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Title**The strategic relevance of manufacturing technology:
an overall quality concept to promote innovation preventing drug shortage**

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GRAPHICAL ABSTRACT:



Figure 1: main steps required for a new equipment introduction in an existing department, affecting substantially an existing process

Abstract

Manufacturing is the bridge between research and patient: without product, there is no clinical outcome. Shortage has a variety of causes, in this paper we analyse only causes related to manufacturing technology and we use shortage as a paradigm highlighting the relevance of Pharmaceutical Technology. Product and process complexity and capacity issues are the main challenge for the Pharmaceutical Industry Supply chain. Manufacturing Technology should be acknowledged as a R&D step and as a very important matter during University degree in Pharmacy and related disciplines, promoting collaboration between Academia and Industry, measured during HTA step and rewarded in terms of price and reimbursement. The above elements are not yet properly recognised, and manufacturing technology is taken in to consideration only when a shortage is in place. In a previous work, Panzitta et al proposed to perform a full technology assessment at the Health Technological Assessment stage, evaluating three main technical aspects of a medicine: manufacturing process, physicochemical properties, and formulation characteristics. In this paper, we develop the concept of manufacturing appraisal, providing a technical overview of upcoming challenges, a risk based approach and an economic picture of shortage costs. We develop also an overall quality concept, not limited to GMP factors but broaden to all elements leading to a robust supply and promoting technical innovation.

Key words: Pharmaceutical Technology; Manufacturing Technology; GMP; HTA; Formulation; Manufacturing Process; Shortage; Quality

Abbreviations:

HTA: Health Technology Assessment; HSE: Health Safety Environment; GMP: Good Manufacturing Practice; EBM: Evidence Based Medicine; QS: Quality System; FP: Finished Product; QbD: Quality By Design; API: Active Pharmaceutical Ingredient; FTE ; PAT (Process Analytical Technology); MAH: Marketing Authorization Holder

1 Introduction

1.1 Manufacturing technology relevance

Aim of this paper is to highlight the relevance and complexity of Manufacturing Technology, which should be acknowledged as a R&D step, recognised as a very important matter during University degree in Pharmacy and related disciplines, measured during HTA step and rewarded in terms of price and reimbursement. Unfortunately, the above elements are not yet properly recognised, and manufacturing technology is taken in to consideration only when a shortage is in place. However, shortage is just the evidence of multifactorial causes that should be handled before the problem raises up. So, we use shortage as a case study to point the attention to the Manufacturing Technology relevance. This paper has several limitations: as a paper aimed to stimulate scientific reflections it deals with a very broad scope ranging from giving practical and specific examples to outlining theoretical concepts; **it deals with estimating the shortage risks only from a manufacturing point of view, although shortages can be caused also by non-manufacturing causes** (*EFPIA, 2014*).

1.2 A product manufacturing process is not forever: changes lead to Manufacturing Technology Research

After a Marketing Authorisation has been obtained, a medicinal product manufacturing process changes several times. Synthetically that is due to: 1) **updating to new regulations**, 2) **upgrade manufacturing to the scientific progress**, 3) **changes due to other causes** such as external factors not dependant on the Marketing Authorization Holder (MAH) and/or Manufacturer.

1. A MAH, and consequently the manufacturing plant in charge of production, is obliged to comply with the principles and guidelines of good manufacturing practice (GMP) for medicinal products (*EU Dir 2001/83, a*). Paragraphs 3.2 and 4.4 discuss how regulations and guidelines, by upgrading quality requirements, need technological research and efforts.
2. *'After an authorization has been issued, the authorization holder must'*, in respect of the methods of manufacture and control registered, *'take account of scientific and technical progress and introduce all needed changes'* (*EU Dir 2001/83, b*). Changes must be approved by the competent Regulatory Authority (see paragraph 3.5), as well as the manufacturer should manage changes via specific procedures and evaluation which are pillars of the pharmaceutical quality system. (*ICH Q10, 2008; Eudralex GMP,a*)
3. Paragraphs 3.3 and 3.4 mention supply chain factors and product complexity leading to changes, not dependant on MAH or manufacturer.

Because of these three main reasons, change and upgrading apply to the manufacturing that should improve continually. It requires R&D efforts throughout the product lifecycle: that's why pharmaceutical industry is facing growing technical challenges for new and old products.

These challenges may lead to a shortage risk as some issues may not be overcome for a variety of reasons, this risk might be measured and preventively assessed (paragraph 4.1).

ICHQ8-Q12 guidelines provide useful concepts to drive the continual progress.

The recent ICH Q12, that is a final concept paper at step 1 already endorsed by the ICH Steering Committee but not yet definitively adopted, recognises that *'the main emphasis at ICH to date has focused on early stages of the product lifecycle'* and so more efforts are necessary at a commercial step. ICQ12 *'provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle'*, and state that *'change management is one of the fundamental components of a PQS as described in ICH Q10 and operates throughout the product lifecycle'*.

Changes are a necessary opportunity of innovation.

By discussing this complex landscape, Authors consider the Manufacturing Technology as a R&D step, and propose the application of ICH concepts in order to promote and reward it as an applied science across commercial manufacturing.

Moreover, collaboration between Academia and Pharmaceutical Industry is pivotal to promote innovation and R&D, able to face changes reducing the shortage risk.

1.3 Shortage as a growing problem

Medicines shortages are a growing problem affecting all sectors of healthcare, both at community and hospital level, and involving a wide range of Countries from USA to EU. Data are emerging on the impact of shortages on several aspects of the quality of care, including risks for patients due to delays in care and/or medication errors, increased work burden on the hospital pharmacists and on the whole medical team for communicating and managing the shortage, and economical burden on hospitals / NHS due both to the FTE (Full Time Equivalent) necessary to manage shortages and the need to buy more expensive therapeutic alternatives.

The European Association of Hospital Pharmacists (EAHP) 2014 survey of medicines shortages in European hospitals, with over 600 responses from 36 European countries, showed that the vast majority of respondent hospital pharmacists agreed that medicines shortages are a current problem in terms of providing the best care to patients and/or operating the hospital pharmacy (86%), affecting hospital pharmacy on a daily or weekly basis (66%) and having a negative impact on patient care (75.4%), including delayed or interrupted treatment, side effects and deterioration in patients' conditions (EAHP, 2014.).

Two surveys conducted in USA by the Institute for Safe Medication Practices (ISMP) in years 2010 and 2012 showed that healthcare providers experience frequent stock depletion of critical drugs, with the need of using alternative medications, dosage strengths or forms, which adds to the complexity of care, and increases the risk of serious errors, especially with high-alert medications (ISMP, 2010 a).

In particular, in the 2010 survey respondents majority reported difficulties associated with drug shortages, such as substantial resources spent investigating the shortage and developing an action plan (82%), difficulty for obtaining a suitable alternative product (80%), significant financial impact (78%), lack of a

suitable alternative product (70%), substantial resources spent preparing and/or administering the alternative product (69%), risk of adverse patient outcomes (64%) (*ISMP, 2010 b*).

In the 2012 ISMP survey, respondents provided a picture of certain and suspected patient adverse events resulting from drug shortages.

The medications most involved in the reported events include: chemotherapy (27%), opioid analgesics (17%); electrolytes (7%); antibiotics (5%); phentolamine (4%); and phytonadione (4%). The majority of events were reported in adults (aged 19-64 years (57%), and 65-80 years (20%). Twenty percent of events involved pediatric patients aged between 0-1 year (12%) and 2-10 years (8%) (*ISMP, 2012*).

2 Shortage risk

2.1 A growing problem

In USA, FDA, Hospitals and Pharmacy Groups report drug shortages as a growing problem, sharply increasing in recent years (*Mitka M., 2011*).

This is confirmed in a recent paper by Hawley et al., analyzing the time trend of emergency medicine (EM) drug shortages during the years 2001 – 2014. These accounted for 33,9% of total drug shortages reported for the period. The prevalence of EM drug shortages fell from 2002 to 2007; but sharply increased by 435% between 2008 and 2014 (from 23 to 123). In total, 321 EM shortages (52.6%) were for drugs used as lifesaving interventions or for high-acuity conditions, and of those, 32 (10.0%) were for drugs without available substitute (*Hawley KL et al., 2016*).

A clear link between shortages and manufacturing quality and issues has been suggested by Wookcock and Wosinska, from the USA FDA Center for Drug Evaluation and Research. Focusing in particular on generic sterile injectables, and using economic theory to evaluate incentives, Authors conclude that a major problem is that the market does not sufficiently recognize or reward quality, resulting in manufacturers having to minimize investments, especially with pressures brought about by new production opportunities, aging facilities, and the economic downturn (*Woodcock, J., Wosinska, M., 2013*).

