator.

When filling electronically, to make your selection please double click on the selection box and under the "default value" section select the "checked" radio button. Save the completed questionnaire in your PC hard drive.

When filling manually please scan the completed questionnaire and save it in your PC hard drive.

Please return the completed questionnaire (electronic version or scanned copy) via e-mail to the principal investigator at N.Shafiei@2009.ljmu.ac.uk.

SECTION B - Participant Details

This section of the questionnaire requires you to give some information about your expertise and type of organization you represent. It is important that we are able to categorise your opinion in relation to your business, regulatory and quality perspective.

Please complete the question 2 with the relevant information. For questions 3 to 5 check/tick all that apply.

1. Expert identification code:	EE-SS-CC-RR-NN - assigned by the investigator
2. Organization name:	
3. Regulatory domain of expertise:	US–FDA ☐ EU-EMA ☐ Other ☐
4. Organization type:	Big Pharma ☐ Small Pharma ☐ Consulting ☐ Contract R/M Organization ☐ R/M - Research/Manufacturing Other: Please specify

5. Experience in: Pharmaceuticals ☐ Biopharmaceuticals ☐

6. Quality domain of expertise: GLP ☐ GCP ☐ GMP ☐ GxP ☐

SECTION C – Pharma Transformation Triggers and Risks

This section asks a number of questions to elicit your opinion about factors that characterise pharmaceutical transformation currently underway in the industry.

Please answer questions 6 to 8 by placing a check/tick in the relevant boxe(s) that indicate your answer. If you also select "other" please specify your answer.

6. Which of the following is a key driver for the current Pharmaceutical Transformation?

Business Environment ☐ Regulatory Environment ☐
Open Innovation ☐
Other (please specify):

7. Which of the following Open Innovation trends do you think is currently practiced in the pharmaceutical industry?

Commercial Partnerships ☐ Increased In Licensing ☐
Research Partnerships ☐ Research Information Sharing ☐
Focus on Combination Products ☐ Focus on Biological Products ☐
Focus on Pervasive Technologies ☐ Externalization of S/W Applications ☐
Other (please Specify):

8. Lack of which of the following will pose a GxP Risk in an Open Innovation environment?

Effective Due Diligence ☐ Effective Product Transfer ☐
Multidisciplinary Regulatory Knowledge ☐ Effective Product Characterization ☐
Technology Validation ☐ Data Security and Integrity ☐
Other (please Specify)

Appendix B2 Continued

SECTION D – Open Innovation and Regulatory Compliance

This section asks a number of questions regarding your experience and opinion on impact of Open Innovation on GxP related activities the relationship between Regulation and Innovation drive in the industry.

Please answer questions 9 to 16 by placing a check/tick in the box that best represents your answer. Optionally use "Comments" field expand on your opinion.

9. Open Innovation will have significant impact on external partner/alliance selection and oversight?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

10. Open Innovation will have significant impact on legal framework for exchange of research information?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

11. Open Innovation will have significant impact on data management in the context of data security, integrity and privacy?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

12. Biological/Biotech products will become major part of the project and product portfolio?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

13. Prevalence of pervasive technologies will require multidisciplinary knowledge and skills to deal with convergent scientific disciplines (e.g. smart implantable drug delivery devices)?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

14. Existing regulatory approaches are adversely impacting the innovation drive in the industry?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

15. Smarter regulatory approach that is responsive to new discoveries while maintaining safety and efficacy standards will improve innovation drive?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

16. Regulatory initiatives such as FDA's Critical Path and EMA's Innovation Task force (ITF) will have a significant impact in industry's innovation drive?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

SECTION E – Assessment of Transformation-Induced Quality Risks

This section asks a number of questions about your experiences regarding Pharmaceutical Quality Risks present in an open innovation environment and their likelihood to cause regulatory compliance problems.

Please answer questions 17 to 35 by placing a check/tick in the box that best represents your answer. Optionally use "Comments" field for additional information.

a) GxP Due Diligence of External Partners and Alliances - Lack of effective GxP due diligence has the potential to result in:

17. Selection of external alliances / partners with significant GxP compliance problems?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

Appendix B2 Continued

18. Adverse GxP inspection outcomes during pre-market evaluation?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

19. Adverse GxP inspection outcomes during post-market surveillance?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

b) Product Transfer - Lack of effective product transfer policy and procedures has the potential to result in:

20. Poor process understanding?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

21. Significant problems with control methods (release testing and cleaning validation)?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

22. Adverse GxP inspection outcomes during pre-market evaluation?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

23. Adverse GxP inspection outcomes during post-market surveillance?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

c) Multidisciplinary Regulatory Approach - Lack of multidisciplinary quality knowledge and skills has the potential to result in:

24. Inability to maintain quality and compliance effectiveness across a range a regulatory situations (e.g. combination products that may require regulatory knowledge of diagnostics, drugs and devices)?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

25. Adverse GxP inspection outcomes during pre-market evaluation?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

26. Adverse GxP inspection outcomes during post-market surveillance?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

d) Biological/Biotech Products

27. Are more complex and difficult to characterise than chemically synthesised products?

Yes ☐ No ☐ Don't Know ☐

Comments

Lack of robust processes for product contamination, sterility and stability control has the potential to result in:

28. Adverse GxP inspection outcomes during pre-market evaluation?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

Appendix B2 Continued

29. Adverse GxP inspection outcomes during post-market surveillance?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

e) Data Security and Integrity - Lack of robust procedures for outsourcing and alliance management has the potential to result in:

30. Data security, integrity and privacy issues during product lifecycle?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

31. Adverse GxP inspection outcomes during pre-market evaluation?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

32. Adverse GxP inspection outcomes during post-market surveillance?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

f) Technology Validation - Lack of validation methods for pervasive technologies has the potential to result in:

33. Unreliable product performance resulting in adverse events or customer complaints?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

34. Adverse GxP inspection outcomes during pre-market evaluation?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

35. Adverse GxP inspection outcomes during post-market surveillance?

Very Unlikely ☐ Unlikely ☐ Likely ☐ Very Likely ☐ Don't Know ☐

Comments

Please initial here Please return the completed questionnaire (electronic version or scanned copy) via e-mail to the principal investigator at **N.Shafiei@2009.ljmu.ac.uk** Thank you for taking time to complete this questionnaire.

