

# From maturity to value-added innovation: lessons from the pharmaceutical and agro-biotechnology industries

## Journal Item

# From maturity to value-added innovation: lessons from the pharmaceutical and agro-biotechnology industries

James Mittra, Joyce Tait and David Wield

ESRC Innogen Centre, Old Surgeons' Hall, High School Yards, University of Edinburgh, EH1 1LZ

*Corresponding author*: Mittra, J. (James.Mittra@ed.ac.uk).

**Abstract:**

The pharmaceutical and agro-biotechnology industries have been confronted both by dwindling product pipelines and rapid developments in life sciences, thus demanding a strategic rethink of conventional R&D. Despite offering both industries a solution to the pipeline problem, the life sciences have also brought complex regulatory challenges for firms. In this paper, we comment on these industries' response to the life science trajectory in the context of maturing conventional small-molecule product pipelines and routes to market. The challenges of managing transition from maturity to new high-value added innovation models are addressed. Further, we argue that regulation plays a critical role in shaping the innovation systems of both industries and, as such, we suggest potentially useful changes to the current regulatory system.

## Introduction to the new life science industries

The new molecular life sciences have transformed a range of R&D-driven industries over the past two decades, particularly in pharmaceuticals and agriculture. Both industries are susceptible to "technological shocks" as new scientific knowledge and path-breaking technologies broaden the spectrum of options for R&D and strategic management. The complexity of the life sciences, and the different implications of biotechnology and genomics for various parts of the R&D process, have created distributed innovation systems and company networks in both sectors [1-3]. Firm strategy is shaped by robust, though ever-changing, multi-layered and sometimes cumbersome regulatory systems that are located outside the core innovation system, but which continue to influence innovation at all times [4]. The success of multinational companies depends on a continuous flow of new, innovative products with clear routes to market and established, well-understood value systems. In pharmaceuticals, these have traditionally been small-molecule blockbuster products in core therapeutic franchises. Similarly, until the early 1990s, the dominant innovation model in the agricultural sector was global commodity crops. In both industries, new technologies, such as high-throughput screening and combinatorial chemistry, were embraced enthusiastically and brought product and process advances in the identification, validation and formulation of new chemicals.

Rapid developments in the life sciences in the late 1980s and early 1990s brought new opportunities and challenges for both industries, and continue to do so today. Just as conventional product pipelines began to reach maturity, the new life sciences offered hope of developing radically different types of product and markets. For the pharmaceutical industry, recombinant proteins in the 1980s, monoclonal antibodies in the

1990s, and more recently stem cells, emerged as potential alternatives to blockbuster small molecule drugs. Similarly, in the late 1980s GM crops presented the agro-chemical industry with a radically new product portfolio disruptive to its prevailing R&D strategy. However, the life sciences also brought new competition for incumbent firms as smaller biotechnology companies with unique knowledge and expertise emerged. The path-breaking nature of the new technologies and products, many with unknown risk profiles and without established routes to market, engender new regulatory hurdles that increase the cost of R&D and generate uncertainty.

Our aim is to explore the evolution of the pharmaceutical and agro-biotechnology industries in the context of emerging life science innovation and new regulatory systems, and suggest key lessons for future governance. We use the term agro-biotechnology in this article to refer specifically to those agrochemical companies that linked with seed companies to produce GM crops. We highlight the opportunities and challenges of managing transition from maturity to a new high-value-added innovation model subject to high regulatory hurdles and hope to spur a broader discussion about the systemic aspects of R&D-driven industries and the role of regulation in shaping innovation.

## From maturity to value-added innovation: challenges and opportunities

Developments in the life sciences have reshaped the pharmaceutical and agro-biotechnological industries. During the 1980s and early 1990s, the largest multinational chemical firms had relatively integrated and complementary R&D strategies. Indeed, some had both health and agriculture divisions. This period of innovative activity was

characterised by a series of mergers and acquisitions as multinationals sought "buy-in" to new technology platforms [5].