Similar conclusions were drawn by Kweder and Dill, also from the USA FDA Center for Drug Evaluation and Research, in the paper entitled “*Drug shortages: the cycle of quantity and quality*” they highlight that the most common cause of shortages is linked to quality or capacity related problems, particularly for sterile injectable products.

Authors underline the need for a commitment to quality, including manufacturing controls and standards and quality- and risk-management systems, as well as the need to consider redundancy and contingency planning. This will require investments, needing economic drivers. Their conclusion is that ‘*it is time for health-care systems to recognize that such costs and economic drivers are essential elements of quality and to see them as worthwhile investments.*’ (*Kweder, S.L., Dill, S., 2013*).

Complex manufacturing processes are more vulnerable to quality risks potentially leading to drug shortages, such as manufacturing of sterile injectable products, and those involving medicines from a biological origin.

However, in most cases it is not easy to quantify the investments needed to minimize and prevent such risks, thus minimizing the risks of a potential shortage.

2.2 Clinical and economical relevance

A few papers and surveys tried to quantify costs currently incurred by NHS and/or healthcare organizations for the management of shortages.

In the USA a survey conducted by the American Society of Health System Pharmacists (ASHP) showed that in year 2010 pharmacists and pharmacy technicians managed drug shortages for a median of 9 and 8 hours per week, respectively (sharply increasing since 2004). Time spent by physicians and nurses was estimated to be less than 1 hour. The esteem for annual labour costs associated with managing drug shortages is \$216 million.

In addition, Authors cite an analysis by Premier Healthcare Alliance estimating that the need to purchase more expensive generic drugs or therapeutic alternatives caused by drug shortages could be costing USA hospitals at least \$200 million annually (*Rola, K., et al., 2011.*).

A USA survey conducted in year 2012 shows that 73% of responders (37/50) estimated a quarterly institutional cost from shortages > \$100,000, and 26.6% (49/184) reported an additional need of 0.6-1 FTE for managing shortages (*McLaughlin, M., et al., 2013.*).

In another survey conducted in USA in year 2011 on the effects of shortages of oncology products, the estimated impact on the resources needs was at least 0.5 FTE (about 20 h/week) for 37% of the 243 participants. In addition, oncology drug shortages resulted in increased costs for 85% (206/243) of the survey participants, and 10% (24/243) experienced issues related to reimbursements of the substitute products (*McBride, A., et al., 2013.*).

2.3 Hospital pharmacist: a pivotal role in the shortage management

In a survey of European Hospital Pharmacists conducted in year 2013, more than 30% of respondents indicated that drug shortages in Europe were associated with increased hospital costs, increased pharmacy and personnel costs and the need of using more expensive alternative drugs (n = 161). Medication errors and substitution with inferior drugs were reported as having occurred sometimes. The total time spent on shortages management by hospital pharmacists was estimated to be 12.8 hours/week (*Pauwels, K., et al., 2015.*).

Claus et al, analysing data for year 2013, estimated the total cost impact for a single hospital pharmacy in Belgium to be 117,281 €, including both gross salary costs for managing the shortages and drug acquisition cost for more expensive therapeutic alternatives (*Claus, B., et al., 2015.*).

The Hospital Pharmacist can reduce a shortage burden by means of galenic extemporaneous preparations, nowadays many hospitals operate in a Quality System ables to supply safe medicines to the patient.

Aim of galenic preparations is to provide the intended medicine, tailored on the patient necessity, if an equivalent industrial product is not available across the distribution channels.

Although many Hospital Pharmacists and Scientific Societies (*SIFO, 2006 ; EDQM, 2009*) issued guidelines aimed to address the galenic preparations toward the highest efficiency in terms of quality and supply availability, many technological limits do not allow to supply all drugs because they require an Industrial quality system, control and manufacturing technology.

3 Manufacturing complexity

Shortage risk has been characterised mainly from a clinical point of view, we also provided some economic data but our aim is to analyse manufacturing causes, although manufacturing is only one of several shortage root causes. Medicines evaluation by reimbursement bodies using HTA, is based primarily on the clinical benefit. However, assessing clinical consequences of a shortage should be the final point of a complex process. In addition, to evaluate the shortage's clinical impact it is important not to overlook evaluating its root causes. Before a drug reaches the patient, there are many and potentially complex manufacturing activities: root causes should be looked for among these activities.

In order to develop the discussion, we provide a snapshot of manufacturing technical complexity. Generally, we have four main challenging factors affecting medicine's availability:

1. Quality as continual improvement
2. Integration of Manufacturing Technology and Quality (i.e.cross contamination as a complexity paradigm)
3. Supply chain
4. Formulation

All of them have interdependences and relationship with regulations and HSE (Health Safety Environment) rules and guidelines.

3.1 Continual improvement of quality: the product lifecycle

In order to exert patient benefit, medicinal products should possess the quality required for their intended use; to achieve this, a Quality System (QS) which entails Good manufacturing practice and Quality Risk Management (QRM) should be in place (*Eudralex, GMP, a*). The first GMP guideline has been published in 1989 (*Eudralex, GMP, b*), many updates and implementations occurred to date.

To provide an overview regarding the QS complexity and its benefits to the patients, we briefly mention three guidelines (ICH Q8, Q9, and Q10) which are the basis of all Pharmaceutical Quality Systems, and principles on how to conduct manufacturing activities.

ICH Q10 complements: GMP, ISO concepts, ICH Q8 and ICH Q9; it describes a QS model which should be implemented throughout the product lifecycle. ICH Q10 states two pivotal principles relevant in dealing with shortages root causes:

1. QS aim is to '*enhance the quality and medicines availability in the interest of public health*' and the product realization is the first ICHQ10 objective (*ICH Q10, 2008*); so, achieving medicines availability is a quality target. This concept is reiterated by ICH Q9, stating that lack of availability should be considered as a potential harm to the patient (*ICH Q9, 2005 a*);

2. ICH Q10, and the QS, should be implemented throughout the product lifecycle facilitating '*innovation and continual improvement, and strengthening the link between pharmaceutical development and manufacturing activities*' (ICH Q10, 2008).

Unfortunately the aim to promote innovation and continual improvement at a commercial stage has not been fully reached, ICH Q12 discusses this topic, **please refer to paragraph 4.3.**

Dealing with medicines, the term innovation is often referred to the clinical outcome, but ICH Q10 entails a huge pharmaceutical technology innovation to maintain the intended medicine's quality also after its marketing authorization.

Aim of this innovation is to implement the product quality over the time, continually and during its lifecycle: development effort is not completed once the product has been granted a Marketing Authorization, but continues across the product lifecycle.

Commercial manufacturing goals are to '*achieve product realization*' and to '*facilitate continual improvement*' (ICH Q10, 2008); this improvement leads to a progressive product knowledge increase.

This innovation requires research and it is research by itself: pharmaceutical development is the manufacturing knowledge root, pharmaceutical technology research allows to develop and apply solutions to achieve the continual improvement of quality.

A manufacturing process requires continual changes, and just few years after its first registration, the current process can be completely different.

ICH Q9 describes a systematic approach for the assessment, control, communication and review of quality risks. Several tools can be applied (FMEA, HACCP, Etc.). ICH Q9 is the backbone of any Quality System (ICH Q9, 2005 a), and it applies widely on ICH Q8 (ICH Q8).

ICH Q8 defines a science- and risk-based vision for product and manufacturing process development, proposing the Quality by Design approach as a tool to achieve quality targets.

Pharmaceutical Development, at a minimum, entails the identification of several elements:

- Quality Target Product Profile (summary of product characteristics ensuring the target quality),
- Critical Quality Attributes (CQA) (physical, chemical, biological, microbiological properties that should be within specific limits to achieve the desired quality).

An enhanced, QbD approach would additionally include:

- Critical Material Attributes (widely known as CMA) and
- Critical Process Parameters (CPP) affecting CQA.

Various activities establishes a design space during the development step, several experiments (i.e. formulation and/or process trials) might be performed varying CPP and CMA and ensuring that within a determined area, called design space, they can vary without affecting the product quality (CQA) (Yu, L. X., 2008; Yu, L. X., et Al., 2014).

This approach has a great importance throughout the development step, but continues also during commercial manufacturing, indeed it is necessary to demonstrate that process or formulation changes do not affect the product quality.

ICH Q12 encourages QbD applications in a scientific and risk based approach for post-approval change management plans (ICH Q12).