B3 - SUMMARY OF COMPLETED PILOT SURVEY QUESTIONNAIRES

LJMU Ethical Approval : 11/PBS/004

SECTION B - Participant Details This section of the questionnaire requires you to give some information about your expertise and type of organization you represent. It is important that we are able to categorise your opinion in relation to your business, regulatory and quality perspecti *Please complete the question 2 with the relevant information. For questions 3 to 6 check/tick all that apply.*		Interview Date 1-Sep-11 AM-BP-SA-UE-01	Interview Date 9-Sep-11 IS-BP-SA-UE-02	Interview Date 15-Sep-11 AD-BP-SA-US-03	Interview Date 16-Sep-11 OI-BP-SA-UE-04	Interview Date 19-Sep-11 IR-BP-SA-UE-05	Interview Date 22-Sep-11 AN-BP-SA-US-06
1. Expert identification code:							
2. Organization name:		Sanofi R&D Quality	Sanofi R&D Quality	Sanofi GQA	Sanofi IQC	Sanofi GQA	Sanofi R&D
3. Regulatory domain of expertise:	US–FDA	x	x	x	x	x	x
	EU-EMA	x	x		x	x	
	Other (please specify):		Japan, latAm		Health Canada	TGA, LatAm	OECD
4. Organization type:	Big Pharma	x	x	x	x	x	x
	Small Pharma						
	Consulting						
	Small Pharma						
	Contract Research/Manufacturing Organization						
	Other (please specify):						
5a. Experience in:	Pharmaceuticals	x	x	x	x	x	x
	Biopharmaceuticals	x			x	x	

Appendix B3 Continued

5b. Years of Experience:	5 to 10						
	10 to 15						
	15+	x	x	x	x	x	x
6. Quality domain of expertise:	GLP				x		x
	GMP	x		x	x	x	x
	GCP		x				
	GxP						x
SECTION C – Pharma Transformation Triggers and Risks *Please answer questions 7 to 9 by placing a check/tick in the relevant box/boxes that indicate your answer. If you also select "other" please specify your answer.*							
7. Which of the following is a key driver for the current Pharmaceutical Transformation?	Business Environment	x	x		x		x
	Regulatory Environment	x	x	x	x	x	x
	Open Innovation	x		x		x	x
	Other (please specify):		1	1		2	
8. Which of the following Open Innovation trends do you think is currently practiced in the pharmaceutical industry?	Commercial Partnerships	x	x	x	x		x
	Increased In Licensing	x	x	x	x	x	
	Research Partnerships	x	x	x	x	x	x
	Research Information Sharing	x					x
	Focus on Combination Products	x			x		
	Focus on Biological Products	x	x	x	x	x	x
	Focus on Pervasive Technologies		x		x	x	x
	Externalization of S/W Applications	1			x		
	Other (please Specify):	1			1	1	2

Appendix B3 Continued

9. Lack of which of the following will pose a GxP Risk in an Open Innovation environment?	Effective Due Diligence	x	x	x	x	x	x
	Effective Product Transfer	x	x	x	x	x	x
	Multidisciplinary Regulatory Knowledge	x	x		x	x	x
	Effective Product Characterization	x	x	x	x	x	x
	Data Security and Integrity	x	x	x	x	x	x
	Technology Validation	x	x	x	x	x	x
	Other (please Specify)		1		3	3	1
SECTION D – Open Innovation and Regulatory Compliance *Please answer questions 10 to 17 by placing a check/tick in the box that best represents your answer. Optionally use "Comments" field to expand on your opinion.*							
10. Open Innovation will have significant impact on external partner/alliance selection and oversight?	Very Unlikely						
	Unlikely						
	Likely		x				
	Very Likely	x		x	x	x	x
	Don't Know						
	Comments:	1					
11. Open Innovation will have significant impact on legal framework for exchange of research information?	Very Unlikely						
	Unlikely						
	Likely				x		
	Very Likely	x				x	x
	Don't Know		x	x			
	Comments:	1				1	1

Appendix B3 Continued

12. Open Innovation will have significant impact on data management in the context of data security, integrity and privacy?	Very Unlikely						
	Unlikely						
	Likely						
	Very Likely	x	x	x	x	x	x
	Don't Know						
	Comments:						
13. Biological/Biotech products will become major part of the project and product portfolio?	Very Unlikely						
	Unlikely						
	Likely				x		
	Very Likely	x	x	x		x	x
	Don't Know						
	Comments:					1	
14. Prevalence of pervasive technologies will require multidisciplinary knowledge and skills to deal with convergent scientific disciplines (e.g. smart implantable drug delivery devices)?	Very Unlikely						
	Unlikely						
	Likely						x
	Very Likely	x	x		x	x	
	Don't Know			x			
	Comments:	1			1		1
15. Existing regulatory approaches are adversely impacting the innovation drive in the industry?	Very Unlikely						
	Unlikely	x	x				
	Likely			x	x		x
	Very Likely					x	
	Don't Know						
	Comments:	1			1		1

Appendix B3 Continued

16. Smarter regulatory approach that is responsive to new discoveries while maintaining safety and efficacy standards will improve innovation drive?	Very Unlikely						
	Unlikely					x	
	Likely		x	x			
	Very Likely	x			x		x
	Don't Know						
	Comments:	1				1	
17. Regulatory initiatives such as FDA's Critical Path and EMA's Innovation Task force (ITF) will have a significant impact in industry's innovation drive?	Very Unlikely						
	Unlikely				x	x	x
	Likely		x				
	Very Likely						
	Don't Know	x		x			
	Comments:			1	1	1	1
SECTION E – Assessment of Transformation-Induced Quality Risks This section asks a number of questions about your experiences regarding Pharmaceutical Quality Risks present in an open innovation environment and their likelihood to cause regulatory compliance problems. *Please answer questions 18 to 36 by placing a check/tick in the box that best represents your answer. Optionally use "Comments" field for additional information.*							
a) GxP Due Diligence of External Partners and Alliances - Lack of effective GxP due diligence has the potential to result in:					1		1
18. Selection of external alliances / partners with significant GxP compliance problems?	Very Unlikely						
	Unlikely						
	Likely				x		x
	Very Likely	x	x	x		x	
	Don't Know						
	Comments:				1		1

Appendix B3 Continued

19. Adverse GxP inspection outcomes during pre-market evaluation?	Very Unlikely						
	Unlikely						
	Likely		x		x		
	Very Likely	x		x		x	
	Don't Know						x
	Comments:	1	2	1	1	1	1
20. Adverse GxP inspection outcomes during post-market surveillance?	Very Unlikely						
	Unlikely	x					
	Likely				x		
	Very Likely		x			x	
	Don't Know			x			x
	Comments:	1		1			
b) Product Transfer - Lack of effective product transfer policy and procedures has the potential to result in:							1
21. Poor process understanding?	Very Unlikely						
	Unlikely						
	Likely				x		
	Very Likely	x	x	x		x	x
	Don't Know						
	Comments:				1	1	
22. Significant problems with control methods (release testing and cleaning validation)?	Very Unlikely						
	Unlikely						
	Likely		x		x		x
	Very Likely	x		x		x	
	Don't Know						
	Comments:						1

