Commentary

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;39:702–712)

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

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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 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;

Table I. Manufactured product events and statutory remedies.

Year	Event	Statutory Remedy	Reference(s)
1901	Thirteen children died who had been given diphtheria antitoxin horse-derived serum during an epidemic in St. Louis; the horse had been infected with *Clostridium tetani*. An investigation determined that the city had processed the antiserum and given it to the children, although it had been known that the horse had contracted tetanus and been destroyed. Also in that year, 9 children died in Camden, New Jersey, after being given smallpox vaccine that had been contaminated by tetanus. It had not been tested for tolerabillity.	Congress passed the *Biologics Control Act* of 1902. This act established the standards of tolerability, purity, and potency, and created the Establishment License Application process that remained in place until 1998, when it was replaced by the Biologics License Application.	4
1906	Investigative reporters of their day found rampant use of drugs, such as alcohol, morphine, and cocaine, and toxic chemicals and metals, such as strychnine, mercury, and lead, without identification on the label. Many infants died of respiratory depression.	The US Congress passed the *Pure Food and Drug Act* of 1906. This act created provisions for adulteration and misbranding and prohibited interstate commerce of such products.	4
1938	Massingill developed a liquid, sweet-tasting formulation of sulfanilamide for pediatric use that contained diethylene glycol, a chemical used in antifreeze, and that is toxic to kidney function. A total of 106 people died, mostly children. It had not been tested for tolerability.	The US Congress passed the *Food, Drug and Cosmetic Act* of 1938. This act created the Investigational New Drug (21 CFR §312) and New Drug Application (21 CFR §314) processes.	4
1955	Cutter Laboratories released incompletely inactivated Salk polio vaccine that led to 56 persons developing paralytic polio and 5 deaths at the time of the initial vaccination campaign, followed by a secondary wave of polio in the community, with 113 persons developing paralytic polio and 5 additional deaths. A pattern of civil suits, liability without negligence, was established. Use of whole cell pertussis during the ensuing 3 decades led to increasing numbers of claims; a gradual crisis of confidence in the use	The US Congress passed the *National Childhood Vaccine Injury Act* of 1986 30 years after the Cutter incident. This act resulted in reduced private tort litigation in state and federal court and provided a prompt, efficient, and fair system of compensation for those who experienced vaccine-related injuries.	5,6

(continued)

Table I. (continued).

Year	Event	Statutory Remedy	Reference(s)
	of vaccines led to the withdrawal of most vaccine manufacturers from the market.		
1962	Merrill sold thalidomide with market approval in Europe, but the FDA would not approve thalidomide because of emerging reports of tolerability-related issues, including phocomelia.	The US Congress passed the Kefauver-Harris Amendments to the *Food, Drug and Cosmetic Act* of 1962. This act required many provisions, including evidence of effectiveness and reporting adverse events to the FDA.	4
1982	Seven people in the Chicago area died after ingestion of acetaminophen* that had been deliberately adulterated with cyanide.	The US Congress passed the *Federal Anti-Tampering Act* of 1983. This act led to antitampering packaging practices.	7,8
1984	The FDA seized >330,000 counterfeit birth control pills (Ovulen-21) from 2 distributors on Long Island, product that had been imported from Panama.	The US Congress passed the *Prescription Drug Marketing Act* of 1987. This act increases safeguards against retail sale of substandard, ineffective, or counterfeit drugs.	9
2008	More than 80 patients died in the United States and Europe after infusion of Baxter's generic heparin that had been adulterated with hypersulfated chondroitin sulfate. The heparin had been sourced from China and was likely adulterated to meet increased market demand after a porcine virus decimated the national pig herd in the previous year.	The US Congress passed the *FDA Safety and Innovation Act* in 2012 and the *Drug Supply Chain Security Act* of 2013. These acts enhance tolerability and quality of drug supply by requiring supply chain pedigree upstream and track-and-trace downstream.	10–12

FDA = US Food and Drug Administration.
*Trademark: Tylenol® (McNeil Consumer Healthcare, Fort Washington, Pennsylvania).