For instance, a change to facilities, equipment, utilities and processes, which may affect the quality, should be properly assessed before coming into operation. It requires involvement and assessment of all QS areas and experts that should evaluate the impact of the change (*ICH Q10, 2008; Eudralex GMP, a*) and it has often as a final result the need to execute process validation batches or qualifying activities to demonstrate that the change does not affect the product quality. The new GMP guideline for qualification and validation (*Eudralex GMP, c*) entails and promotes the application of QRM and QbD principles also to commercial batches. The traditional approach is still accepted but the QbD approach will be progressively implemented, so with time a change to process parameters may require a formulation assessment as well as the application of statistical tools for data evaluation. **From a practical point of view, this means that the development stage is extended to the entire product lifecycle.** ICH provided examples of how ICH Q10, Q9, Q8 integrate during commercial manufacturing activities, a pivotal step is “*Continual Process Verification and Continual Improvement*” where ICH Q8 is applied also to the “*On-going analysis and trending of process data, (multivariate SPC, etc.)*” and to the “*Evaluation of process changes and associated effect on intermediates and products*”. Moreover ICH Q9 may be applied at the same stage for “*Manage risks of process or material attribute change (including changes within or outside of design space)*” (*ICH, 2010.*)

This continual improvement affects all pharmaceutical products, despite their selling price or clinical innovation.

ICH Q10 states two pivotal concepts, necessary to understand the challenge to maintain alive and updated a Marketing Authorization independently from the product type. To allocate appropriate resources is a quality commitment; one of the two concepts states ‘*Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness*’ (*ICH Q10, 2008*). Therefore, quality and business aspects are strictly related: the business ensures financial sustainability of having in place adequate resources to maintain the product quality.

The process complexity is often related to its innovativity, so conventionally it is considered that biological products (*Kweder, S.L., Dill, S., 2013*), nanoparticles (*Panzitta M. et al, 2015*) and personalised medicines (*Rantanen, J., Khinast, J., 2015*) are products more difficult to produce than others. This is true theoretically, but not always in practice. Many legacy medicines, non sterile and based on a chemically synthesized API may be as difficult to produce as biological products or NP. As shown in the following paragraph, any medicine independently from its clinical innovation should comply to recent regulations in terms of GMP and HSE; and concepts such as continual improvement (i.e. multivariate analysis for historical manufacturing data), are relevant to improve the product quality (*ICH 2010*).

3.2 Manufacturing Technology and Quality: cross contamination as integration complexity paradigm

Cross contamination (intended as contamination of product A with unwanted product B) is a risk to be carefully evaluated when different products are manufactured at the same facility. Woodcock et al. highlighted cross contamination and the lack of dedicated facilities as a critical factor affecting drug shortage (Woodcock, J., Wosinska, M., 2013.).

We would like to provide a brief description of the technical challenges to be worked out; in order to show the interrelation between technical difficulties, regulatory constraints, timeline and costs. A recent EMA guideline (EMA, 2014) and the revised Chapter 3: Premises and Equipment (*Eudralex GMP, d*) upgraded requirements necessary for manufacturing different medicinal products at the same facility. The aim is that cross-contamination should not exceed the maximum allowable carryover limit, intended as the allowed contamination of product A with the unwanted product B. Guidelines allow manufacture of different products at the same facility (*multishared facility*) only if the carryover limit is under the Permitted Daily Exposure (PDE), calculated taking into account the toxicological evaluation of the involved substances. When PDE is not available, or when an alternative approach cannot be adequately justified, or when proper measures cannot control the cross contamination risk, dedicated facilities are required.

Measures to match GMP criteria are costly and time-consuming and they are interdependent with other regulations (i.e. HSE).

From a **toxicological** point of view, the PDE formula requires availability of many non-clinical toxicology data. However, these data often are not available for old medicines, because many years ago the ICH safety guideline detailing type and extent of non-toxicological data necessary for registration (*ICH*) was not in place.

Therefore, additional time and costs are necessary to find out relevant toxicological data or to develop an alternative approach, also for medicines successfully manufactured by using the current standard generally based on LOEL (Low Observed Effect Level)/1000 or minimum daily dose/1000. Once the PDE has been established, an overall risk assessment of the current processes should be carried out in order to reduce the risk; **technical** measures (i.e. isolator) and **organizational** measures (i.e. production on a campaign basis) should be put in place (*Eudralex GMP, d*). Establishing manufacturing campaigns can reduce the manufacturing flexibility and increase the manufacturing lead time, both are shortage risk factors; setting up technical measures embodies high technology equipment like isolator or high containment connection (*AFI, 2012*).

Introducing new equipment involves four macro stages:

1. Cost and benefit evaluation
2. Careful integration with existing equipment and process, complex engineering projects
3. GMP impact assessment (e.g. qualification, validation)
4. Impact assessment on other compulsory regulations (e.g. Health Safety Environment)

Point 1 is fundamental: in general, profits generated by each project or product should at least cover its costs, otherwise there is no sustainability. HPAPI (High Potent API) are generally and conventionally considered as API with a therapeutic dosage below 10 mg/day and are critical materials with respect to cross contamination; the estimated production cost for a HPAPI is 33% higher than a not HPAPI (AFI, 2012), partly due to major equipment cost. Moreover, the most advanced high containment production lines could have a regulatory impact, sometimes requiring preventive inspection/evaluation by Regulatory Authorities before coming in to operation (EMA, 2014 .c). When a new equipment is introduced in an already approved process, making a substantial change to the process, it is necessary to produce at least 6 months comparative stability data in order to demonstrate that the process change does not affect the product quality (EMA, 2011).

Figure 2 shows main steps for the introduction of a new containment equipment in an existing department, same steps apply in case of an equipment change on existing process, and are a general approach required for replacing any equipment involved in the primary production (materials in touch with raw materials, intermediates and drug product).

After the cost and benefit assessment, a **Technical** assessment is necessary to understand the process performance, type and equipment size, in order to be compliant with the manufacturing demand. This is another pivotal project step: it is fundamental to have a demand forecast in compliance with the process capacity. One size does not fit all volumes, in general, each manufacturing process has a minimum and maximum range: wide reductions or increases cannot be matched because they might be outside the operative capability.

Several **GMP** steps should be performed, each one needs documents which should be laid down in compliance with the respective guideline in order to

- perform a change control evaluation (ICH Q10, 2008)
- evaluate the new equipment characteristics -URS, DQ-
- ensure construction and shipment as per approved requirements – FAT, SAT –
- verify the correct assembling and installation at the manufacturing site - IQ –
- test that performances are compliant with the required standard - OQ, PQ –
- and finally the suitability throughout the medicinal manufacturing process PV (Eudralex GMP,c) .

This process can take several months or years.

The cross contamination topic deserved such a long examination because the API relevance is increasing in time: the global HPAPI market involves prevalently drugs for cancer, diabetes, and cardiovascular diseases. The overall market was worth US\$12.6 bn in 2014, with an estimated CAGR of 7.8% between 2015 and 2023. It is projected to be valued at US\$25.1 bn by 2023 (Transparency Market Research, 2016.).

However, GMP requirements affect all API, without considering if their selling price is high or low: for example, a few injectable cytotoxic drugs under shortage (*Goldsack, J.C., et al., 2014.; Kehl, K.L., et Al., 2015.; Gogineni, K., et Al., 2013.*).

Although they are not innovative from a clinical point of view, they require state of the art plants to be manufactured.

3.3 Supply chain complexity

The supply chain is the end to end process entailing all steps and players necessary to provide the medicine (*PwC*), and it became more complex during recent years, challenging the manufacturer's ability to maintain it under control (*EFPIA, 2011*).

It is out of the scope of this paper to deal with such a huge matter, anyway a brief mention to changes to demand, regulatory and GMP constraints can provide a feeling of the problem complexity.

From a MAH (Marketing Authorization Holder) perspective, demand fluctuation and regulatory/GMP changes can affect external factors such as availability of API, excipients and equipment - and on internal factors such as personnel, formulation and process.

Not every aspect can be are under the primary MAH's control, because regulations changes or medicine demand fluctuations impact on a variety of secondary suppliers. For example, the MAH (and/or the manufacturing site) must select the API supplier assessing that it is GMP compliant (*EMA, 2014 b.*), in addition the API manufacturer should be successfully inspected by a competent Regulatory Authority (*EMA, 2014 c.*).

Also excipients should be acquired from GMP-compliant manufacturers (*European Union, 2015*) and a recent regulation strengthen the importance of risk assessment criteria throughout the selection process (*European Union, 2011*), their relevance as CMA increases by the time. Also, it is crucial liaising with manufacturers in order to have stable supply with tight quality specifications limits.