Appendix B3 Continued

23. Adverse GxP inspection outcomes during pre-market evaluation?	Very Unlikely						
	Unlikely						
	Likely			x	x	x	
	Very Likely	x	x				
	Don't Know						x
	Comments:				1		1
24. Adverse GxP inspection outcomes during post-market surveillance?	Very Unlikely						
	Unlikely						
	Likely				x	x	
	Very Likely	x	x	x			
	Don't Know						x
	Comments:						
c) Multidisciplinary Regulatory Approach - Lack of multidisciplinary quality knowledge and skills has the potential to result in:				1	1	1	

Appendix B3 Continued

25. Inability to maintain quality and compliance effectiveness across a range of regulatory situations (e.g. combination products that may require regulatory knowledge of diagnostics, drugs and devices)?	Very Unlikely						
	Unlikely						
	Likely		x				x
	Very Likely	x		x		x	
	Don't Know				x		
	Comments:	1				1	

Appendix B3 Continued

26. Adverse GxP inspection outcomes during pre-market evaluation?	Very Unlikely						
	Unlikely						
	Likely						x
	Very Likely	x	x	x		x	
	Don't Know				x		
	Comments:	1	1				1
27. Adverse GxP inspection outcomes during post-market surveillance?	Very Unlikely						
	Unlikely						
	Likely						x
	Very Likely	x	x	x		x	
	Don't Know				x		
	Comments:	1					
d) Biological/Biotech Products							
28. Are more complex and difficult to characterise than chemically synthesised products?	Yes	x	x	x	x	x	x
	No						
	Don't Know						
	Comments						
Lack of robust processes for product contamination, sterility and stability control has the potential to result in:			1	1	1	1	

Appendix B3 Continued

29. Adverse GxP inspection outcomes during pre-market evaluation?	Very Unlikely						
	Unlikely						
	Likely						
	Very Likely	x	x	x	x	x	x
	Don't Know						
	Comments:						

Appendix B3 Continued

30. Adverse GxP inspection outcomes during post-market surveillance?	Very Unlikely						
	Unlikely						
	Likely						
	Very Likely	x	x	x	x	x	x
	Don't Know						
	Comments:						1
e) Data Security and Integrity - Lack of robust procedures for outsourcing and alliance management has the potential to result in:				1			
31. Data security, integrity and privacy issues during product lifecycle?	Very Unlikely						
	Unlikely						
	Likely		x			x	x
	Very Likely	x		x	x		
	Don't Know						
	Comments:	1		1		1	1
32. Adverse GxP inspection outcomes during pre-market evaluation?	Very Unlikely						
	Unlikely						
	Likely		x		x	x	x
	Very Likely	x		x			
	Don't Know						
	Comments:	1		1	1	1	
33. Adverse GxP inspection outcomes during post-market surveillance?	Very Unlikely						
	Unlikely						x
	Likely		x		x	x	
	Very Likely	x		x			
	Don't Know						
	Comments:	1				1	1

Appendix B3 Continued

f) Technology Validation - Lack of validation methods for pervasive technologies has the potential to result in:			1	1			
34. Unreliable product performance resulting in adverse events or customer complaints?	Very Unlikely						
	Unlikely						
	Likely						x
	Very Likely	x	x		x	x	
	Don't Know			x			
	Comments:						
35. Adverse GxP inspection outcomes during pre-market evaluation?	Very Unlikely						
	Unlikely					x	
	Likely				x		x
	Very Likely	x	x				
	Don't Know			x			
	Comments:				1		
36. Adverse GxP inspection outcomes during post-market surveillance?	Very Unlikely						
	Unlikely						x
	Likely				x		
	Very Likely	x	x			x	
	Don't Know			x			
	Comments:				1	1	1

STUDY PROTOCOL

A Survey of expert opinion on Pharmaceutical Quality Risks

PROTOCOL NUMBER:
NS_PhD_LJMU_SP_1.0

PROTOCOL VERSION:	Draft 1	Draft 2	Draft 3	Draft 4	Draft 5
	Draft 6	Draft 7	Draft 8	Version 1.0	
PROTOCOL DATE:	23 Feb 11	3 Mar 11	25 Mar 11	29 Apr 11	1 Jun 11
	3 Jun 11	4 Jun 11	7 Jun 11	8 June 2011	

PRINCIPAL INVESTIGATOR:
Nader Shafiei, PhD Student, School of Pharmacy & Biomolecular Sciences, Liverpool JMU

STUDY SITE:
Not Applicable

STUDY DATE:
Start Date: June 2011 End Date: Dec 2011

STUDY SUPERVISORS:
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Collaborators:
Sanofi-aventis Pharmaceuticals, 200 Crossing Boulevard, Bridgewater, NJ 08807, USA

GOVERNING POLICIES/PROCEDURES:
Code of Practice for Research (LJMU)
Obtaining Informed Consent for Research Participation (LJMU)
Data Protection and Retention of Research Data (LJMU)
File Management, Backup and Recovery (LJMU)

Appendix B4 Continued

1 BACKGROUND AND RATIONALE

1.1 Pharmaceutical regulations and quality

Historically the pharmaceutical industry is heavily regulated particularly in Europe Union (EU) and the United States (US) with the primary aim to protect and promote public health but also to respond to unexpected crisis. Since the pharmaceutical industry develops and manufacture products that affect patients' quality of life, world governments have a keen interest in the industry and its products.

The regulatory environment in the EU is driven by the need to ensure free movement of goods and protection of public health [Hartmann]. Regulatory procedures have been standardised and the European Medicines Agency (EMA) has been established to approve medical products for all EU countries (Tancer, 2002; Li Bassi, 2003).

In contrast, the regulatory environment in the US has been shaped by series of reactive steps of legislation adaptation in response to public health crises [Borchers, Slater]. This led to the establishment of the Food, Drug Administration (FDA) in 1906, which was primarily charged to protect public health. Since its inception, it has gained additional responsibility to advance public health by helping to speed innovations that make medicines safer, more effective and affordable. Up to 1980s the focus of regulators was Centred on crisis management and public health protection - a basic mission that has remained consistent over the years [US Supreme Court].

A review of the regulatory events indicates that since 1980s there has been a gradual change in regulatory direction towards a greater focus on public health promotion, international harmonization, innovation, and risk management.

The regulatory harmonization is achieved through the International Conference on Harmonization (ICH). Launched 20 years ago, ICH brings together the drug regulatory authorities of Europe, Japan, and the United States, along with the pharmaceutical trade associations from these three regions, to discuss scientific and technical aspects of product registration. It is ICH's mission to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines (ICH Anniversary, 2010).

