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

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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 highliting 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.

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

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.

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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, 2010a).

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, 2010b).

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 and 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, 2011).

This is confirmed in a recent paper by Hawley et al., analysing 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 et al., 2016).

A clear link between shortages and manufacturing quality and issues has been suggested by Wookcock and Wosinska, from the