Equipment suppliers should adapt the technological solutions to the regulations, e.g. regarding materials in contact with the product (*Eudralex GMP, d*). In addition, for high complex equipment they should ensure prompt maintenance and assistance (preventive and extraordinary) in order to prevent and manage failures. The external maintenance contract should specify responsibilities and a technical agreement should be in place (*Eudralex GMP, e*): however, nothing can protect the pharmaceutical industry from external factors affecting the business continuity of an equipment manufacturer. As shown in the previous paragraph, an equipment change should be carefully evaluated before it is implemented.

Many other external players are involved, i.e. distributors should be GDP-compliant (*European Commission, 2013*) in order not to affect the product quality; packaging suppliers often have to provide materials and solutions to ensure product traceability in compliance with the anti-counterfeiting policy (*European Union, 2011*).

To add on complexity, each pharmaceutical industry supplier relies on secondary suppliers, e.g. API suppliers are buying starting materials from other suppliers.

There are many players and activities before and after the manufacturing process: maintaining an overall control is extremely complex.

Achieving the right capacity (intended as ability to satisfy the product demand) is a challenge equivalent or bigger than achieving the right quality (*AT Kearney, 2014*). When even a single player has GMP-compliance problems, the identification, qualification, and validation of an alternative supplier can take months or years, e.g. for replacing an API supplier.

3.4 Formulation and product complexity: capacity constraints

The product formulation has a pivotal impact on its lifecycle. Although formulation is an early research step, because the product should meet the patient needs highlighted by Clinical Trials (*Yu, L. X., et Al., 2014*), formulation changes may be needed for a variety of reasons through the product lifecycle. Each change entails a series of GMP activities, e.g. process validations, regulatory activities, ICH stability studies. Formulation updating is a continual process to maintain alive the product with a suitable quality.

For instance, an API supplier change for an oral solid formulation involves several technical steps such as process validation and stability studies (*EMA, 2011; Eudralex GMP, c*); in some case (e.g. for BCS class I and III, conventional release) in order to avoid a bioequivalence study, a bio waiver can be provided, but in-vitro dissolution tests must satisfy a F2 test assessing the absence of statistically significant differences between the old and the new formulation (*FDA, 2015*) (*EMA, 1998*). An API supplier change can occur several times during the product lifecycle. Moreover, excipients are a major source of variability and require development efforts, this variability may be investigated via QbD approach (*Yu, L. X., et Al., 2014*). Furthermore, when quality data are not sufficient to demonstrate the comparability between the current and the modified process, clinical data may be required, such as a bioequivalence study (*FDA, 2015; EMA, 1998*), in particular for biotechnological or nanoparticle based products, that are very difficult to characterise (*EMA, ICH Topic Q 5, 2005*).

Beside nanotechnological and biotechnological products and Drug Delivery Systems which often have a complex formulation, the already mentioned changes due to new regulations or to supply chain fluctuations increase the technical challenge **even for simple formulations** (see **figure 4** and refer to **chapter 4.4**). Frequently, MAH delegates manufacturing activities to Third Parties, also called Contract Manufacturing Organization (CMO). Nowadays, most CMOs modified their name and scopes, becoming CDMO, where D stands for development, meaning that development is part of the manufacturing process (*American Pharmaceutical Review, 2016*).

Product complexity generates capacity constraints. In a survey involving 235 bio pharmaceutical industry decision-makers, 57.9% declared some level of constraints as follow: minor relevance (24.6%) moderate relevance (20.2%), or severe relevance (4.7%). The required activity to avoid capacity constraints is **development**, which entails four main topics:

- 1) developing better downstream purification technologies,
- 2) developing better-performing disposable, single-use products

- 3) developing “modular” production systems,
- 4) developing cost effective disposable, single-use products. (*Langer, E., 2013.*)

No manufacturing activity can be performed without strong formulation and pharmaceuticals skills, and there is an increasing formulation complexity, not only for biological or nanoparticles medicines. Indeed, new formulations can boost the therapeutic efficacy of old drug, for example chronotherapy formulations. The body follows a 24-hour cycle named circadian rhythm. The suprachiasmatic nucleus regulates this cycle and nearly all body functions, including those affected by the drug delivered. The chronotherapy approach synchronizes the drug properties in accordance to the natural rhythm of the body (*Zaheeda K. et Al., 2009.*)

Many chrono-pharmaceutical oral technologies have been developed (CONTIN, CEFORM, CODAS, Diffucaps, etc.) each one correlates in a peculiar way the formulation characteristics to the desired pharmacokinetic profile (*Zaheeda K. et Al., 2009.*)

To be noted, the development of a modified release formulation allowing the chronotherapeutic approach is not a recent path: for instance, many products aimed at a chronotherapeutic approach to hypertension have been developed in the past and are still successfully employed today (*Smith DH, et Al, 1999.*; *Hermida, R.C., 2010*; *Eradiri, O., Middha, K.K., 1997*). Generally their selling price is not so high.

But these technologies have several critical process parameters (CPP) and many Critical Materials Attributes (CMA) to be assessed via a QbD approach; they are complex and also a minimal change to the formulation (e.g. excipients) or to the manufacturing process requires a dissolution profile comparison and a biostudy (*FDA, 2015*; *EMA, 1998*). Therefore, these products have an intrinsic complexity and in order to comply with recent regulations, they require expensive lifecycle maintenance activities and long improvement timeline. This is usually not accounted for in the determination of their reimbursement price.

3.5 Regulatory impact and overall time for a change in pharma industry

All factors above mentioned require long and complex technical activities. Although the cost constraint might be minimized by using more efficient resources, the time required for these activities cannot be shortened. Below reported timeline refer to variation in EU.

Guidelines and regulations define and regulate variations to a Marketing Authorization dossier in the EU (*European Commission 2008*; *EMA 2011*; *European Commission*). In general variations are classified as administrative minor variations (Type IA), minor variations (Type IB) and major variations (Type II).

Although regulatory requirements may change depending upon different conditions of each specific variation, generally a new API introduction, a new Manufacturer introduction or the change/introduction of an excipient which may affect the product quality may require: the availability of validation batches, up to 6 months of stability data, and 30-120 days for the regulatory approval.

Taking into account the time necessary for the validation batches manufacturing, results assessment or for the preparation of any other necessary GMP relevant document in addition to the regulatory process, **easily extends the timeline to over 1 year.** Moreover, 1 year may be the best case because when a change

does not meet with regulations requirement, it can not be submitted; therefore, further activities and time are necessary.

4 Discussion

4.1 Shortage risk factor to be included in the HTA process

Once acknowledged that manufacturing technology is a pivotal factor, some actions can be put in place in order to manage and evaluate the shortage risk. Many factors contribute to drug shortages: economic, technical, demand fluctuations (*Kweder, S.L., Dill, S., 2013*), (*Woodcock, J., Wosinska, M., 2013*). To reward quality, in order to assess the overall shortage risk, an analysis of the missing minimization measures related to this topic should be performed, e.g. lack of manufacturing redundancy, lack in manufacturing incentives to reward quality.

FDA laid down a strategic plan for preventing shortages, and proposed Redundancy, Capability, and Capacity as factors that may reduce the shortage risk; we try to translate these factors in measurable variables to quantify the risk (see **table 2**) (*FDA*).

A comprehensive thought on the shortage risk assessment has been done, involving scientific associations and regulators; resulting in a paper presenting a model for assessing the shortage risk (*PDA, 2014*).

In this paper, *ISPE Drug Shortages Task Team* defined several “building blocks” to be considered in assessing the shortage risk:

- Corporate Quality Culture
- Robust Quality System
- Metrics (specific to drug shortages)
- Building Capability – for example, organizational and personal competencies
- Business Continuity Planning – for example, crisis management
- Communication with Authorities

Moreover the *PDA* technical report *Risk-Based Approach for Prevention and Management of Drug Shortages* provides a guide to identify and manage drug shortage risks, primarily evaluating the patient impact, e.g. if there are therapeutic alternatives or not.

We propose a simple risk assessment exercise (see **Table 1**), that might help MAH and Regulatory Authorities to quickly assessing the shortage risk in relation to manufacturing complexity.

The Risk ranking and filtering table is based on the correspondent tool described on ICH Q9 (*ICH Q9, 2005 b*) and identifies main factors potentially affected by the manufacturing complexity as described in the previous paragraphs: Capacity, Sustainability and Technics. This risk filtering table concentrates on manufacturing factors, that have been scarcely evaluated so far. To build an even more comprehensive evaluation tool for shortage risks, this table could be further integrated with a quality compliance factor. However, this would entails even more variables and require a dedicated risk analysis, that would be out of

scope of the present paper. Moreover, quality compliance is a parameter generally well assessed by using QRM tools.