Innovation in this context relates to establishment of a robust regulatory science program aimed at strengthening advances in biomedical sciences. Regulatory science is critical to effectively translate cutting edge developments in science and technology into promising products and therapies for the patients who need them. Just as biomedical research has evolved over the past few decades, regulatory science must also evolve in important and powerful ways (FDA Priorities, 2010; EMA Roadmap, 2010).

Risk management is another key regulatory focus that intends to define a framework to improve regulator's ability to adjust the level of regulatory scrutiny commensurate with public health risk, a major component of which concerns inspection of pharmaceutical company's laboratory, clinical, manufacturing, and distribution practices.

There is a key difference between the pharmaceutical and other industries regarding product quality, safety and data-integrity. In the pharmaceutical industry quality practices are mandated by law and require establishment of an independent internal *Quality Unit* whereas in most other industries quality is often a voluntary activity. Within the pharmaceutical context, the health authorities accomplish their regulatory scrutiny through review of new product applications and inspection of laboratory, clinical, manufacturing, and distribution practices. The regulators rely on the industry to do internal supervision through their *Quality Unit.* The role of the *Pharmaceutical Quality* (through the *Quality Unit*) is to establish and monitor internal standards to ensure product quality, patient safety and data integrity from the GxP[8] perspective. The extent to which each pharmaceutical company meets GxP requirements has a direct impact on their ability to obtain approvals for their products and maintain the marketing authorization for those products.

1.2 What is the problem?

The change in regulatory direction stated above, is because the pharmaceutical industry in the last couple of decades has experienced a significant decline in productivity despite revolution in

[8] GxP - Good *Laboratory / Clinical / Manufacturing / Distribution* Practices

biomedical sciences and increasing Research & Development (R&D) expenditure. According to FDA, the problem exists because the current medical product development path is becoming increasingly challenging, inefficient, and costly. FDA in its 2004 landmark publication "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" (FDA CPI, 2004) illustrated that between 1993 and 2003 the agency saw a significant drop in a number of new chemical and biologic applications submitted for approval. This, the agency claims is because rising costs of product development often force the innovators to focus their efforts on products with potentially high market return. This consequently poses a major public health concern since less resources is deployed on products targeted for important public health needs such as rare diseases, prevention indications, or individualised therapies. This and other factors such as dramatic increase in number of non-domestic R&D and manufacturing facilities (due to globalization) and diversity and complexity of medical products and processes (due to advances in pharmaceutical sciences) also play a key role in regulatory bodies to make transformational changes in how they work with the industry to protect and promote public health.

1.3 What are the regulators doing?

Both the FDA and EMA have strategic initiatives to address the innovation problem. The FDA's national strategy for transforming the way FDA-regulated medical products are developed, evaluated, and manufactured involves the Critical Path Initiative (CPI).

In Europe the EMA initially started by establishing the Innovation Task Force (ITF) in 2001. EMA expanded this effort through the publication of its March 2007 report "Innovative Drug Development Approaches" with the aim of identifying scientific bottlenecks to the development of innovative medicines, both in the industry's R&D and in the academic environment.

Review of the outlined reports and related documents revealed the following common innovation enablers:

- Better product safety toolkit and standards - show that product is adequately safe for each stage of development
- Better product effectiveness toolkit and standards - show that product benefits people
- Better product manufacturing toolkit and standards – show product manufacturability, that it can go from laboratory concept to a manufacturable product
- Better product quality risk management toolkit and standards – show that the level of regulatory scrutiny can be adjusted commensurate with public health risk

1.4 What is the industry doing?

To address the innovation problem the industry has been going through significant transformational changes affecting the business model (R&D, manufacturing, etc.), regulatory compliance and technology. Open innovation (Chesbrough, 2006) is a key characteristic of the ongoing industry transformation. In the open innovation paradigm centralised and internally focused approach to innovation is becoming obsolete and the pharmaceutical companies are not only trying to create value internally but increasingly leveraging external sources of innovation (small biotech, universities, research partnerships, etc.). Industry transformation triggers are characterised by the literature review conducted as part of the current PhD effort titled "Science and Risk Based Pharmaceutical Quality". The important point to note is that the transformation triggers in the context of open innovation paradigm pose considerable challenges to Pharmaceutical Quality which needs further research which is the main subject of this Study Protocol.

The industry is also fully engaged with the ICH effort on establishing international quality guidelines as an enabling toolkit to help improve innovation, as detailed above.

1.5 What is role of Pharmaceutical Quality?

Achievement of the goals implied in the outlined common innovation enablers requires expertise throughout the medical product lifecycle, including contribution of the *Pharmaceutical Quality* (OECD, 1997; ICH E6, 1996; PIC/S, 2009). To harmonise practices for this contribution the regulatory agencies and industry started collaboration under the auspices of the ICH. This effort resulted in the following important quality guidelines that have been adopted internationally:

- Pharmaceutical Quality Risk Management – provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality (ICH Q9, 2005)
- Pharmaceutical Development – describes the process for presenting the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process (ICH Q8, 2005)
- Pharmaceutical Quality Systems - describes model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle (ICH Q10, 2008)

1.6 Literature Search: transformational triggers

The regulatory and industry transformation has already been characterised via literature review and supported by archive analysis (Flynn, 1990) - i.e. validation of literature findings through existing empirical evidence. Review of 82 articles (1998 to 2009) yielded a total of fourteen transformation triggers of which the following four were determined to have the highest importance and were selected for further analysis (see highlighted rows in Table 1 below). The open innovation trends for each of the four transformation triggers were identified and the associated transformation-induced quality risks were determined (Figure 1).

Qualitative analysis of the literature identified the fourteen transformation triggers referenced below as the key drivers for the industry transformation. The four selected triggers are the most prevalent within the articles studied, have the strongest empirical evidence, and pose substantive challenge to regulatory science since they introduce innovative changes to the way medical products are discovered, developed, manufactured and registered. This is why they are selected for further analysis.