Table II. Segments of manufacturing activities and associated PV-interfacing activities.

Manufacturing Activities	PV-Interfacing Activities
Upstream sourcing of raw materials	Domain of PV: investigation of clusters of adverse events or of product complaints
Manufacturing processes	
Detection of deviations during manufacturing process, for example, increased percentage of cracked vials	Domain of manufacturing: deviations are evaluated for SOP-driven assessment or potential work-around
Detection after release, for example, wrong capsule size in foil pack or wrong package insert included in package	Domain of PV: deviations may be classified as critical, major, or minor. Detection after release is assessed for potential effect on patients; results inform depth of recall, which can be class 1, 2, or 3.
Detection during scheduled stability testing after release of lots into market, for example, out of specification for release specification tests	Domain of PV: as above, deviations may be classified as critical, major, or minor. Detection after release is assessed for potential effect on patients; results inform depth of recall, usually class 3.
Downstream processes	Domain of PV: product complaints are assessed for potential effect on patients; results inform depth of recall and can be class 1, 2, or 3.

PV = pharmacovigilance; SOP = standard operating procedure.

(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 severity may arise, as in the following example descriptions of graduated severity.[14] Critical severity is a deficiency in material, product, system, or service that can affect the quality, tolerability, or efficacy of a product or can lead to life-threatening conditions for the patient or customer. Alternatively, a critical deviation can be any deficiency that can lead to a noncompliant product or to a situation that may be cited by regulatory authorities as critical. Major severity is a noncritical deviation that may affect the quality, tolerability, or efficacy of a product or the ability to meet good practice requirements. Minor severity is a deviation not classified as critical or major that potentially affects a good practice system, utility, equipment, material, component, environment, or documentation but does not affect product quality, tolerability, or efficacy. Deviations may be detected during the manufacturing process or after release of lots, including during stability testing.

Role of Pharmacovigilance

In the process of determining the root cause of the defect, manufacturing quality may request pharmacovigilance professionals to provide a health hazard evaluation (HHE) when the product has been released and is being used by patients because manufacturing defects may potentially be associated with medical risks. Thus, an HHE must include a determination of whether the manufacturing defect in lots that have been released is associated with AEs. Evaluation steps include queries of the company's safety database to include searches for reports with the affected lot numbers for possible effects on the safety profile of the product under assessment. Table III provides examples of the types of manufacturing issues that

Table III. Examples of possible manufacturing issues, potential adverse events, and MedDRA search strategies to be considered during health hazard evaluations.

Examples of Potential Manufacturing Issues*	Example of Potential Adverse Events	Search Strategy: LLT or SMQ[15]
Microbial contamination at any point in process	Infection or complications associated with infection	Infection: hepatic,† oropharyngeal†
Source materials out of specification	End-organ toxic effects and compromise of function	Renal impairment,‡ hepatic impairment‡
Release parameters: out of specification	Hypersensitivity reactions: local or systemic	Hypersensitivity†
Especially for biologics: out of specification for release parameters	Infusion-related events, eg, thrombo-embolic events of particulate matter	Infusion related: no terms identified
Particulates: out of specification	Lack of effect	Lack of efficacy or effect†
Postrelease: out of specification for stability parameters		

LLT = lower-level term; MedRA = *Medical Dictionary for Regulatory Activities*; SMQ = standard MedDRA query.
*May occur before or after release.
†SMQ.
‡LLT.

could occur and the associated, potential AEs and search strategies.

Signal detection principles that could be applied to basic lot review include the following: (1) selection of all AEs with lot numbers of interest, as provided by manufacturing quality; (2) adjustment of frequency of event of interest for exposure of patient population of interest; (3) choice of data cutoff and comparable control interval in recent past for comparison; (4) choice of appropriate descriptive, or summary, statistics for central tendency (usually median or mean) and spread (usually variance, SD, or interquartile range) in assessing before and after periods; (5) selection of parameters of interest for analysis (eg, total AEs per lot for all lot numbers); (6) correlation with manufacturing information (eg, complaints associated with lot numbers); (7) application of quality control charting (QCC) methods; and (8) following QCC parameters of interest during both intervals and making comparisons.