Before taking some decision affecting critical factors for the supply continuity, for instance setting price and reimbursement, it would be useful to assess **proactively** and **in advance** the impact of that decision. **Considering that there are more comprehensive evaluation tools**, some of which has been already above mentioned, our aim is to translate the general principles in practical aspects, **in order to provide a picture of the difficulty to translate simple concepts into measurable variables**. Moreover, we would like to point the attention to three main AREAS needing evaluation, being conscious that the proposed score system and risk factors individuated can not be universally applied. The proposed risk filtering is no product-specific and should cover a wide variety of medicines with different critical factors impacting on their shortage risk, so the table it is not intended to be universally applied but should be customised on a case-by-case basis.

Moreover it should be periodically updated as each risk factor may change its score by the time. The proposed evaluation is a strictly technical assessment and might be useful as an **initial trigger** in order to establish a risk ranking and address available resources towards higher risk situations, in full compliance with ICH Q9 principles (*ICH Q9, 2005 a*).

Our aim is to synthetize in one simple table the pivotal elements to be taken into account in the evaluation of the shortage risk from a technical point of view.

- We identified four risk areas - *Capacity, Sustainability, Technics* - each one contributing by the same extent to the risk ranking (from 1 to 10 points).
- Each risk area is divided in several risk factors to be measured, since the score for each area can not be more than 10, each risk factor is adjusted as per a correction factor.
- The total score varies from 3 (minimum overall risk) to 30 (maximum overall risk); a specific score identified as an acceptable risk should be properly justified.

Each risk factor is justified by the following main reasons:

- All **capacity** factors (**a,b,c,d,e,f**) reflect the robustness of main steps relevant for the daily supply continuity; any measure leading to a redundant capacity can mitigate the risk. The FP resupply time (**c**) means how long it takes to make available the drug, therefore it entails: manufacturing activities, batch release, shipment.
- (**f**) is expressed in terms of stock pile and not in terms of resupply time because: a) the API can be retested at the end of its shelf life (*ICH Q7*); b) it has a shelf life longer than FP; c) an API change requires time, due to the need of GMP activities and regulatory approval before being implemented.
- **FP selling price (g)**: a numeric ranking cannot be set in advance because the selling price evaluation is different for each type of drug.
- **FP annual turnover (h)**: it reflects the product relevance for manufacturing activities sustainability; generally products generating a small turnover have a challenging cost/benefit balance.

- Both **technical factors (i,l)** reflect the intrinsic product complexity, which can be divided in process and formulation complexity. **It is relevant to recognise it as a very important factor because** for example Drug Delivery Systems or nanoparticles may lead to parameters to be handled within tight limits in order to achieve the desired quality (*Panzitta et Al, 2015*). Moreover, also for apparently simple formulation the API might be intrinsically less stable: stability is an intrinsic API property that sometimes can be only partially increased by formulation **and requires more technical efforts to achieve the desired** quality.

4.2 One Quality concept does not fit for all drugs

In their comprehensive paper Woodcock and Wosinska (*Woodcock, J., Wosinska, M., 2013*) stated that concerning sterile cytotoxic drug shortages ‘*the fundamental problem is the insufficient market reward for quality (including reliability of production) stemming from the buyers’ inability to observe it*’. The same concept has been highlighted by Kweder and Dill.

Panzitta et al described how and how important is performing a medicine full technological assessment in addition to clinical assessment during the Health Technology assessment step (*Panzitta M. et Al, 2015*).

The shortage risk evaluation (**table 2**) above proposed evaluates the production reliability and might be used during the pharmacoeconomic step in order to address a medicinal policy aiming at rewarding quality.

The shortage risk is linked to the **overall quality**, which is linked to the **resources** necessary to maintain the product compliance and solve any **technical** problems leading to capacity constraints: **this might be named the quality rewarding cycle (figure 2)**

These tools may improve the *ability of the buyers to* acknowledge the quality value; however it is not sufficient. **Probably it would be useful to broaden the quality concept, that is too often related only to achieving a desired GMP-compliance level.**

Eudralex chapter I describes the Quality Management as a “*wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice*” (*Eudralex, GMP, a*).

The quality should entails not only merely the GMP standard achieved, but also recognise “*all matters, which individually or collectively influence the quality of a product*” such as the effort to prevent

drug shortages, the capability to manufacture complex formulations with a high level of process control, the period of absence of significant findings during regulatory authority inspections.

Rewarding and recognising this effort could be an effective policy to prevent shortages, establishing a proactive policy and acting directly on the shortage root causes related to manufacturing issues.

In doing so, a broader quality concept might be assessed, considering all the critical steps necessary to supply a safe medicine, in the **right quantity**, at the **right time** (see **figure 3**)

1. **shortage risk:** as mentioned, in addition to the risk assessment table described in this paper, several useful tools have been proposed in order to assess the shortage risk (*PDA, 2014*). Moreover, ICH Q9 states that a loss of product quality or availability can harm the patient (*ICH Q9, 2005 a*). So, it is pivotal to include the economic driver in a shortage evaluation: quality requires resources (*ICH Q10, 2008*), and resources come from adequate selling prices: the link between resources and quality should be in place (**figure 2**).
2. **Technology (see paragraph 3):** these factors drive the medicine manufacturing; only if manufacturing scientists handle them efficiently a reliable supply can be put in place. However, the technical complexity does not affect only shortage risks, since it is in relation with all product quality characteristics. For instance, it correlates with the difficulty for certain formulations or processes to maintain compliance with new regulations.
3. **Quality curriculum (manufacturing site):** as per technology factors, the manufacturing site quality curriculum contributes to the shortage risks assessment, but also to the overall medicine quality. A manufacturing site that is regularly and successfully inspected by regulatory authorities, not only minimizes the medicine shortage risks, but also ensures the right quality without supply concerns.
4. **Lifecycle maintenance:** activities burden deployed in order to keep alive the marketing authorization contributes to the overall quality. Timely updates to recent regulations and the burden of activities necessary to continually improve the product quality should be critically assessed as an overall quality factor. Factors 1,2,3 can be deployed in several ways to achieve the overall quality; efforts towards implementing state of the art processes or preventing shortage risks should be measured, acknowledged and rewarded. Only if properly rewarded, they can generate the resources necessary to achieve the product quality (**figure 2**)

Finally, as quality problems lead to medicine shortages, a pharmaceutical industry able to maintain high quality standards should be acknowledged as an important factor for patient safety, also in terms of shortage prevention (*AIFA, 2016*).

4.3 Manufacturing technology as key research point

As described, pharmaceutical manufacturing requires research but ensure quality improvements, for instance working in compliance with recent GMP and HSE regulations can grant levels of containment higher than those achievable just a few years ago.

Although manufacturing is the link between laboratory and patient and its criticality is evident in case of shortage, it is not acknowledged as an important pharmaceutical research step.

This is acknowledged for highly engineered products (*Rantanen, J., Khinast, J., 2015*), but our paper shows that changes occurring during the lifecycle as well as growing quality requirements need technological research also for conventional products.

Two out of 4 Quality by Design objectives underline the critical link between manufacturing and patient:

1) product quality specifications to be achieved through the manufacturing process should reflect the patient needs, 4) “*After regulatory approval, effort should continue to improve the process to reduce product variability, defects, rejections, and recalls*” (*Yu, L. X., et Al., 2014*).

Traditionally R&D research is intended and funded as drug discovery and clinical trial stages; however, to reach the patient a medicine must be manufactured; as detailed above, the manufacturing process requires strong research. **If we do not consider the manufacturing process as a R&D step, we may discover innovative products but we might not be able to manufacture them.**

In order to prevent drug shortages, as an action other stakeholders should consider, FDA suggests that also manufacturing technology innovation should be supported, in addition to drug discovery and development, that are financed through a variety of economic incentives. By doing so, shortage root causes related to quality might be prevented and the manufacturing technology can support the growing innovation: ‘*manufacturing processes and technologies must keep pace with advances in drug research and development*’. (FDA)

Notably, this applied research is fundamental for upgrading current processes, to achieve a continual quality improvement and to ensure supply continuity, even for old products.

ICH Q10 states “*throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities*”.

To integrate research knowledge into routine manufacturing, the ICH Q10 proposes the *Knowledge Management*, that “*is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components*” (*ICH Q10, 2008*).

For instance, process knowledge gained during development activities is the basis to develop the commercial manufacturing process and to implement the Quality by Design approach.

However, ICH Q8 to Q11 did not fully reach their aim to enhance the post approval operational flexibility, and facilitate the continual manufacturing development; partly because there is a lack of harmonization at regulatory level, but mainly because ICH guideline were addressed towards the early development stages.