However, this "combination strategy" ended around the late 1990s. The two sectors separated their capabilities and pursued autonomous strategies of innovation through both merger and acquisition activities and strategic alliances. It became clear to senior managers that synergy between agriculture and pharmaceuticals at the discovery-level was profitable only when both sectors were primarily interested in the source of chemical novelty, but not in the "gene" area [5,6]. Functional genomics could benefit both sectors, but disparities in profit margins [7] and technological and economic differences [8] did not make for long-term positive synergies.

*Responding to the "problem of maturity"*

In the early 1990s, both sectors struggled as conventional chemical-based products reached maturity and R&D pipelines narrowed. By "maturity", we mean molecules had already been developed for easy targets and were now off-patent, so no longer generating large profits, and industry was concerned about the long-term sustainability of conventional blockbuster R&D models. Both sectors searched for new R&D options. In agriculture, strategic planning focused on 'a combination of chemical and biotechnology developments with varying degrees of synergistic interaction' [9,10]. Companies embraced diversity in technological development [11]. As product pipelines matured, three distinct company strategies emerged to exploit the new life science trajectory (Box 1).

Innovation strategies are cumulatively dependent on a company's past history [12,13], and the resources and 'dynamic capabilities' of a firm influence its patterns of innovation [13]. The innovation strategies of agro-biotechnology companies in the 1980s and 1990s varied, depending on their existing strengths in product development and technology trajectories along with their overall vision for the future. GM crops were a disruptive technology for most multi-national agro-biotechnology companies still benefiting from patented agro-chemical products, but were attractive to firms that had reached the limits of small molecule chemical innovation.

In pharmaceuticals, the maturity problem and desire to move to high-value-added biotechnology-based products was also a driver of organisational change and restructuring. Traditionally, pharmaceutical R&D was a serendipitous activity in which chemical compounds were randomly screened and tested on known disease targets. Lead molecules were then optimised to produce lead candidates for further development. In the 1980s and 1990s, advances in molecular biology, synthetic chemistry and screening technologies reshaped this R&D process [14] and created economies of scale and scope [15]. The emergence of potentially transformative life science technologies led to major industry restructuring, through internal reorganisation and merger, acquisition and strategic alliance activity [2,16,17]. Firms now coordinate an increasingly diverse range of R&D capabilities alongside the "normal" processes of organic growth [18]. However, despite the promises and strategic visions presented by the life sciences, various factors challenge large firms' dominance in therapeutic innovation (Box 2).

Together, these challenges, amongst others [24], continue to shape the evolution of the pharmaceutical sector and strategic management of R&D within individual firms,

with new R&D models and product development strategies emerging. For example, GSK developed Centers of Excellence for Drug Discovery in 2000, leading to its current decentralised R&D Hub structure [25,14], and most multinationals exploit public-private partnerships in both research and development. A good example is Pfizer's current investment in Scotland's Translational Medicine Research Collaboration (TMRC); focused on the identification and validation of novel biomarkers for drug development.

Both the pharmaceutical and agro-biotechnology industries have been forced to confront the challenges and opportunities of the molecular life science paradigm in the context of maturity of conventional product pipelines. For pharma, life science investment and attendant organisational restructuring has been primarily a response to the challenges of therapeutic innovation, rather than a revolutionary, pro-active attempt to fully embrace a life science-based innovation trajectory. Innovation spending in agro-biotechnology has moved towards GM seed technology, with total agro-biotechnology R&D expected to equal agrochemicals in 2009 [26].

Our research on both the agricultural and pharmaceutical industries has shown that multinationals do not always share common objectives and strategies; rather, strategy is an evolutionary process based on firms' unique histories, internal competencies and routines, market position and future expectations [2,9,14]. The long-lead times in pharmaceutical and agro-biotechnology R&D mean that the precise benefits of any restructuring initiative and implantation of new strategy take time to emerge. Nevertheless, product innovation and company strategy is also determined by the regulatory environment and it is to this important aspect that we now turn.