Transformation Triggers	Relative importance derived from literature	Open Innovation Trends (prevalence of)	Transformation-induced Quality Risk areas
Healthcare Management Focus – T1	6		
Fully Integrated Pharma Network – T2	**3**	External Partnerships In-Licensing	Effective Due-Diligence Effective Product Transfer
Personalised Medicine – T3	**1**	Combination Products Biotech Products	Multidisciplinary Reg. Knowledge Product Characterization
Virtual R&D – T4	11		
Translational Research – T5	**4**	Research Partnership Information Sharing	Effective Due-Diligence Data Security and Integrity
Adaptive and In-life Trials – T6	12		
Global Harmonization – T7	9		
Science & Risk Based Regulations – T8	7		
Live Licensing – T9	13		
Enforcement – T10	14		
Biotechnology – T11	8		
Nanomedicine – T12	10		
Bioinformatics – T13	5		
Pervasive/ Cloud Computing – F14	**2**	Tiny Smart Implantable Devices Externalization of s/w Solutions	Technology Validation Data Security and Integrity

Table 1 - Transformation Triggers

Fully Integrated Pharma Network: refers to a business model where pharmaceutical companies would have a fully integrated global network that includes other pharmaceutical or biotech companies, universities, organizations, and even individuals in some cases.
Personalised Medicine: is Centred on specific treatments and therapeutics best suited for an individual.
Translation Research: describes a bi-directional sharing of knowledge and ideas by the scientific and clinical disciplines to develop diagnostics that reliably select the mechanisms leading to breakthrough therapeutics.
Pervasive Computing: this is characterised as an environment saturated with computing and communication capability. Smart medication packaging, tiny wireless sensors implanted on the patient body to monitor various vital signs, and remote monitoring devices to determine how patients respond during clinical trials are just some examples.
Cloud Computing: is a computing model consisting of services that are commoditised and delivered in a manner similar to traditional utilities such as water, electricity, gas, and telephony. In such a model, users access services based on their requirements without regard to where the services are hosted or how they are delivered.

Transformation-induced quality risks for these four triggers are listed in Table 1. These quality risks can potentially result in major adverse regulatory compliance outcomes if not managed properly. In order to facilitate development of a pharmaceutical *Quality Risk Model* for the new environment the relationship between transformation-induced risks and the regulatory compliance outcomes must be characterised. This goal will be achieved through a survey which remainder of this document will describe.

1.7 Importance to the Pharmaceutical Industry

There is academic research in support of the common innovation enablers highlighted in section 1.3 (NIH Research, 2009); EMA Research, 2010). The research is mainly concentrated on the safety and efficacy aspects. Although *Pharmaceutical Quality* is playing a key role however there is no academic research to support this fact. Furthermore there is no academic research exploring the *Quality Risk Model* needed to cope with the new environment. Review of the 38 most cited quality management articles published between 1989 and 2009 revealed only 2 articles that studied pharmaceutical industry. Neither of these articles focuses on the industry transformation. Therefore, there is a real need for research to characterise the regulatory evolution and industry transformation, identify the most important transformation triggers, determine the impact on *Pharmaceutical Quality*, and develop a *Quality Risk Model* for the new environment.

2 SURVEY AIM

The aim of this survey research is to determine the opinions of people who are experts in the field of pharmaceutical innovation regarding transformation-induced quality risks and its impact / influence on regulatory compliance.

3 SURVEY DESIGN

3.1 Design Overview

The research study involves a questionnaire-based survey with participants who are experts in the field of Pharmaceutical Quality. The survey will be piloted to ensure the reliability and validity of the questionnaire and the robustness of the data analysis methods. The design approach and methodology used for data collection / analysis are described below for the piloting activity as well as the actual survey:

<u>Piloting the survey (mixed method – qualitative and quantitative)</u>

- Purpose is to i) assess validity and reliability of the questionnaire and ii) robustness of the data analysis method selected for the actual survey
- Design approach will be based on cognitive interviewing using verbal probing technique
- Data will be collected using the interview notebook
- Collected data will be analyzed using qualitative description of the emerging themes, quantitative description of the classified observations, and quantitative analysis of the responses to the questionnaire

- Expected outcome is improved questionnaire and confirmation that the selected data analysis method for the actual survey is appropriate

Conducting the survey (quantitative method)

- Purpose is to solicit expert opinion on the relationship between the transformation induced quality risks (independent variables) and regulatory compliance (dependant variables)
- Survey design is based on relational non-experimental fixed method (Robson, 2002)
- Data will be collected using the questionnaire in appendix 3
- Collected data will be analyzed using descriptive statistics
- Expected outcome will be the frequency distribution for the independent variables and the description of the relationship between independent and dependant variables

3.2 Questionnaire Design

The questionnaire has been designed to measure expert opinion with questions being derived from the literature. It is important to note that the questions are compiled around four categories of pharmaceutical transformation triggers, open innovation, transformation-induced quality risks, and regulatory compliance outcomes in alignment with the literature review. This is demonstrated by comparing key topic in the questionnaire with topics highlighted in Figure 1.

The questionnaire contains a number of close-ended questions based on Likert Scale with four options (Leal et al., 2007): 1. Very Unlikely 2. Unlikely 3. Likely 4. Very Likely including an option for Don't Know. The rationale behind choosing a four-interval measurement scale is to avoid gravitation toward Centre and encourage the participants who are recognised experts in this field to take a clear stance. The questions are categorised into four sections with an additional section focusing on participant instructions and definition of terms, these are listed below:

Section A: Definitions and Instructions to the participants
Section B: Participant Details
Section C: Pharma Transformation Triggers & Risks
Section D: Open Innovation and Regulatory Compliance
Section E: Assessment of Transformation-Induced Quality Risks

a) Piloting the Questionnaire

The questionnaire will be piloted to determine its reliability and validity by interviewing participants recruited from the collaborator organization (sanofi-aventis – Table 2) using the cognitive interviewing method (Robson, 2002; Carmines, 1979, Wallis, 1999).

Pilot interview participants	**Quality experience in**	**Product type knowledge**	**Domain of regulatory knowledge**
EA-BP-SA-UE01	Pharmaceutical Development Clinical Development	Biologics	US (FDA) EU (EMA)
AM-BP-SA-UE02	Pharmaceutical Development	Pharmaceutical Biologics	US (FDA) EU (EMA)
IS-BP-SA-UE03	Clinical Development	Pharmaceutical	US (FDA) EU (EMA)
IA-BP-SA-US04	Pharmaceutical Development	Biologics	US (FDA)
IA-BP-SA-EU05	Manufacturing	Pharmaceutical	EU (EMA)
IR-BP-SA-UE06	Manufacturing	Pharmaceutical Biologics	US (FDA) EU (EMA)

Table 2 – Questionnaire Piloting: Participant list and profile

b) Cognitive Interviewing

During piloting, the cognitive interviewing methodology will be applied using the verbal probing technique (Wallis, 1999). The focus of the verbal probing will be on the survey questions. A one-hour interview will be set up with each of the participants during which the interviewer asks the

survey question, the participant answers, the interviewer then asks for other specific information relevant to the question, or to the specific answer given. In general, the interviewer "probes" further into the rationale and basis for the response. Key benefit is to improve the questions by exploring issues relating to participant comprehension and identify structural problems such as erroneous skip patterns and unclear layout during the interview process.

