International Journal of Pharmaceutics 509 (2016) 492–498

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Emerging technology: A key enabler for modernizing pharmaceutical manufacturing and advancing product quality

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ARTICLE INFO

Article history:
Received 4 April 2016
Received in revised form 26 May 2016
Accepted 27 May 2016
Available online 31 May 2016

Keywords:
Pharmaceutical manufacturing
Product quality
Emerging technologies
Innovation
Regulatory science

ABSTRACT

Issues in product quality have produced recalls and caused drug shortages in United States (U.S.) in the past few years. These quality issues were often due to outdated manufacturing technologies and equipment as well as lack of an effective quality management system. To ensure consistent supply of safe, effective and high-quality drug products available to the patients, the U.S. Food and Drug Administration (FDA) supports modernizing pharmaceutical manufacturing for improvements in product quality. Specifically, five new initiatives are proposed here to achieve this goal. They include: (i) advancing regulatory science for pharmaceutical manufacturing; (ii) establishing a public-private institute for pharmaceutical manufacturing innovation; (iii) creating incentives for investment in the technological upgrade of manufacturing processes and facilities; (iv) leveraging external expertise for regulatory quality assessment of emerging technologies; and (v) promoting the international harmonization of approaches for expediting the global adoption of emerging technologies.

Published by Elsevier B.V.

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1. Introduction

The U.S. Food and Drug Administration (FDA) Pharmaceutical Quality for the 21st Century Initiative aims to promote *a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight* (U.S. Food and Drug Administration, 2004a). Over the past decade, there has been substantial progress toward this vision; however, at the same time, the FDA mission has been confronted with new and increasingly complex challenges. Drug shortages and product recalls in the United States have occurred at unprecedented rates, limiting patient access to critical medicines and undermining health care. The FDA has determined that these problems most often reflect deficiencies in pharmaceutical quality and manufacturing, such as the utilization of outdated manufacturing technologies and equipment for drug production at their maximum capacity. The Agency believes that strategic efforts to encourage and sustain improvements in pharmaceutical quality and manufacturing are critical to the FDA mission of ensuring safe, effective and high-quality drug products are consistently available to the patients who need them.

Building upon the progress of the 21st Century Quality Initiative, new initiatives are outlined here for consideration by the broad community of stakeholders due to their potential to modernize the pharmaceutical development and manufacturing.

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http://dx.doi.org/10.1016/j.ijpharm.2016.05.058
0378-5173/Published by Elsevier B.V.

These initiatives aim to facilitate the adoption of emerging technologies through (i) advancing regulatory science for pharmaceutical manufacturing; (ii) establishing a public-private institute for pharmaceutical manufacturing innovation; (iii) creating incentives for investment in the technological upgrade of manufacturing processes and facilities; (iv) leveraging external expertise for regulatory quality assessment of emerging technologies; and (v) promoting the international harmonization of approaches for expediting the global adoption of emerging technologies.

2. Challenges for pharmaceutical manufacturing

Pharmaceutical manufacturing, in general, continue to confront a number of challenges, which result in unacceptably high occurrence of product recalls and drug shortages (U.S. Food Drug Administration, 2016; U.S. Food and Drug Administration, 2013) The number of product recalls has surged over the past couple of years including recalls classified as Class I, denoting a situation in which there is a reasonable probability that the use of, or exposure to, the violative product will cause serious adverse health consequences or death (see Fig. 1) (U.S. Food Drug Administration, 2016). In 2014, pharmaceutical recalls were mainly due to the presence of particulate matter in liquid dosage forms and the failure to meet the product quality specifications upon scale-up (Stericycle ExpertSolutions, 2015). Alarming shortages of critical drugs have occurred over the past few years. Many of these drug shortages were attributed to the use of outdated equipment, reliance on aging facilities operating at maximum production capacity, and lack of effective quality management systems. A 2012 FDA analysis of data collected from manufacturers indicates that 66% of production disruptions leading to shortages resulted from either efforts to address product-specific quality failures or general efforts to remediate a problematic manufacturing facility (U.S. Food and Drug Administration, 2013).