## Regulation and its impact on innovation strategy and product development

Regulation has significant impact on R&D-driven industries, such as pharmaceuticals and agro-biotechnology, and partly explains the long product lead times that distinguish these industries from most others, although even without formal regulation firms would still need to invest time and resource to establish product safety. Nevertheless, changes in standards for safety and efficacy do have time/cost implications for industry [27]. A significant effect of regulation in agro-biotechnology has been to increase costs, over conventional non GM varieties, by approximately 0.5 to 13.5 million USD [28]. We argue that regulation is the dominant shaper of both the innovation system and markets for innovative products in pharmaceuticals and agro-biotechnology. Specifically, it can constrain life science innovations through the complex, expensive and lengthy requirements imposed on developers of new drugs or pesticides. It has been recently suggested that clinical trials required by European regulators to compare biosimilar products with corresponding biologic brands are unnecessary and may impede the development of biosimilars of more complicated biologics [31]. Although this particular example is focused on biosimilars rather than novel biologics, it does highlight how regulation impacts on innovation. The nature of the regulatory system for any given product can dictate the type of firms able to develop such products [4].

To highlight the role and influence of regulation on both sectors, we look briefly at two "disruptive technologies"; GM crops in the agro-biotechnology sector; and stem cells/regenerative medicine in the pharmaceutical sector. The systemic interactions of regulation and innovation for these two sectors and technology platforms are highlighted. A background to life science regulation is provided in Box 3.

*Path-breaking Versus Path-Dependent Products and Regulation*

Scientific knowledge and technological advances in biotechnology have led to radically new path-breaking products in health and agriculture, including GM crops and stem-cell-based therapies. In both cases, regulation has been considered crucial, but with no precedent for establishing a robust governance framework. In cases of new technologies, one can either look for existing regulatory regimes within which to place new product ranges, or design new path-breaking regulatory frameworks to meet the specific properties of the new technology. Based on our research [28-30], we consider it important to question the relationship between the emergence of path-breaking innovations and the putative need for path-breaking regulatory systems.

Path-breaking innovations do not always require novel regulatory mechanisms. GM crops were a path-breaking technology - the agro-biotechnology industry expected that they would be disruptive and move the sector onto a new high value-added innovation model - but it was unclear for quite some time after heavy investment what the nature of the regulatory regime would be. While companies can cope with radical changes to their innovation systems, when these challenges are coupled with uncertainty in markets and regulatory systems that are outwith their control, disruption to the entire sector can be magnified [4].

Innovation that is "path-breaking" for one company or sector may of course be "path-dependent" for another. For example, it was not inevitable that GM crops would be developed and marketed only by what were then agro-chemical firms, for which they were clearly path-breaking; GM crops disrupted the prevailing innovation model,

simultaneously impacting company R&D strategy (i.e. requiring a shift from chemistry-to biology-based development and production systems), markets (i.e. seed markets are very different from pesticide markets), and regulatory systems. In the 1980s and early 1990s, it was equally likely that food and seed companies would develop the technology. For these companies, the technology was path-dependent [4,30].

A complex set of interactions between policymakers at European, U.S. and international levels, as well as among the agro-biotechnology, food production and distribution, and seed industry sectors, contributed to the overall framing of GM. It would have been beneficial to guide policymakers to adopt the regulatory system that applied to the industry sector for which the technology was path-dependent; in this case the seed companies. The regulation of GM crop varieties would have been easier (perhaps regulated under plant breeders' rights) if the initial developers had been seed firms. This path-dependent regulatory approach may have made a difference to the direction of innovation in GM crops today and also to European public perception of the technology.

This analysis also applies to the pharmaceutical sector in the case of stem cells and regenerative medicine. Stem cells, like GM crops, are potentially highly disruptive of prevailing pharmaceutical R&D systems, markets and regulatory systems. They require modification of company R&D strategies, moving from small-molecule innovation to complex biologics, and markets, which are very different to conventional blockbuster drug markets (smaller patient populations and delivery mechanisms for the product are far more complex, expensive and uncertain). The nature of the regulatory requirements also determines whether such products are developed by conventional multinational drug companies or smaller tissue engineering firms. In parallel with the GM crop example,