QCC, mentioned in numbers 7 and 8, refer to methods invented by Walter Shewhart in the 1920s and were among the standard quality control tools developed and organized by W. Edwards Deming for decades following World War II.[16,17] QCC is one of a family of statistical process controls for identifying outliers. In its simplest form, it tracks the number of items of interest, such as a particular AE, over time. Adjusting the rate of reporting for estimates of the amount of drug on the market in a given interval and determining descriptive statistics for each interval can be easily performed.[18] QCC is a standard tool in manufacturing quality control today.

Downstream Activities

Characterizing the Gap

Once the product is released from corporate control and prepared for delivery, it is transported by any of a combination of land transports, sea container ships, and air transports to distribution centers, where the product is maintained under controlled storage conditions until transport to final destinations: retail and hospital pharmacies, clinics, and physician offices. These postrelease activities include few of the types of rigorous regulatory controls notable for manufacturing before the time of release and for postadministration AEs experienced by patients. This gap is noteworthy for the potential issues presented in Table IV.

Role of Pharmacovigilance

The present opioid epidemic in the United States is reminiscent of the methamphetamine epidemic of the first decade of the 21st century in that unexpected

Table IV. Downstream activities in the gap.

Downstream Manufacturing-Related Activity	Examples of Manufacturing Issues With PV-Interfacing Activities
Transportation (land, sea, air): documentation of whether appropriate environmental conditions are met for product shipping, warehousing, and eventual distribution to pharmacy, clinic, or HCP office	Failure to maintain cold chain during transportation Damage to shipping package that compromises product and packaging integrity
Controls and documentation: variable; for example, SOPs; but it is uncommon to have adequate documentable adherence to specifications	Diverted (theft) product out of controlled channels that is subsequently maintained under undocumented storage conditions
End user (pharmacy, clinic, HCP office): whether proper conditions are met for product storage and eventual administration to the patient	Failure to maintain cold storage during loss of power
Controls and documentation: variable; eg, SOPs; but temperature excursions in physicians' offices is common, calling into question integrity of cold-chain products, including vaccines	Contamination of vials that are reintroduced into supply channels Diversion (theft) of abuse-potential drugs, such as opioids[19] Contamination after surreptitious use of diverted multiuse syringes with abuse-potential drugs[20]

HCP = health care professional; PV = pharmacovigilance; SOPs = standard operating procedures.

drugs are posing abuse-potential challenges.[21] Methamphetamine was being easily manufactured from inexpensive over-the-counter drug products, including pseudoephedrine, a drug commonly found in cold medications.[22] The US Congress legislated the 2005 *Combat Methamphetamine Epidemic Act* that required record keeping and limited daily distribution of pseudoephedrine.[23] Currently, loperamide and butylscopolamine pose newly identified, similar abuse-potential risks for opioid-addicted persons.[24,25] Pharmacovigilance departments of companies that manufacture these drugs could well receive reports of product abuse or misuse, implicating their products in illicit manufacture of methamphetamine. Furthermore, the companies' pharmacovigilance departments would also likely be involved in related activities: (1) confirmation of the role of their products in the illicit manufacture of methamphetamine, (2) assessment of the potential risk, (3) determination of whether additional labeling precaution is warranted, and (4) recommendation of whether or not behind-the-counter provisions of the *Combat Methamphetamine Epidemic Act* should apply to their products.

Clusters of AEs in the safety database may have multiple explanations: for example, coincidental concurrent exposures to other drugs or to environmental agents in the same geographic area, prompting from recent publications or local news sources, and simple coincidence. Manufacturing issues may also be suspected. Regardless of the actual association with manufacturing, because of the importance of maintaining a low threshold for following up, suspicions can be expected to prompt an investigation into whether the AEs can be traced to particular lots. Consequently, pharmacovigilance professionals would contact manufacturing quality to review the manufacturing record for the lot(s) in question.