ICH Q12 recognises that ‘*The main emphasis at ICH to date has focused on early stages of the product lifecycle (i.e., development through launch). A similar focus is now needed for the commercial manufacturing phase in order to fill the gaps in the implementation and fully realize the opportunities promised by ICH Q8 to Q1.*

The commercial manufacturing is acknowledged as a huge research area, critical for the product quality and for the supply chain management necessary to achieve a reliable supply (*ICH Q12*).

4.4 Growing quality requirements

Eudralex Volume 4 is "*The rules governing medicinal products in the European Union*" and contains guidance for the interpretation of the principles and guidelines of good manufacturing practices (*Eudralex GMP, f*). Part I comprises basic requirements for medicinal products. **It is composed by 9 Chapters, 8 out of 9 (more than 85%) have been updated during the last three years.** Since these chapters set the main principles to be adopted during manufacturing, their implementation extensively affects all manufacturing activities.

In the EMA guidelines on the **quality of medicines** (*EMA quality Guidelines*) '*Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to **interprets** and **applies** the detailed requirements for the demonstration of quality, safety and efficacy that are in the **Community directives***'. MAHs should comply with the guidelines and any deviation should be properly justified. The number of guidelines that became effective during the last 10 years increased progressively (**see figure 4**); however this trend only provides a general picture of the regulation constraints requiring to upgrade the technical and quality system. It is not a qualitative evaluation since each guideline may affect manufacturing activities by a different extent.

Last 10 years had a massive impact on how quality activities are conducted. The process for manufacturing, controlling and releasing a batch became more complex, affecting lead-time and production costs, resulting in an overall quality increase.

Growing quality requirements and complex manufacturing processes turned the manufacturing activities from a routine activity into research: again, manufacturing should be acknowledged as a critical R&D step. As a consequence, it is necessary not only to invest more resources, but it is also fundamental having skilled people.

4.5 Pharmaceuticals as a key role

Pharmaceutics is the "*Science of preparation of drugs, dosage forms, and drug delivery systems taking into account the pharmacokinetics and pharmacodynamics of the drug as well as its physical and chemical properties*", and clearly entails all disciplines necessary for the manufacturing technology (*Breuer, E., et Al., 2009.*).

Skilled pharmaceutical technologists are fundamental for manufacturing research activities, and skilled people are the first and most important pillar of a Pharmaceutical Quality System. Eudralex Chapter I states that "*competent personnel, and suitable and sufficient premises, equipment and facilities*" should be available (*Eudralex, GMP, a*).

All pharmaceutical professionals should operate according to the quality system, should be committed to a progressive quality improvement (*ICH Q10, 2008*), should increase their technical skills by continual

training and should develop knowledge useful to translate regulatory requirements into technical solutions.

(Eudralex GMP, g)

GMP requirements underline the importance of personnel expertise, which should increase in order to manage the growing complexity of regulations and technical problems.

It is worthwhile to fund academic research on pharmaceutical technology as well as funding student education program to have highly skilled manufacturing professionals *(Rantanen, J., Khinast, J., 2015)*, able to face the growing complexity of products and processes.

A survey involving 235 decision makers across the Biopharmaceutical industry, highlighted as a main predictable capacity constraint factor the inability to hire new, experienced technical and production staff *(Langer, E., 2013)*.

The trend of pharmaceutical education is towards an increasing knowledge in biologic or social sciences, but it seems to underestimate the relevance of pharmaceutical technology. To the contrary, a pharmaceutical technology education program should be put in place, including disciplines necessary to face the growing product, processes and quality complexity *(Rantanen, J., Khinast, J., 2015)*. Moreover, it would be ideal having **more integration between academia and industry**, as academia is the main source of pharmaceuticals knowledge, the source of skilled pharmaceutical technologist and can support industry in facing manufacturing challenges.

4.6 Growing manufacturing complexity

Manufacturing technology has evolved rapidly in recent years, for instance with the introduction of a Continuous Manufacturing (CM) approach by using new tools such as PAT (Process Analytical technology) or Continuous Flow Chemistry *(Rantanen, J., Khinast, J., 2015)*. In order to promote CM upgrading, ICH issued a specific guideline *(ICH Q12)*. A QbD approach often entails PAT; also when production is traditionally carried out per batches, a robust QbD can sustain the PAT application. This requires the application of a true research step *(Sherif, I. F. B., Narang, A. S., 2016)*.

This evolution is in progress and entails a strong collaboration between Academia and Industry *(Rantanen, J., Khinast, J., 2015)*. Manufacturing technology is a huge research field to be explored. This is clearly evident during early development stages; before going into clinical stage, a safe and reproducible production process should be in place. EMA has in place an initiative to provide financial and administrative assistance to micro, small and medium-sized enterprises (SMEs). The 2012 report mention that of the major objections at day 120, 39% were related to quality, with focus on in process validation, specifications and stability data *(EMA, 2013)*. The 2014 report highlith that objections at day 120 were related to Quality (46%), clinical and safety (47%), and non clinical development (7%); 51% of objections encountered in marketing authorisation applications for biologics were on quality topics vs. 41% in dossiers for chemical entities. *(EMA, 2014 d)*

ETPN (The European Technology Platform on Nanomedicine) published a white paper providing evaluation in determining if applications submitted as H 2020 projects are foreseeable to become available therapies: Manufacturing and Physicochemical Characterization are considered key translational activities to be empowered by knowledge and infrastructure. Therefore, both a European Nano-Characterisation Laboratory (EU-NCL) and GMP production pilot lines for clinical batches will support academics and Small Medium Enterprises to develop their products for validation in clinical trials, prior to transfer to Contract Manufacturing Organization (*ETPN*).

Several tools can be used to characterize and develop a manufacturing process, all of them can be successfully implement via QbD. Beside basic QbD tools such as Quality Risk Management and DoE, mechanistic process modelling allows exploring the process properties and variability via process simulation (*Rantanen, J., Khinast, J., 2015*).

Twenty years ago, in order to characterise a process, it would have been sufficient manufacturing 3 batches and perform routine analysis (release and stability). Nowadays, Computational Fluid Dynamics can simulate fluidic and multiphase systems (such as stirred tanks, crystallizers, bioreactors), aiming at understanding in detail the mixing dynamics, identifying dead zones, or characterizing the shear rate distribution for shear-sensitive products (*Rantanen, J., Khinast, J., 2015*). Particle Based System techniques, mainly DEM (Discrete Element Methods) that consider dense powder flows, allow to simulate the interactions among solid particles. Fluid–Solid-Particle Systems simulating tools characterise solid particles that are fluidized or suspended in a liquid (*Rantanen, J., Khinast, J., 2015*).

However, the manufacturing process evolution does not involve only techniques to “predict” process performances. To enhance the overall process understanding and to enable applications such as PAT, the analysis of “historical” process data is equally important. Knowledge can be gained through public data analysis (i.e. literature), or throughout analysis of non publicly available data (such as process data). This prior knowledge is fundamental for the QbD approach (*Yu, L. X., et Al., 2014*). The Pharmaceutical Industry has many available data, however their analysis and interpretation is complex. The application of data analysis tools is a pivotal example of how Academia and Industry can perform research applied to routine processes, proactively identifying potential areas of improvements (*Meneghetti, N., et Al, 2016*).

QbD and all other techniques above described apply not only to highly complex products, but also to traditional formulations (e.g. oral solid formulations) (*Kushner, J. et Al, 2014*) and foresee an increasing collaboration between Academia and Industry (*Nabil Souihi, Melanie Dumarey, et Al, 2013*).

5 Conclusion

5.1 A new research perspective

During the product lifecycle, changes are necessary; their causes are not always under MAH control. It means that just a simple excipient change requires both time (months) and pharmaceuticals knowledge, but it

is a development stage necessary to maintain the product in the market: without this continual development stage the medicine might not reach the patient.

The extent of this development is not related to the medicine clinical innovativeness but is related to its technical complexity, and also non-innovative products, such as some cytotoxic drug or low dosage formulations, may require a strong development effort to achieve the necessary quality upgrading.

Production value and clinical value are anticyclical in time: generally, one decreases with time and the other increases (*Panzitta et Al, 2015*).

A shortage event underlines the necessity to consider manufacturing as a critical step:

- 1) production is the link between laboratory and patient
- 2) without manufacturing, R&D efforts are useless
- 3) continual improvement of quality requires continual manufacturing research.

The payers and provider pharmaceutical policy, at public or private level, should acknowledge this and collaborate with Academia to **view manufacturing as a critical research step**, exactly as drug discovery or clinical trials.

5.2 A preventive assessment

It is well known that the collaboration among different players is fundamental to prevent drug shortages. Manufacturers and pharmacists are the most important early sources of information, with manufacturers having a growing role thanks to their proactive analysis of the shortage risks and data sharing with Authorities such as the FDA (*Kweder, S.L., Dill, S., 2013*). However, evaluation and collaboration are not sufficient. Manufacturers and pharmacists are involved in shortages management; since they have the competences to evaluate the root cause they should be involved early, in dedicated programs or at the HTA step, in order to prevent any economic policy potentially increasing shortages risk.