194 stem cells would be path-breaking for pharmaceutical multinationals, but path-dependent
195 for smaller tissue engineering companies. Comparison with GM crops would suggest that
196 if regulation of stem cells could be framed to be path-dependent for the smaller
197 companies, we might see faster and more innovative development and uptake of novel
198 therapies. However, if regulation continues to align more closely with the sector to which
199 the technology is path-breaking (multinational pharmaceutical firms), which appears to
200 be the case with the Advanced Therapies Regulation in Europe
201 [http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:P
202 DF], we could see delays in the development of therapies and few small, innovative
203 companies independently developing stem cell products. Whilst it is of course essential
204 that stem cells and regenerative medicine products meet the key requirements of safety
205 and efficacy, the question is whether the conventional regulations that apply to small
206 molecule blockbuster products, and more conventional biologics, are appropriate for stem
207 cells; especially when they may be a barrier to innovation. Whilst there are myths and
208 uncertainties about the regulatory gaps and barriers to regenerative medicine [32], there is
209 as yet no clear route to market for many small companies developing the technology and
210 regulatory guidelines can be vague and ambiguous. Lessons from the regulation of GM
211 crops may help us to develop regulatory processes for stem cells that encourage, rather
212 than impede, those companies best placed to innovate in this area.
213
214 **Conclusion: key lessons for new "smart" approaches to regulation**
215 Regulatory systems tend to evolve incrementally over long time periods, which make
216 them susceptible to becoming inflexible and out-of-step with the latest innovations and

technologies. Furthermore, regulation can become so complex that modifications to one set of regulations have unforeseen consequences for other parts of the regulatory system and for the innovation community. However, *de novo* creation of path-breaking regulation for path-breaking technology also poses difficulties and challenges and could just as easily discourage innovation as encourage it.

From our extensive research exploring innovation and regulation interactions in the pharmaceutical and agro-biotechnology sectors [2-6; 9, 10, 14, 30] we consider there to be a number of key lessons for better governance of innovative life science technologies, such as GM crops and stem cells [Box 4].

The life sciences continue to be of high strategic importance to both developed and emerging economies and shape many innovative industries. But life science innovation is largely dominated by a relatively small number of multinational companies, and regulatory systems often serve to maintain the status quo. Regulation is an insurmountable barrier to many small start-up companies with innovative ideas that challenge prevailing orthodoxy. Whilst it would of course be inappropriate to lower safety and efficacy standards for life science-based products, the development of a smarter approach to regulation, which we have outlined, could bring about a more favourable climate for innovation.

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**Box 1. Agro-biotechnology company strategies**

Distinct strategies were employed by leading agro-biotechnology companies. These strategies were conceived in response to external pressures, including low farm commodity prices and income; erosion of profit margins; more aggressive competition as a result of agribusiness restructuring; and the emergence of new technologies, such as genetic modification and molecular marker technologies, which challenged conventional farming practice. The narrowing of chemical pipelines also crucially drove this need for a new strategic vision. Companies employed these different strategies to respond to maturity and pressures in the innovation environment.

*"Buying the route to market"*

Monsanto (from the 1980s) and Dupont both invested heavily in building the GM technology base for the world's major commodity markets: corn, soya and cotton. Moving from selling agrochemicals to selling seeds required a new marketing strategy, and both companies invested large sums in acquiring seed companies. Monsanto invested $8bn alone between 1996 and 1999 and DuPont purchased Pioneer in 1999 for $7bn [9].

*"Collaboration along the route to market"*

AgrEvo, Zeneca, Novartis, Rhone Poulenc and Dow also invested significantly in building a GM technology base throughout the 1980s, but they focused more on collaboration with seed companies rather than on outright purchases. This was a more incremental strategy which gathered momentum in the mid 1990s.

373 *"Jumping on the bandwagon"*

374 BASF and Bayer were intentionally several years behind other agro-biotechnology
375 companies in investing in GM technology, preferring to wait and to benefit from the
376 experience of other companies. BASF began investment in the mid-1990s and Bayer in
377 the early 2000s.

378

**Box 2. Key challenges facing the pharmaceutical industry (1990s – present day)**

**1. Decline in productivity** despite increases in R&D investment. The problem of product maturity coupled with low productivity led to perception of "innovation deficit" that continues today [19]. Since 1996, the number of small molecules approved by regulators has been in decline and the number of new active compounds discovered has remained constant. Companies are not generating enough new compounds in-house for sustainable growth [20].