The pilot interview notebook will be used to collect the observations. The notebook will contain the questions, participant's response to the questions, and classification of any comments that the participant makes related to the question or the survey procedure. The participant comments are classified into the following categories (each category within the notebook will have an associated selection box for the interviewer to choose depending on the nature of the comment):

Reliability related comments:

- Survey procedure
- Logical layout and flow of the questions
- Clarification for better understanding
- Spelling or grammatical errors/suggestions

Validity related comments:

- Appropriateness of the measurement scale
- Challenges to the usefulness/validity of the question

This interview captures two types of data. Participant's responses to survey questions and participants comments relating to the reliability and validity assessment. The actual survey will not start until the piloting activity is completed and the ensuing improvements are implemented.

c) Reliability and Validity Assessment

i) Reliability of the data collection method:

Pilot data relating to participant comments will be analyzed with the aim of improving the reproducibility of the survey questionnaire. As a comparative exercise the same data may be analyzed statistically using Cronbach's alpha (Gliem, 1993).

ii) Validity of the data collection method:
The purpose of the validity assessment is to improve fitness of the questionnaire for its intended use. This involves assessment of validity with respect to questionnaire content, structure and participant sampling (external validity). The *external* validity is improved using the purposive sampling method, the *construct* validity is assessed and improved during cognitive interviewing, and *content* validity is derived from the literature.

iii) Validity of the data analysis method:

The participant response data captured during piloting activity will be analyzed to confirm the appropriateness of the selected data analysis method.

iv) Qualitative description of the emerging themes:

The data from the cognitive interviewing will be categorised into themes, which in turn will inform the actions needed to improve the questionnaire and the associated survey procedures.

d) Questionnaire Anonymisation

The questionnaires will be anonymised according to the following Pseudo-Code procedure:
EE-SS-CC-RR-NN
EE – Expert's second letter of first name and second letter of last name
SS – BP for Big Pharma / SP for Small Pharma / CO for Contract Organization / CN for Consulting organization / OT for Other

CC – First two letters of participant's organization name
RR – Regulatory Domain of Expertise; US for FDA / EU for EMA / UE for both
NN – Participant ID. A sequential number assigned based on the order in which the questionnaires are sent to the participants.

Example: AA-BP-SA-UE-05 -> Nader Shafiei_Big Pharma_Sanofi_US & EU_5th questionnaire sent

A link file containing the participant details and the corresponding anonymised code will be stored in the dedicated LJMU network folder.

3.3 Participants

The participants of the study will be recognised experts in the field of Pharmaceutical Quality. They will have strategic view of the pharmaceutical quality in their respective organization, are typically the go-to person on matters of quality and regulatory compliance and often represent their companies in external academic or industry organizations. They should have multidisciplinary quality expertise with exposure[9] to quality issues affecting the medicinal product lifecycle[10], and experience in the pharmaceutical or biopharmaceutical industry as an employee or a service provider.

Combination of representative (the primary sampling method) and snowball sampling offers the best guidance for participant selection (Robson, 2007). The sample will be taken from representative of the population, which is characterised by the organizations that make up the sampling frame (see next section). Snowball sampling will be used as an aid to the representative sampling, which requires the principal investigator to use his contacts as informants to identify potential candidates from the sampling frame.

a) Sampling Frame

Sampling frame is the source of the eligible population from which the survey sample is drawn. Potential candidates for the study will be recruited from the following organizations. These organizations are representative of the population since they provide a forum where Pharmaceutical Quality experts gather and formulate solutions to challenging regulatory problems and publish their work.

- Drug Information Association
    - Quality Risk Management special interest group
- European Federation of Pharmaceutical Industries Association (EFPIA)
    - Compliance working group
- International Society for Pharmaceutical Engineers (ISPE)
    - Board of directors
- International Conference on Harmonisation
    - Quality working group
- Journal of Quality Assurance
    - Editorial board (co-editors with pharmaceutical background only)
- Parenteral Drug Association
    - Quality Systems interest group

The participant confirmation requires contact with the candidates, which will only commence after approval of this study protocol by the LJMU REC.

b) Inclusion Criteria

Candidates meeting the following criteria will be selected for the survey:

[9] Exposure to quality issues affecting two or more elements of the medicinal product lifecycle
[10] Lifecycle: laboratory > clinical > registration > manufacturing > distribution > surveillance

- Those who have quality and compliance knowledge in good laboratory, clinical, and/or manufacturing practice AND
- Those who have experience with US (FDA) regulations and/or EU (EMA) regulation AND
- Those who have current working knowledge of quality relevant to medicinal products based on pharmaceuticals and/or biologics

c) Participant Withdrawal and Replacement

- Participants can withdraw from the study at any time.

3.4 Procedure

The survey conduct has two key steps: i) participant awareness and informed consent ii) questionnaire completion. Potential candidates will be contacted by telephone to secure their verbal consent to participate in the survey. The telephone conversation will last up to 30 minutes and will focus on explaining the information leaflet, instructions on how to complete the questionnaire and addressing any process related questions that candidates may have. During the telephone conversation it will be explicitly stated that participation in the survey is voluntary and there is no obligation to contribute to research study. The telephone conversation stops at this point and if the candidate consents he/she will be considered as a "participant" in the study. Prior to the teleconference meeting an e-mail containing electronic copy of the information leaflet (see appendix, ref: NS-PhD_LJMU_PIL_01) and the questionnaire (see appendix, ref: NS-PhD_LJMU_QAR_01) will be sent to the candidates. After the phone conversation an e-mail containing a brief statement referencing the summary of the phone conversation and that the candidate had verbally consented to take part in the survey will be sent to the participant. The LJMU e-mail (N.Shafiei@2009.ljmu.ac.uk) will be used for all e-mail communication.

The participants will be asked to complete the questionnaire offline and return the completed electronic or scanned copy to the above e-mail address. The questionnaires will be checked for completeness upon receipt and the participant will be contacted to address any gaps. The study conduct is closed once all the completed questionnaires are received and any subsequent communication with the participant to address problems is concluded.

4 SURVEY DATA

The completed questionnaires (electronic or scanned version) and any associated e-mail correspondence will be stored on dedicated LJMU network folder which is password protected. All survey documentation will be retained for 5 years after completion of research in accordance with the LJMU regulations. Questionnaires will be anonymised to safeguard the identity of the participants, their organization and facilitate confidentiality (see below).

The Questionnaire data will be transferred to a computer for further analysis. Combination of hard disk encryption and password protection will be used to minimise unauthorised access. The study data residing in the computer will be backed up to the LJMU secure network folder on a daily basis. After the study completion, any analysis results residing within the computer will be removed securely.

