

Developing Systems to Support Pharmacovigilance of Biologic Products

November 15, 2013

Meeting Summary

Introduction

Biologic products like vaccines have dramatically altered medical practice and disease prevention for more than a hundred years. In the last several decades, major advances in genetic bioengineering technologies have revolutionized the biologics innovation space and yielded an impressive diversity of recombinant therapeutic proteins, antibodies, and DNA vaccines. Targeted molecular medicines, in particular, have greatly enhanced clinicians' abilities to treat cancers and other complex conditions. However, along with biologic product-driven advances in medicine have come several challenges related to supporting pharmacovigilance of these products.

Biologics tend to be much larger and more complex and sensitive molecules than small molecule drugs, and exhibit some natural structural variation. As a result, different manufacturers' versions of a biologic product – and even different batches or “lots” of the same biologic product – cannot be considered structurally identical. Instead, approved biologic products fall within a narrow range of structural and clinical similarity. Pharmacovigilance challenges are compounded by the fact that many biologic products are injectable and administered by a provider in an infusion center or physician's office, or by a caregiver in a patient's home. In many instances, the product's manufacturer or specific batch are not adequately captured in these settings.

Gaps in pharmacovigilance systems across different health care settings pose a risk for biologic products. For example, passive surveillance systems that rely on reporting by patients and providers often lack critical information, such as lot numbers, which are necessary for identifying safety concerns with a specific batch of a biologic product. Furthermore, active surveillance systems that leverage health insurance claims and other electronic data may be hindered by coding that makes it difficult to identify whether or not a particular product was administered to a patient that suffered an adverse event. In order to better protect public health, pharmacovigilance systems will need to evolve alongside new biologic products and accurately capture their use in both passive and active surveillance systems.

The Changing Regulatory Landscape and Considerations for Pharmacovigilance

Biologic products now hold prominent positions on the list of top-selling drugs,¹ and the top six biologics accounted for nearly 40 percent (over \$7 billion) of Medicare Part B drug spending in 2010.² The high cost of many biologic drugs has serious implications for access to these products, as spending on biologics is expected to continue increasing as a share of federal drug expenditures. With this in mind, Congress included the Biologics Price Competition and Innovation (BPCI) Act as part of the Patient Protection and Affordable Care Act in 2010. The BPCI Act establishes an abbreviated pathway for

¹ Lindsley, C. (2013). The Top Prescription Drugs of 2012 Globally: Biologics Dominate, But Small Molecule CNS Drugs Hold on to Top Spots. *ACS Chemical Neuroscience* 4:905-907. Retrieved December 17, 2013, from <http://pubs.acs.org/doi/pdf/10.1021/cn400107y>.

² Government Accountability Office (2013). Medicare: Information on Highest-Expenditure Part B Drugs. Retrieved August 14, 2014 from <http://www.gao.gov/assets/660/655608.pdf>.

licensure by the U.S. Food and Drug Administration (FDA) of biosimilar and interchangeable biologic products to reduce costs for developers, increase market competition, and pass savings on to payers and consumers.

While an abbreviated pathway for approving generic versions of chemically synthesized small molecule drugs has been in place for decades,³ no analogous pathway has been established in the U.S. to approve biologic products that are biosimilar to an approved reference product. FDA is currently finalizing guidances related to the evaluation and approval of biosimilar products. The draft guidances were released in February 2012.⁴

Diverse stakeholders are evaluating strategies to strengthen safety surveillance for all biologics, as well as the biosimilar products that will be introduced by this pathway. On November 15, 2013, under a cooperative agreement with FDA, the Engelberg Center for Health Care Reform at Brookings convened an expert workshop, “Developing Systems to Support Pharmacovigilance of Biologic Products.”⁵ Representatives from FDA, FDA’s pharmacovigilance data partners, academia, health care, and other stakeholder groups met to evaluate mechanisms that could improve data collection and quality for biologics adverse event reporting, taking into account the complementary systems used to identify and validate safety signals. Participants noted that pharmacovigilance systems should continue to be refined to integrate new data types and to address pharmacovigilance needs as they arise. Some participants felt that pharmacovigilance efforts could be served in the long-term by “track and trace” provisions in the recently passed Drug Quality and Security Act, which will require product identifiers on all drugs and biologics, although full-scale implementation of these measures is likely a number of years off.

Background on U.S. Pharmacovigilance Systems

FDA’s pharmacovigilance efforts rely on several systems that take complementary approaches to data collection and evaluation. Workshop participants discussed the primary surveillance tools used by FDA and outlined the potential strengths and limitations of the various approaches.