**2. High attrition rate of compounds**, particularly during Phase II clinical trials. Lack of demonstrable safety and efficacy has been the principal cause of attrition, which partly explains why companies experiment with new "translational sciences" [21,22], particularly those centred on identifying and validating novel biomarkers.

**3. Rising overall costs of drug discovery** owing to the need for new, experimental methodological approaches to R&D; increasing internationalisation of research and its competitive environment, and increasing demands from regulators and healthcare providers. In 2007, the cost for a firm to bring one product to market was estimated to be $800 million USD [23].

**4.** Some early biotechnology firms were successful in **transforming themselves into large multinationals** (Amgen, Genzyme, Genentech and Geron); but later growth in biotechnology has been slow. Today the chances of a small biotechnology firm becoming a large, independent company appears bleak given the high barriers to entry.

**5.** There are now more **partnerships between public and private institutes** to pool information and attempt delivery of niche products, including orphan drugs and products vaccines for developing countries. Nevertheless, the dominant model continues to rely on "blockbuster drugs" rather than targeted drugs for niche markets. Despite the promises of the life sciences, multinational pharmaceutical firms did not seek to fully transform themselves into biotechnology companies; in contrast to some of the agro-biotechnology companies like Monsanto. Indeed, there has not yet been a pharmaceutical equivalent to Monsanto.

**Box 3: The nature of regulation in the life sciences**

Whilst it is obvious that regulation impacts product development, we suggest that the impact of regulation is much more far reaching than just ensuring goods are safe, effective and high-quality – [28]. It determines overall company strategy, the types of firm that will succeed in bringing products to market, and the structural dynamics of the sector as a whole. For example, if we compare the lightly regulated Information and Communication Technologies ICT sector with the heavily regulated life sciences, the former has a much greater turnover of products and capabilities arising from technological innovation. In ICT, small start-up companies can quickly become major players by developing innovations that challenge the status quo. Most candidates for product development in the health and agricultural sectors will fail (only one out of approximately 200,000 molecules initially screened will make it to product launch); therefore, innovation in life sciences appears far more linear than industries such as ICT [29]. Life science innovation is dominated by a small group of multinationals, which we argue is partly due to the fact that the regulatory system poses an insurmountable barrier for many new entrants with innovations that threaten to disrupt the status quo.

The markets for life science products are also different from most other industries, inasmuch as few are marketed directly to consumers. Pesticides and GM crops are sold to farmers, and new medicinal products are mainly sold to health services [10]. The unique combination of regulation and markets for life sciences has therefore had major impacts on the structural dynamics and strategic management of both the pharmaceutical and agro-biotechnology sectors.

**Box 4 : Key lessons for good governance of the life sciences**

(1) Regulatory initiatives can have significant, rapid and positive influences on the innovation system. Such insights on successes should be used as exemplars when designing regulatory systems for new innovations.

(2) Regulations appropriate for one area can have unexpected and/or negative impacts when applied to other areas. Application of conventional clinical trial systems to stem cells could be a major constraint, with adaptations to mechanisms such as the 'hospital exemption route' for the development of therapies for named patients perhaps a better way to facilitate innovation. This problem becomes more likely and significant when regulators lack knowledge and understanding of the new technologies.

(3) A regulatory policy that is *enabling* in that it encourages positive change in industry strategies and appropriately *discriminates* among products on the basis of socially and economically relevant criteria, will generally be more effective and efficient than a policy that is *indiscriminate* and seeks to *constrain* what it considers undesirable behaviour.

(4) The *enabling* criterion affects the rapidity with which a particular regulatory policy can exert influence, while the range, scope and appropriateness of its *discrimination* among products and processes will determine its effectiveness in guiding desirable product development.

(5) Path-breaking regulation for path-breaking technology should not be the norm but the last resort once all other options have been exhausted. Other options might

include a focus on ‘substantial equivalence’. If the new technology or product is substantially equivalent to an existing product, path-breaking regulation should not be necessary.

(6) In considering which regulatory precedent is most appropriate for a new technology, a useful approach would be to prioritise the regulatory system for the industry sector for which the innovation is path-dependent rather than path-breaking. This would ensure the sector better positioned to quickly take forward the product to market is encouraged to do so.