Pharmacovigilance activities may include similar considerations as for basic lot review signal detection principles. Issue detection can occur at any point after completion of packaging: during release, after distribution, or during scheduled stability testing. Examples are provided on the European Medicines Agency website.[26]

No matter from which direction an investigation is initiated, that is, by either manufacturing quality seeking assistance from pharmacovigilance or pharmacovigilance seeking assistance from manufacturing

quality, one of the key impediments to a thorough investigation is the common underreporting of lot numbers in association with AEs. Except for AEs reported in association with vaccinations or treatment of patients with rare diseases,[27] the reporting of lot numbers in association with AEs for small molecules is commonly <10%.[28] Without lot numbers, it is exceedingly difficult to evaluate a signal for a possible quality issue, either geographically because of the inability to identify all patients who experienced AEs after administration of particular lots or temporally because of the variable lengths of time spent in different supply channels.

Biologicals

Up to this point, distinctions have not been made regarding the handling of small-molecule drugs and large-molecule biologicals. However, biologicals raise special issues for pharmacovigilance departments, as thoroughly discussed by the European Medicines Agency.[29] First, with the advent of biosimilar products and the potential for interchangeability, it is critical that proper identification be made of the specific product that is being reported in association with the patient's AE. Second, because of the greater inherent variability in product characteristics of biologicals, it is also important to include the batch number.

MALFEASANCE

Manufacturing malfeasance is a global issue that undermines public confidence in the integrity of pharmaceutical products.

Counterfeit Products

A recent World Health Organization Fact Sheet on this topic groups all these affected products under the rubric of substandard, spurious, falsely labeled, falsified, and counterfeit medical products.[30] In their survey of the issue, the World Health Organization identified 920 medical products, from all therapeutic categories, inclusive of innovator and generic medicines.

Pharmacovigilance departments must have a high index of suspicion of substandard, spurious, falsely labeled, falsified, and counterfeit products under 2 very different presenting circumstances: (1) when there are reports of drugs not working or having a lack of effect that would raise suspicions of inactive, or potentially counterfeit, ingredients; and (2) when there are unusual presenting circumstances that would raise suspicions of contaminated or otherwise adulterated products with potentially harmful chemicals. This was the case with heparin that had been adulterated with hypersulfated chondroitin sulfate as a falsified substitute for bona fide heparin. Examples of suspicious AEs include unusual or uncharacteristic events or a constellation of events for the drug under consideration, hypersensitivity reactions, and infusion-related events for parenterally administered products (Table III).

Diversion

The FDA has reported on the scope of product diversion, describing a large-scale criminal enterprise.[19] In addition, another important type of diversion threat has also been recognized, that of diverting opioid-filled syringes for personal use by hepatitis C virus (HCV) infected health care professionals who then restocked subsequently HCV contaminated syringes and needles in hospital pharmacies, exposing unsuspecting health care professionals and patients to HCV. Schaefer[20] reported that an estimated 30,000 patients were potentially exposed during 4 such outbreaks during an 8-year period, and a major research medical center announced a settlement after a federal investigation that uncovered lax control of opioid drug products.[31] Pharmacovigilance departments of companies that manufacture injectable opioids or other abuse-potential drugs in syringes could very well have received MedWatch forms identifying patients who were injected with their products and subsequently infected with HCV. In addition, if there were clusters of reports, as could have been the case, the pharmacovigilance and manufacturing quality departments would have been faced with critical management situations because, unless there were evidence or suspicion for counterfeit or diverted products, it would have been assumed that legitimate products were somehow becoming contaminated. One potential solution is the transition of abuse-potential injectable drugs to single-use syringes. This issue has been discussed elsewhere.[27]

As with counterfeit products, pharmacovigilance professionals must have a high index of suspicion of possibly diverted products when presented with increased rates of reporting of any of the following: expired products, product not working, product having a lack of effect, or constellations of AEs that are unusual, atypical, or inconsistent with the recognized profile of the drug, particularly unusual infections that might suggest

contamination. This latter example was the situation that occurred in 2002 and again in 2012 that led the US Congress to pass the *Compounding Quality Act* of 2013 after fungus contamination of injectable steroids prepared by compounding pharmacies that was responsible for the deaths of >60 patients.[32–34]