5 ETHICAL CONSIDERATIONS

5.1 Informed Consent

Informed consent for survey participants will be performed in compliance with the LJMU procedure on "Obtaining Informed Consent for Research Participation". The content of this study protocol incorporates the 11 key points stated in the LJMU procedure.

Initially verbal consent of the participant will be secured during the awareness discussions (via telephone). Subsequently an e-mail containing a brief statement referencing the summary of the telephone conversation and that the candidate had verbally consented to take part in the survey will be sent to the participant. In addition a statement will be included in PIL and the questionnaire to clearly indicate its voluntary nature and the fact that returned completed questionnaire implies participant's consent.

5.2 Research Ethics Committee (REC) Review

This Study Protocol will be submitted to LJMU REC for review. The survey research will NOT commence recruitment until this protocol is fully and unconditionally approved by the REC.

5.3 Data Dissemination

The anonymised results will be used in the publication of a PhD thesis and in papers in a number of prestigious peer-reviewed scientific journals.

6 SURVEY SCHEDULE

Activity	**Milestone**	
Study Protocol Preparation	Jan - March	2011
Submission to LJMU REC for review	April	2011
LJMU REC approval	July	2011
Questionnaire Design and Piloting	July - Aug	2011
Industry Expert Survey	Aug – Dec	2011
▪ Expert Recruitment	Aug	
▪ Expert Awareness	Sep	
▪ Questionnaire Dissemination	Sep	
▪ Return of Completed Questionnaires	Sep - Dec	
▪ Follow-up non Respondents	Jan	2012
Data Analysis	Jan - Feb	2012

Study Cost:
There is no monetary impact since all the survey material will created and exchanged electronically. Time and effort of the principal investigator (PhD student) and the participants (collaborator and industry experts – estimated at 2 hours per expert, which includes the teleconference and completion of the survey) is needed for successful completion of this survey.

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B5 – PILOT PARTICIPANT COMMENTS DURING COGNITIVE INTERVIEWS

Section/ Question	Sub-section / Sub-question	Individual Participant Comments
Section A	Entire survey	Quality Risk - should also include business decision to take a risk that may result in a regulatory finding (tolerable risk). Should refine the definition to include this.
Section B	Entire survey	Questions in general are suggestive and could be rephrased to make them open
Q6	GxP	Consider Good Research Practices (GRP)
Q7	Regulatory Environment	FDA regulation is driving Pharma companies offshore
Q7	Open Innovation	The old model of in house R&D outlived its usefulness
Q7	Other (please specify):	Current blockbusters are running out of patent and this is partly responsible for industry transformation. Traditional science has reached its limits and another key driver is to find new innovative way of discovering drugs. Open innovation is more of an outcome of transformation and not the driver. Regulatory environment had not changed significantly and hence is not a key driver.
Q7	Other (please specify):	How about mergers and acquisitions
Q8	Externalization of S/W Applications	Clarify terminology of the software application to include GxP data and the service component.
Q8	Externalization of S/W Applications	Provide some examples: Data management, Product Technical Complaints, Pharmaco-vigilance. Also clarify if "Apps" also covered. (Apple, Smart Phone, etc.)
Q8	Externalization of S/W Applications	Not in the GMP arena (for GMP data)
Q8	Externalization of S/W Applications	Consider replacing "externalization" by outsourcing.
Q8	Other (please Specify):	Information and Knowledge Management
Q8	Other (please Specify):	Partnership and research information sharing and Biotech are the current hot topics.
Q8	Other (please Specify):	Develop an approach for managing quality in a new environment. The agencies are pushing us to develop a quality system similar to GMP which may not completely be appropriate for the OI environment. Do we need a new quality approach?
Q9	Multidisciplinary Regulatory Knowledge	This is related to combination products
Q9	Multidisciplinary Regulatory Knowledge	Because of sharing information across boundaries

Appendix B5 Continued

Section/ Question	Sub-section / Sub-question	Individual Participant Comments
Q9	Effective Product Characterization	Product characterization means critical quality attributes and critical process parameters.
Q9	Effective Product Characterization	If you don't have full characterization it will impact product transfer
Q9	Technology Validation	Terminology ambiguous – consider selection of new technology
Q9	Technology Validation	define Technology validation as Equipment and Systems)
Q9	Other (please Specify)	Clear legal and quality agreements to support the open innovation environment
Q9	Other (please Specify)	Suggest keeping Data Security and Data Integrity as separate questions. Security is more involved with technical aspects and Integrity is important from data validity perspective
Q9	Other (please Specify)	How do we convert data to knowledge and be able to search and sort. E.g. how can we mine information from old products?
Q9	Other (please Specify)	Changing regulatory environment (e.g. EMA regulation on audit of entire API supply chain)
Q9	Other (please Specify)	Lack of IP protection in emerging regions (e.g. China, India, Brazil, etc)
Q10	Certain elements of the Open Innovation as indicated in question 7 will impact partnership and others may not such as pervasive technologies.	
Q11	There is a risk associated with the OIL model in that partners normally associated with research realise their business potential and as such negotiate their worth accordingly.	This is a new paradigm - with the demise of the old in house R&D
Q11	In order to have protection from an IP perspective the legal framework must be clearly defined. Especially true from a GRP perspective.	
Q15	Likely depending on the area; e.g. Sterile products or medical devices.	We may not make improvements to products because it means opening the CMC dossier

Appendix B5 Continued

Section/ Question	Individual Participant Comments	Individual Participant Comments
Q15	It is my impression that the regulatory expectations will always be in place and are designed to protect the patient. Documentation and institutional knowledge data management are purely good scientific practices and not blockers of innovation.	We are less likely to consider truly innovative technologies because of the regulatory risk.
Q15	The work gets done but perhaps not in the most effective and efficient way. There is a need for the agencies to take a pragmatic approach which they don't do easily (e.g. investigator flexibility).	
Q16	The current regulatory structure is capable of innovation because of political pressures on the regulators from the legislators (US perspective only).	The chances of smarter regulatory approaches keeping pace with innovation are highly unlikely simply because they are political and bureaucratic organizations.
Q17	In the current regulatory environment these are not effective programs. Example: the concept of QBD is not yet proven to be successful)	Not familiar with these initiatives
Q17	Very few companies took advantage of PAT because the trust factor with the regulatory authorities	Innovation is there regardless of what is happening in regulations. I am making the assumption that they are not making the innovation environment more negative.
Section E	This question ignores the fact that there may be remedial controls to control associated GxP Risks.	a) Look more at the value of effective due diligence. Multidisciplinary GxP Due Diligence
Section E	b) I was thinking of transfer products to outside alliances not bringing products inside. The focus is Inbound but the question could be taken either way.	c) Define multi-disciplinary more clearly
Section E	c) Ask the question in the context of why you need it. The use of “Lack of” xxx is suggestive. Consider changing the measurement scale also.	c) Is this also across regulatory agencies (i.e. knowledge of US, EU, LatAm etc…)?
Section E	d – Lack of…) This is a no-brainer based on the composition. May be the question should be composed differently.	D – Lack of…) The question is suggestive, rephrase.
Section E	d – Lack of…) very suggestive	d – Lack of…) Suggestive, consider rephrasing. Avoid use of the word “lack of”.
Section E	e) Provide some product/patient related examples. Are we talking about the whole gambit (including the GCP areas)	f) Same comment as e). Instead of focusing on “Lack of” may be have a grading scale. Lack of is “all or none”
Section E	f) A GMP, GLP, GCP example would help to answer this question. E.g. smart blister packs. This technology is too futuristic!	
Q18	Additional question to ask would: Which of the following factors drive the selection process: Efficacy/Safety, Market Potential, GxP Compliance	Scientists have enough knowledge to pick up on significant compliance issues.