As shown, in order to develop an effective policy aimed at preventing drug shortages it is fundamental to involve pharmaceuticals professional who are dealing with the root cause of shortages.

In a previous work, Panzitta et al suggested to include Pharmaceuticals Experts in the panel of experts involved in the HTA process; this involvement would ensure a better evaluation of pharmaceuticals properties potentially leading to patient's benefit or harm.

By doing so, a medicinal product could be evaluated in depth analysing its clinical effects by the conventional EBM approach, as well as its other aspects supporting the clinical effect, involving pharmaceuticals experts able to assess the critical points sustaining the clinical evidence (**see figure 5**).

To date, Regulatory Agencies react to shortages when they are already happening, or just before, and this might not be sufficient to prevent harms to the patient. Actions deployed can reduce impact on the patient, e.g. allowing medicine import from foreign countries (*AIFA*), or introducing regulatory flexibility enhancing suppliers continuity (*Kweder, S.L., Dill, S., 2013*), but cannot act on the root cause. As every activity in the pharmaceutical field is highly regulated, it takes several years to be deployed. Therefore, we

might estimate years in advance a shortage's potential root cause (manufacturing related) and a proper strategy for preventing it can be put in place. For doing so, we should actively involve pharmaceutical experts capable of evaluating the possible impact of regulations and price policy on the overall products availability. If we react to a shortage, we have to spend resources to repair harms already in place (*McBride A, et Al, 2013.*) a preventive action requires less resources.

Anyway, any policy aimed at preventing shortages cannot be simply based on the medicine price, since there are a variety of potential root causes, besides economic causes, e.g. regulatory or quality constraints. In pharmacoconomics, one of the most important step is the cost analysis (*Drummond, M.F., et Al, 2012.*) which should entail a society perspective, understanding what is the impact of a drug policy on the overall society. Although it is one of the HTA best practices (*Drummond, M. F. et Al, 2008*) it is seldom applied. The impact of a pharmaceutical policy is evaluated only in terms of pharmaceutical expenditure variation, without evaluating the impact on the society (other government expenses, citizen expenses). A price increase granted to prevent shortages and stimulate the manufacturing activities might be classified as a pharmaceutical expenditure increase; this gives only a limited perception of the situation. If a medicine has a price too low for being produced, and becomes unavailable on the market, most probably it will be replaced by an alternative and more expensive medicine.

In conclusion, medicine shortages due to manufacturing causes are a complex problem, needing technical evaluations.

5.3 A proactive approach

One of ICH Q10 aims *'is to Achieve Product Realisation To establish, implement and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers'*.

A shortage (manufacturing related) means lack of product realization. In order to prevent a potential shortage at each evaluation step potentially impacting the manufacturing process, experts with manufacturing knowledge should be involved and encharged of satisfying the patient needs. Health care professionals and patients are the final users of a complex process; any potential decision impacting on the medicinal product manufacturing, i.e. HTA step, pharmaco-economic policy and new regulatory requirements should be taken by involving professionals with a proper manufacturing knowledge, able to assess the impact of these critical decisions on a potential shortage risk.

Nowadays, manufacturing involves taking into account biopharmaceutical properties, material properties (excipients, API), manufacturing technology and product properties as part of an integrated process. This complex integration should match with the final product's increasing complexity, as nanoparticles, biopharmaceuticals, personalised medicines are coming in to therapy (*Rantanen, J., Khinast, J., 2015; Panzitta, M., et Al, 2015*). In addition, API increasing potency and higher quality demand result in increasing production complexity also for traditional formulations or legacy products.

ICH Q10 states the principles that could be the basis for a proactive shortages prevention policy. **Manufacturing knowledge, continual improvement, risk based decision** are the pillars to assess, understand, prevent and handle shortages root causes (manufacturing related). However, these pillars should be managed in a proactive way, considering pharmaceutical technology as a pivotal discipline and making investments to prevent potential drug shortages. Quality by Design aims at stimulating a proactive approach, directing resources towards understanding the processes in order to prevent quality defects. (Yu, L. X., et Al., 2014). This should be preferred to a reactive approach, in which resources are used only to correct a quality defect that already come up.

ICH Q12 can be viewed as the synthesis of the concepts discussed so far:

1. **Manufacturing Technology as research:** ICH Q12 recognizes the commercial manufacturing phase, which includes the product lifecycle maintenance, as a topical area needing implementation of ICH Q8 to Q11 concepts. As we shown in the articles, that implementation means research and development of new tools and technical solutions at a commercial stage.
2. **Pharmaceutics experts as stakeholders:** ICH Q12 *will also impact many stakeholders involved in the manufacture of pharmaceuticals, therefore it is important that EWG members have expertise in quality systems, pharmaceutical development and manufacturing of chemical, biological and biotechnological products.*
3. **Proactivity:** ICH Q12 develops a post approval (lifecycle) management plan concept aimed to proactively identify and assess changes (*ICH Q12*). FDA proposed short term actions in order to mitigate supply disruptions preventing they become shortages, and long term actions aimed to prevent the shortage root causes: one long term action is to promote manufacturing technology innovation (*FDA*).

A pharmaceutics knowledge would give us the ability to preventively assess and manage manufacturing related shortage root causes. However, this step requires an initial economical investment. As explained by Kweder and Dill, all actions aimed at maintaining a robust supply chain (i.e. manufacturing redundancy) will be a cost for the payers. This is the investment cost to **upgrade from a reactive to a proactive** manufacturing related shortages management policy (**see figure 6**). Probably this cost would be justified because it will generate future cost saving also from a societal point of view (*Kweder, S.L., Dill, S., 2013*).

Giving the right medicine at the right time is an enormous benefit for the patient and it is the aim of anybody involved in pharmaceutical manufacturing. Authors remind that shortage has several causes often not manufacturing related, whereas this paper is conceived to deal just with manufacturing technology assessment.

This paper is conceived as just a reflection and a starting point to stimulate further debate.

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Figure 1: main steps required for a new equipment introduction in an existing department, affecting substantially an existing process