Regarding lack of effect, clinicians may submit such reports when there is no evidence of any pharmacologic activity, especially when the clinician has prior experience with a particular drug and does not see evidence of what is usually expected. Thus, it is important for the pharmacovigilance professional, on receiving such reports, to be aware of the background rates of the categories noted above. If there is a sudden, or even a gradual, increase in the reporting rate of such reports, an investigation may be warranted with a view to considering the possible causes.

Drug Supply Chain Security Act

The US Congress passed the *Drug Quality Security Act* in 2013[13] (Title I: *Compounding Quality Act* and Title II: *Drug Supply Chain Security Act*. The *Drug Supply Chain Security Act* provides a framework for building an electronic, interoperable system that will identify and trace legitimate product, down to the package level, and detect illegitimate product that enters the supply chain. These capabilities will provide significant support to pharmacovigilance activities by reducing the risk to patients of experiencing AEs caused by counterfeit, diverted, or tampered product.

DISCUSSION

The major catastrophic, drug product–related events that led to statutory remedies in the United States (Table I) have long been of historical interest. For the purpose of this discussion, increasing attention has recently been paid to ways of reducing risk and enhancing prevention as the discipline of pharmacovigilance has taken shape. Pharmacovigilance and manufacturing, in particular, manufacturing quality, have drawn closer together as each has needed the other to address maturing issues in their respective disciplines.

As an example of the interdependence, manufacturing quality has needed pharmacovigilance professionals to assess the effect of (1) manufacturing process deviations, usually out-of-specification results from ongoing post-release, protocol-specified testing; or (2) product complaints filed by customers, which can include any of a range of issues, including such things as damaged packaging or containers, incorrect labeling, product past expiry date, and discolored product. Pharmacovigilance departments have developed HHE processes to provide standardized approaches to assessing the given issues, the work product of which informs decision makers about the potential health risks to patients and about the depth of potential recalls of product. As an example from the other direction, pharmacovigilance has needed manufacturing quality professionals to provide information about manufactured lots when assessing clusters of reports. Additional areas of process and content interdependence can be expected as the *FDA Safety and Innovation Act*, *Drug Supply Chain Security Act*, and the *Falsified Medicines Directive* are rolled out.

SUMMARY

It is well recognized that the field of pharmacovigilance has evolved significantly during the past couple of decades, but its roots go back to the early 20th century when 13 children died after being given diphtheria antitoxin serum prepared from a horse that had been infected with *Clostridium tetani*. Since that event, there have been 8 major statutory remedies in response to 7 fatally catastrophic events related to use of manufactured product and 1 event related to the discovery of counterfeit manufactured product.

During the entire range of the manufacturing process from source material to packaged product, pharmacovigilance has opportunities to contribute to the maintenance of the integrity of the product, for example, through conducting HHEs when product complaints are filed, to inform decision makers about the risk to patients. Likewise, manufacturing quality supports pharmacovigilance in providing lot information when clusters are detected in the safety database.

Through collaboration between pharmacovigilance and manufacturing quality, the recent passage of the *FDA Safety and Innovation Act* and the *Drug Supply Chain Security Act* in the United States and the adoption of the *Falsified Medicines Directive* (directive 2011/62/EC) in the European Union have the potential to significantly reduce the risk to patients of experiencing AEs caused by counterfeit, diverted, or tampered product.

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CONFLICTS OF INTEREST

Versions of this content were presented: Marcus Evans, May 20, 2013, Philadelphia; CBI June 18, 2014, Philadelphia. These presentations were made while I was employed by Genzyme, a Sanofi company, which provided salary, bonus and stock options during my employment. I otherwise received no financial support from industry; the sponsoring companies (CBI, Marcus Evans) provided travel and hotel. No one else influenced my content during the preparation of this manuscript.

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