FDA’s passive surveillance system makes use of adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS). Manufacturers and distributors are mandated to pass on to FDA any adverse event reports received by the company,⁶ and reports may also be voluntarily submitted by health care providers, institutions, and patients or patient caregivers. Of the 1.2 million adverse event reports collected in FAERS, FDA representatives reported that around 20 percent of reports are for therapeutic biologics; adverse event reports related to the use of vaccines are collected in a similar database called the Vaccine Adverse Event Reporting System (VAERS), which receives between 30,000 and 40,000 reports annually.

³ “Drug Price Competition and Patent Term Restoration Act of 1984.” (PL 98-417, 24 September 1984). Retrieved December 17, 2013, from <http://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf>.

⁴ FDA. (2012). Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Retrieved February 24, 2014, from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.

⁵ This meeting summary, and other materials for this workshop, was prepared by the Engelberg Center for Health Care Reform at Brookings, and do not represent the views of FDA.

⁶ See “Postmarketing reporting of adverse experiences.” 21 C.F.R. 600.80. Retrieved February 25, 2014, from <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=600.80>.

There are limitations with the FAERS data. For example, FAERS data are correlative and in most cases it is not possible to determine if a medical product is the cause of a reported adverse event or if the event is unrelated to product exposure. While FAERS collects primary data on adverse events, which are useful for identifying safety signals, these data are submitted voluntarily by patients and providers and are often under-reported. In addition, data quality is variable and many reports are incomplete. Participants commented that inaccurate reports from consumers or health care providers can misattribute adverse events (e.g., innovator product name given in place of the generic or vice versa). Finally, because the system does not have an accurate way to measure overall utilization of these products, and adverse events are underreported, it is impossible to calculate the incidence of an adverse event from FAERS data. For these reasons, FAERS is primarily used for identifying safety signals, and in most cases cannot be used to determine if a drug caused the reported adverse event.

FDA also makes use of an active surveillance system. FDA's Sentinel Initiative pilot, Mini-Sentinel, is a collaboration of about 20 data partners that utilizes existing healthcare data to conduct safety surveillance on its regulated medical products. Over the past five years, they have built a national distributed data network of claims records, electronic health records (EHR), and clinical data for conducting active medical product surveillance. The Mini-Sentinel pilot has conducted safety surveillance for more than 345 million person-years of observation time since 2000. The system is also beginning to be used for routine prospective surveillance for newly approved products.

Under certain circumstances, FDA can require manufacturers to conduct clinical trials, observational studies, or create registries to evaluate a safety issue. Registries that collect data on patients with a specific condition or procedure may also be maintained by federal or state governments, universities, provider/hospital groups, specialty societies, non-profits, or private groups, and can be used for pharmacovigilance purposes.

Biologics Pharmacovigilance Challenges

Biologic products pose unique challenges for pharmacovigilance systems. Participants noted that adverse events associated with biologic products may not be as well defined as they are with small molecule drugs. The most serious adverse effects associated with the use of biologic products tend to be related to immune response. These effects, classified under the umbrella of immunogenicity, are often not easily measured or monitored. For example, some may occur long after the administration of a biologic product, making them difficult to detect. Furthermore, it may be difficult to distinguish adverse events from the normal progression of a complex, serious disease. Additional biologics pharmacovigilance challenges are discussed in the following sections.

Data Capture Challenges

The ability of pharmacovigilance investigators to retrospectively identify a biologic product depends in great part on the setting in which the product was dispensed and administered. Health care settings differ with regard to how details are captured in health care records and claims, leading to varying levels of granularity. In particular, products dispensed and administered in a provider setting may be difficult to identify and very few data are captured on products given in an in-home setting. Participants commented that many biologic products have complicated product lifecycles that make them difficult to follow through the chain of use to a patient's bedside.

Many biologic products used in inpatient settings will be prepared by an in-house pharmacy after being ordered by a provider. These products may need to be reconstituted, diluted, or otherwise prepared for use (e.g., drawn up into a syringe). During this process, the product's original packaging may be

discarded, making it difficult to incorporate product-level information (e.g., batch or lot numbers) into a patient's medical record. There are some products equipped with removable stickers or barcodes, as well as pre-packaged ready-to-use dosage forms, which facilitate recording in medical records. However, these types of products are not common.