Due to economic factors, supply chains for many APIs and final drug products span several countries. Furthermore, under the current manufacturing infrastructure that relies heavily on batch processes, intermediates may not be immediately processed. Instead, they are stored in containers and shipped around the world to the next manufacturing facility. Therefore, the drug product manufacturing is potentially susceptible to multiple supply and facility vulnerabilities. The effect of globalization may be reflected in the product recall data. For instance, 26% of drug recalls reported to the FDA were international in nature, impacting more than one country in 2014 (Stericycle ExpertSolutions, 2015).

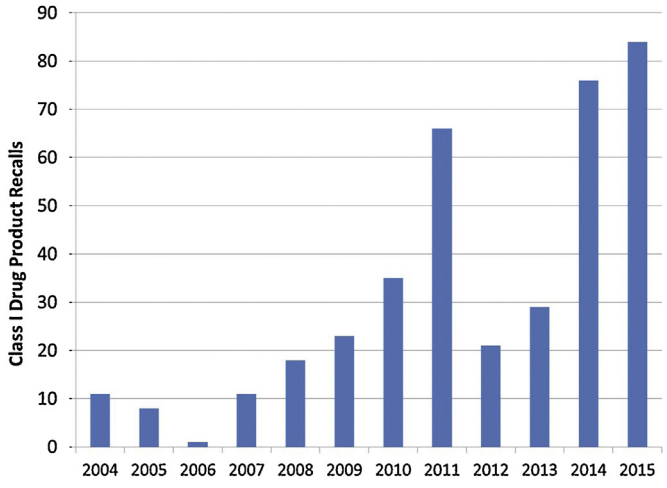

Fig. 1. Number of Class 1 Drug Product recalls per year (U.S. Food Drug Administration, 2016; Gaffney, 2016) . A Class I recall, denotes a situation in which there is a reasonable probability that the use of, or exposure to, the violative product will cause serious adverse health consequences or death. Recalls for misbranding (i.e. product marketed without an approved NDA/ANDA) were removed from the data set to focus on recalls initiated due to quality issues.

The current regulatory framework may be perceived as providing a barrier to the implementation of manufacturing advancements to help address underlying issues leading to drug product recalls and shortages. The current regulatory framework could cause manufacturers to submit supplements as they strive for continuous improvement, owing to the common practice of *locking in* an applicant's manufacturing process before it is fully optimized. This effect is evidenced by the increasing number of post-approval supplements received by the FDA for review over the past decade. The large number of post-approval supplements creates a drain on FDA resources that could otherwise be dedicated to other public health priorities. Furthermore, managing the continuous improvement and optimization of manufacturing processes is becoming more complex in the global marketplace.

Due to differences in the pharmaceutical regulatory environment in various regions, the timeline between filing the first regulatory submission and final global approval for the implementation of manufacturing improvements can be several years. Over the time period, the manufacturer needs to supply patients in the various regions utilizing different manufacturing processes. This creates logistical challenges and therefore slows the implementation of innovative technologies which can improve product quality and availability.

3. Potentials of emerging technologies for addressing pharmaceutical manufacturing challenges

Drug makers have used cutting-edge science to discover medicines, but they have generally manufactured these medicines using techniques that have not progressed much over the past two decades. Accelerating the development and adoption of pharmaceutical manufacturing innovations, the so-called "emerging technology," is needed to keep pace with advances and evolution in drug clinical research and development. It is also a key component of long-term strategies aimed at addressing the underlying causes of product recalls and shortages.

Emerging technologies can lead to more robust manufacturing processes with fewer interruptions, fewer product failures, and greater assurance that pharmaceutical products manufactured will consistently provide the expected clinical performance. By definition, emerging technologies have two key characteristics: novelty and impact. That is, the technology or the application of a technology needs to be substantially novel and unique in the pharmaceutical industry, and the implementation of such a technology has the potential to transform the capability of the manufacturing sector, thus improving product safety and quality. Emerging technologies could be an innovative or novel: (1) product manufacturing technology, such as the dosage form; (2) manufacturing process (e.g., design, scale-up, and/or commercial scale); and/or (3) testing technology. As an example, contemporary aseptic manufacturing facilities that are highly automated and use isolators and other modern separation technologies have the potential to increase the robustness of aseptic processes, decreasing the risk of contamination from the manufacturing line (U.S. Food and Drug Administration, 2004b).

The manufacturing technologies for pharmaceutical processes, which are largely batch in nature, are relatively inefficient and less understood compared with processes in other chemical industries. Utilization of such manufacturing technologies has limited the agility and flexibility of the pharmaceutical manufacturing sector