Appendix B5 Continued

Section/ Question	Individual Participant Comments	Individual Participant Comments
Q19	Assuming we have products that are in both stages	This assumes that there is no risk mitigation strategy from a point of initial contract to the Pre-Approval Inspection.
Q19	Clarify premarket. Are we talking about Pre Approval Inspection or early development?	The inherit risk exists but the probability of it happening is lower because most of the companies would aim to have reasonable level of compliance to begin with.
Q19	Don't understand the question clearly. Are you referring to agency inspection or internal. Is it pre IND? The response differs based on if the product is acquired pre IND or Pre NDA depending on Agency involvement (is key). After agency review of submissions.	The problem is not the likelihood. Even if the likelihood is not that high you do not want to have this situation since it will be costly. May be to rephrase using different scale. Focus on inherent risk. One question on Risk and another on Likelihood.
Q20	By this point the registration dossier is submitted and most of the potential GxP issues have been resolved.	Clarify if we are talking about a product that was procured prior or post PAI
Q21	Process understanding comes before the transfer. Assumes that you have good process understanding in the first place.	Assuming that source site has a good process understanding in the first place
Q22	Assumption that Due Diligence on lab methodology is already performed	
Q23	Depends on the robustness of the process	Does it really matter to ask this question in the context of pre vs. post? If the question is consolidated the likelihood would be "Likely".
Q23	Product transfer is the first place that the agencies tend to gravitate to.	
Q24	None	None
Q25	From perspective of regulatory knowledge it is clear that individual responsibility can no longer be sustained and teams of experts in associated fields will be required to maintain quality and compliance effectiveness.	Product with a delivery device. One part is regulated by the Drug side and other parts by the device side and of course there is a lot in between.
Q26	Related to knowledge management and being able to provide expert advise in all the fields related to the product	This is substantiated by increase on warning letters that highlight lack of regulatory knowledge at the clinical investigator site and sponsor level (e.g. Under device regulations the Investigator has direct reporting requirements to the FDA while under the drug regulations. He does not).
Q26	No need to have pre and post. Consolidate into one question. If so the answer would be "Likely" based on the answer to 25.	

Appendix B5 Continued

Section/ Question	Individual Participant Comments	Individual Participant Comments
Q27	Related to knowledge management and being able to provide expert advice in all the fields related to the product.	
Q28	This makes sense purely from a size of the molecule which dictates complexity	
Q29	None	None
Q30	Potential for very strong patient safety issue!	
Q31	Logically seems appropriate to select this response.	Privacy should be linked to the patient not the product
Q31	The response is focused on GMP aspects: e.g. CMC data, stability data, etc.	This could also include risks from legal/IP perspective (in addition to compliance).
Q32	Potential problems in gaining approval	If we start the alliance in the wrong footing with substandard procedures it is highly likely that this would result in compliance problems later on.
Q32	Regulators don't always inspection this topic. Consider an additional measurement scale (somewhat likely)	Agencies are catching up and in due course this could be very likely (example – Quality technical agreements being the hot topic)
Q33	Potential product recall, product withdrawal, etc	Agencies are catching up and in due course this could be very likely (example - Quality technical agreements being the hot topic)
Q33	Assumption being that the legal and Intellectual Property issues would be addressed	
Q34	None	None
Q35	Regulators don't always inspect this topic. Consider an additional measurement scale (somewhat likely)	
Q36	This is where the regulators will see the adverse event	Regulators don't always inspect this topic. Consider an additional measurement scale (somewhat likely). The average inspector does not probably understand the technology. Not expert in this field of technology.
Q36	How about the expertise of the Regulatory Reviewers (e.g. CMC review)?	By this time there should be enough checks and balances in place to ensure reliability. Most likely already been inspected and approved by the agency.

APPENDIX C: Submitted and Published Papers

Shafiei N, Ford JL, Morecroft CW, Lisboa PJ, Taylor MJ. Characterization of the Evolution of the Pharmaceutical Regulatory Environment. *PDA Journal of Pharmaceutical Science and Technology*. 2013; 67:297-306.

Shafiei N, Ford JL, Morecroft CW, Lisboa PJ, Taylor MJ, Mouzughi Y. Transformation in the Pharmaceutical Industry – a systematic review of the literature. *PDA Journal of Pharmaceutical Science and Technology*. 2013; 67:105-122.

Shafiei N, Ford JL, Morecroft CW, Lisboa PJ, Taylor MJ., Mouzughi Y. Transformation in the Pharmaceutical Industry – a systematic analysis of the operational evidence. *PDA Journal of Pharmaceutical Science and Technology*. 2013; 67:307-322.

Shafiei N, Ford JL, Morecroft CW, Lisboa PJ, Taylor MJ., Mouzughi Y. Transformation in the Pharmaceutical Industry: transformation-induced quality risks - a survey. *PDA Journal of Pharmaceutical Science and Technology*. 2013; 67:229-246.

Training, Seminars, Conferences Attended:

During my PhD research I attended the following training, conferences, or seminars.

- Online LJMU training:
  - Being a Part-time Researcher
  - Information Skills
  - Writing skills (focusing on academic papers, dissertation, etc.)
- Pharmaceutical Quality Risk Management (hosted by PDA)
- FDA Inspection Assignment Strategy (hosted by the ISPE)
- Series of lectures on Immunology & Inflammation (hosted by SUNY University)
- Provided an oral presentation on pharmaceutical transformation to the Quality Intelligence Taskforce in Sanofi
- Attended PDA 2012 annual meeting