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Opportunities for Collaboration at the Interface of Pharmacovigilance and Manufacturing

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ABSTRACT

A case can be made that much common ground exists between pharmacovigilance and pharmaceutical manufacturing. Of the 8 major US statutes that shaped the pharmaceutical industry since early in the 20th Century, 7 followed fatally catastrophic events related to the use of a manufactured product, and 1 followed the discovery of a counterfeit product. To facilitate an understanding of the interplay between pharmacovigilance and manufacturing, it is convenient to divide manufacturing into 3 categories: (1) upstream sourcing of materials: pharmacovigilance plays an important role when adverse event clusters are seen during routine vigilance detection processes and the suspicion turns to possibly contaminated source material, (2) the manufacturing process itself: pharmacovigilance may be called on to conduct a health hazard evaluation if a manufacturing deviation is detected after product release (the assessment can inform the depth of a recall), and (3) downstream distribution and product use: there is only light regulation of the interval between product distribution after manufacturing release and just before administration to patients, a time during which product may be subject to an out-of-specification determination for environmental controls or subject to malfeasant activities, such as counterfeit substitution or product diversion. Recently introduced statutory remedies, including the *FDA Safety and Innovation Act* and the *Drug Supply Chain Security Act* in the United States and the *Falsified Medicines Directive* (directive 2011/62/EC) in the European Union, can provide capabilities to support pharmacovigilance signal management activities that have the potential to reduce the risk to patients of experiencing adverse events caused by counterfeit, diverted, or tampered product. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: behind-the-counter, counterfeit pharmaceuticals, pharmaceutical manufacturing, pharmacovigilance, product diversion.

INTRODUCTION

The association between pharmacovigilance and pharmaceutical manufacturing is, at first consideration, not obvious. However, a case can made that much common ground exists between these 2 pharmaceutical disciplines. This commentary provides a brief overview of the historical roots shared by these 2 disciplines, explains key areas of interplay today, and then discusses the critical topic of malfeasance, including counterfeit products and product diversion.

HISTORICAL ROOTS

Adverse events (AEs) can be organized and discussed in several ways. AEs can be typed according to cause: expected, based on pharmacologic action; unexpected and idiosyncratic; chronic effects after long-term use; and delayed effects.[1] AEs can be typed according to the characteristics of a range of classes of drugs (Council for International Organizations of Medical Sciences VIII, designated medical events) or primarily associated with specific drugs (Council for International Organizations of Medical Sciences VIII, targeted medical events).[2] AEs can be typed according to the specific drugs that resulted in the US Food and Drug Administration (FDA) black box warnings or market withdrawal.[3] Finally, AEs that led to statutory remedies can also be grouped together.

Of the 8 major US statutes that shaped the pharmaceutical industry since early in the 20th century, 7 followed fatally catastrophic events related to the use of a manufactured product, and 1 followed the discovery of a counterfeit product. These events are identified in Table I, which briefly describes each event and the associated statutory remedy. These events

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have led to permanent and deeply significant changes in much of pharmaceutical research and development.

MANUFACTURING

For the purpose of this discussion, activities related to manufacturing can be conveniently divided into 3 segments: (1) upstream: supply sourcing of raw materials up to the point of receipt by the manufacturing facility; (2) manufacturing process: the stepwise, batch production of intermediates that leads to active pharmaceutical ingredient (API) or drug substance, then to formulated product, and finally to release of the packaged product by the manufacturing facility; and (3) downstream: controlled flow of product through legally controlled distribution channels, including transportation, warehousing, and penultimate location in hospitals, pharmacies, or physician offices, up to the point of administration to the patient for prescribed use (Table II).

Upstream Sourcing

Overview

All sourced raw materials that go into preparing the API or drug substance are sourced from outside suppliers, with the common exception of water, which is usually prepared on site as water for injection. At intake, documentation checks and screening tests are performed. However, before the heparin tragedy in 2008, the suppliers of the suppliers had not routinely received the same degree of scrutiny, allowing financially motivated adulteration of source material to take place, resulting in >80 deaths on 2 continents. The Council and the European Parliament subsequently adopted the *Falsified Medicines Directive*[11] in 2011 and the US Congress passed the *FDA Safety and Innovation Act*[12] of 2012 and the *Drug Supply Chain Security Act*[13] of 2013.

The *FDA Safety and Innovation Act* requires, in part, (1) a risk-based approach for performing tolerability and regulatory activities, (2) tightened collaborations with regulatory agencies of other governments, and (3) establishment of a unique facility identifier system intended to enhance global supply chain management and security.

The centerpiece of this legislation is a requirement that manufacturers develop a product pedigree for each manufactured product. A pedigree is an electronic record that contains information about each transaction that results in change of ownership, from receipt of initial source or raw materials, through acquisition and sale by ≥ 1 wholesalers, manufacturers, or pharmacies, until final sale to a pharmacy or other entity that furnishes, dispenses, or administers the drug; all together, these lines of information constitute a complete track-and-trace process. A pedigree is designed to address threats to the supply of legitimate prescription drugs from entry into the supply chain of counterfeit, diverted, or tampered products.

Role of Pharmacovigilance

None of the activities in this upstream segment explicitly requires standard operating procedure–directed pharmacovigilance involvement in real time before product release because none of the upstream, source or raw, materials have yet to be manufactured into products that are permitted to be administered to patients; however, as the heparin adulteration case revealed, it is possible for malfeasant (adulterated) source material to be incorporated into finished product then to find its way through the entire manufacturing process and finally to be released into commercial channels without detection until it had been administered to patients who experienced fatal or otherwise serious AEs. Thus, suggestion of a cluster of AEs in patients should prompt at least consideration of the potential for malfeasant activities related to upstream materials.

Manufacturing Process

Overview

A high-level overview of manufacturing activities commonly includes the following major process steps: (1) batch production of the bulk API; (2) preparation of final formulation, including addition of excipients; (3) preparation of finished product, potentially involving sterile processing procedures for parenterally administered products, that includes container and closure systems; (4) completion of the testing protocol as part of release specifications, including stability; (5) packaging that includes primary packaging for end user and secondary packaging for shipping; and (6) postrelease stability testing that follows a protocol-driven procedure through the expiry date of lots in distribution.

During any aspect of the entire manufacturing process, deviations from specified processes of varying