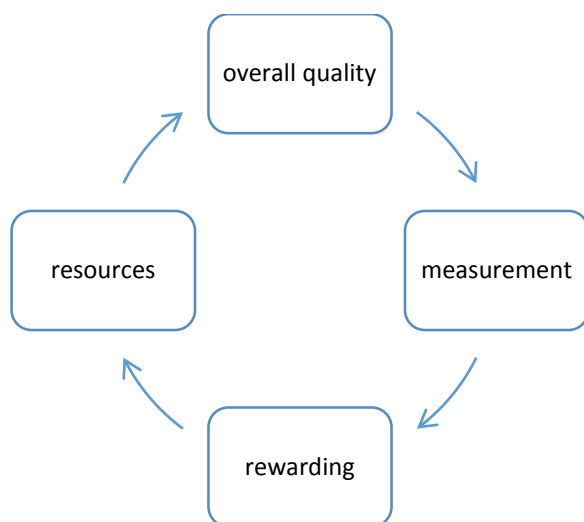


Figure 2:The quality rewarding cycle

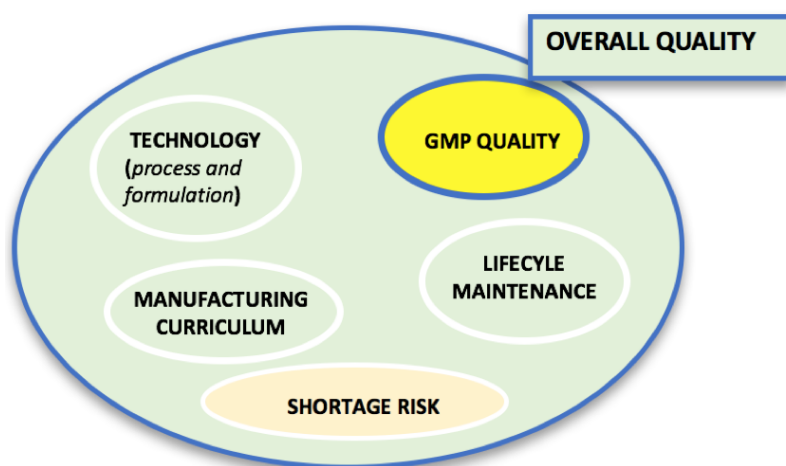


Figure 3: overall quality concept

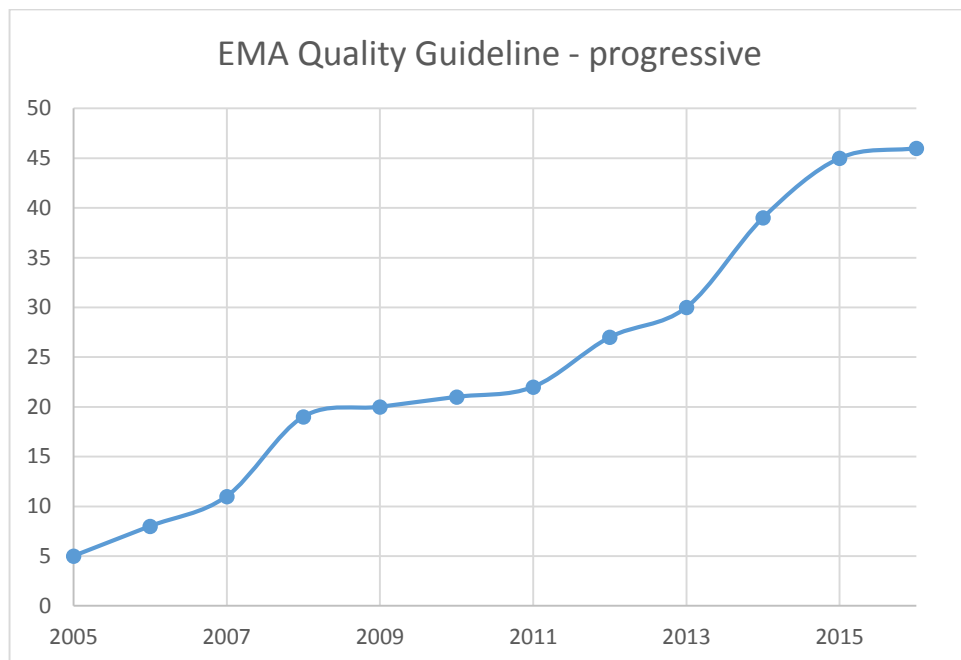


Figure 4: N° of EMA guidelines on quality Vs year, trend indicates number of guidelines progressively came in operation

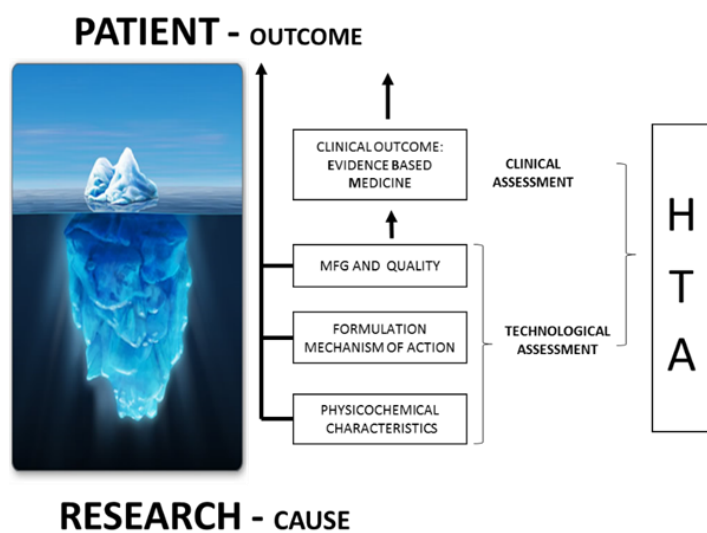


Figure 5: an HTA integrated approach (*Panzitta et Al, 2015*)

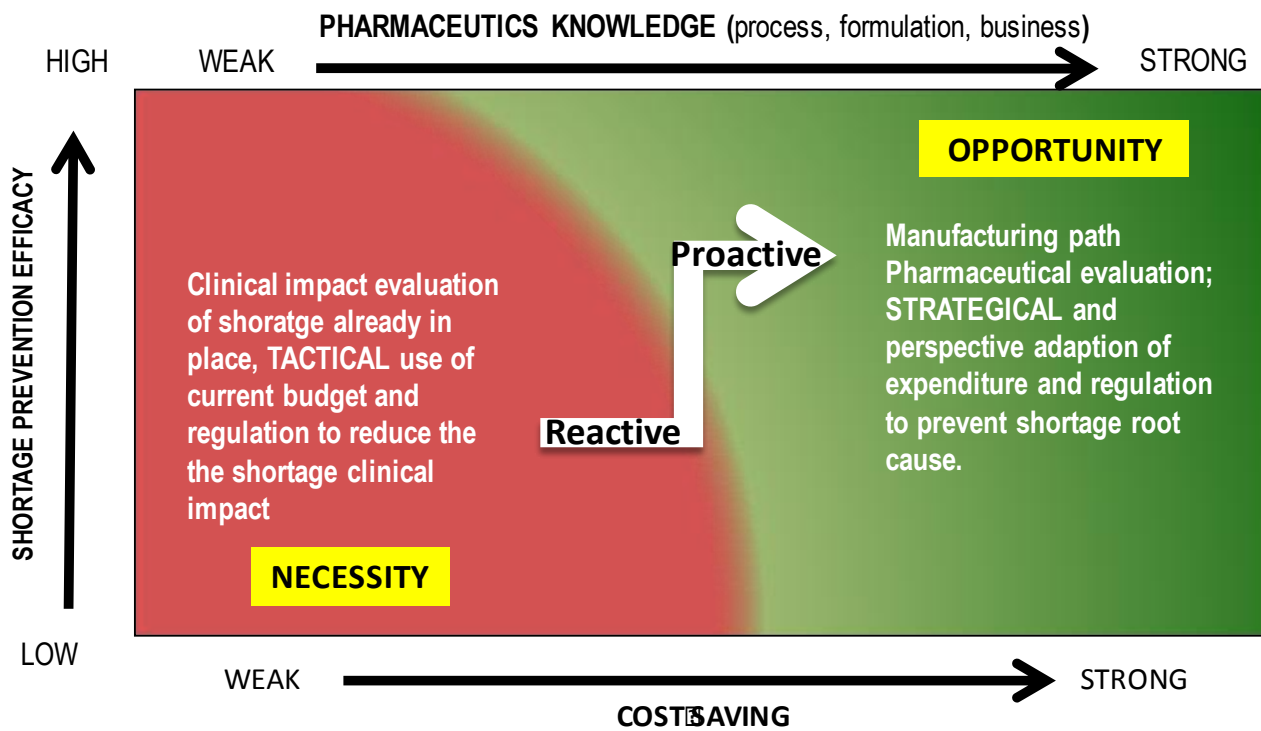


Figure 6: upgrading from a reactive to a proactive shortage management policy

Table 1: risk ranking and filtering for shortage purposes

AREA	Risk Factor	1	2	3	4	5	Correction factor	
CAPACITY	A	FP manufacturing site (other measures leading to a risk reduction should be accounted, for example <i>1 site without redundant capacity</i> may put in place measures reducing the overall risk to lower figures)	2 or more sites, each one with several production lines and redundant capacity	Only 1 site with several production lines and redundant capacity	Only 1 site with several production lines without redundant capacity	Only 1 site, only 1 production line with redundant capacity	Only 1 site, only 1 production line without redundant capacity	0.165
	B	FP manufacturing site location (ICH area)	≥ 3	N/A	2	N/A	1	0.165
	C	FP resupply time (expressed as FP shelf life %)	$10 <$	$> 10 - 20 \leq$	$> 20 - 30 \leq$	$> 30 - 40 \leq$	> 40	0.165
	D	API or other critical materials manufacturing site	2 or more sites, each one with several production lines and redundant capacity	Only 1 site with several production lines and redundant capacity	Only 1 site with several production lines without redundant capacity	Only 1 site, only 1 production line with redundant capacity	Only 1 site, only 1 production line without redundant capacity	0.165
	E	API or other critical materials manufacturing site location (ICH area)	3	N/A	2	N/A	1	0.165
	F	API or other critical materials stock pile (expressed as FP shelf life %)	> 120	$> 90 - 120 \leq$	$> 60 - 90 \leq$	$> 30 - 60 \leq$	$30 \leq$	0.165
SUSTAINABILITY	G	Selling price	Very high	High	medium	Low	Very low	0.5
	H	FP annual turnover (expressed as % of Company turnover)	$> 9 \%$	$> 6 - 9 \leq$	$> 3 - 6 \leq$	$> 0.5 - 3 \leq$	$0.5 \leq$	0.5
TECHNICAL	I	Formulation intrinsic complexity	Low	Medium – low	medium	Medium-high	High	0.5
	L	Manufacturing process complexity (including analytical)	Low (easily reproducible)	Low – medium	medium	Medium – high	High (not reproducible)	0.5

		tests)						
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