Effectively capturing product-level information is an important aspect of pharmacovigilance because it helps prevent class-level regulatory actions that could reduce access to critical medications. For example, with better product-level information, pharmacovigilance investigators could determine that safety risks were only associated with a particular batch of a single manufacturer's product, as opposed to all batches of the manufacturer's product or products in the same class made by other manufacturers. This knowledge could be used to ensure access to safe and effective medications while supporting interventions directed towards the products with true safety risks.

In order to better capture product-level information, some large provider systems have developed back-end integration systems to follow products from the provider's order to the pharmacy to the patient. Another approach being implemented in some systems is to generate and apply unique barcodes in the pharmacy that can be scanned or recorded at bedside, connecting the administered product to the patient's medical record. While these types of mechanisms may become more prevalent as providers implement meaningful use of EHR, they can be burdensome, particularly for smaller institutions, and are far from being standard across providers.

Better data capture in all care settings could potentially be improved by addressing data quality and complexity issues and considering how data are collected at the point of care. Participants were particularly concerned, however, about creating additional burdens for providers, and highlighted the need to capitalize on existing infrastructure. Chart review and other verification approaches can be very expensive and time consuming and key information, such as stickers and barcodes, often are not integrated into EHR. Stakeholders commented that a broader approach could be taken to gathering information on adverse events, and that the best sources of information may be the patient or family members. Blended research strategies were also proposed, in which registries could be linked to a patient's EHR.

Coding

Mini-Sentinel repurposes data from health care claims, which are structured and collected by payers to provide reimbursement for products and services provided in diverse health care settings. One of the significant challenges facing the Mini-Sentinel system as a secondary data user is that data may not be optimized for pharmacovigilance research. The data needs of payers have shaped how data are captured at the point of care and stored, and these needs can diverge significantly from the needs of secondary users and researchers. Additionally, there is a great deal of variation between payers' systems and the extent of data capture.

Different reimbursement models for inpatient and outpatient health care claims have driven different demands for coding specificity in inpatient and outpatient settings. Use of medical products dispensed by pharmacies in the outpatient setting is typically reimbursed under a health plan's pharmacy benefit and will be reimbursed using National Drug Codes (NDCs), which are drug-, manufacturer-, and dosage-specific. Participants noted that stringent requirements for accurate product identification (and supporting data, like the number of days' supply) as well as electronic prescribing systems have driven high data quality on products dispensed by pharmacies in the outpatient setting.

However, because biologic products are often administered in an inpatient setting or by physicians who procure the products themselves, they are also more likely to be covered under an insurer's medical benefit plan, which uses different coding standards than the pharmacy benefit. Biologics covered under a plan's medical benefit are likely to be reimbursed using a Healthcare Common Procedure Coding System (HCPCS) code. HCPCS codes initially were implemented to simplify the extensive NDC system and make administration and claims processing more efficient. HCPCS codes for medical products are not specific to a manufacturer, and multiple products may share the same code. For instance, the 11 brands of intravenous immunoglobulin all share the same HCPCS code.⁷

The Centers for Medicare and Medicaid Services (CMS), which generates HCPCS codes, generally only assigns an original code for new products that have a distinct clinical application. Products that are therapeutically equivalent, such as generic versions of an innovator product, or similar in clinical efficacy and indication (e.g., intravenous immunoglobulins) are typically assigned the same HCPCS code.⁸ CMS has the authority to create unique HCPCS codes for specific products, but this process can take several years. Prior to assigning a unique HCPCS code, nonspecific temporary codes are used.

Stakeholders underscored the importance of ensuring that pharmacovigilance approaches that rely on claims data from an insurer's medical benefit are able to distinguish between reference products and biosimilars. Participants were sensitive to the need to balance stakeholder objectives when considering how claims are used for reimbursement and secondary purposes, such as comparative effectiveness research and pharmacovigilance. Stakeholders also commented that while nonspecific codes may be sufficient for reimbursement, particularly for products that are priced similarly, other mechanisms are likely needed to support accurate product identification in pharmacovigilance efforts that rely on health care claims data. A participant explained that in some cases, it may be possible to differentiate between products that share a HCPCS code using a combination of diagnosis codes, unit prices, total cost prices, infusion or injection codes, and dosing frequency, but this does not present an efficient solution for pharmacovigilance research.

Mini-Sentinel recently conducted a feasibility study on blood products that identified differences in data capture between inpatient and outpatient settings. The investigators reported that the majority of blood product exposures were captured in the outpatient setting, but capture was less complete for inpatient administrations.⁹ Participants cautioned that while there might be sufficient data volume to support pharmacovigilance, the inpatient data may not be representative. Variability in data capture was also observed between and within data partners, with large health care systems and academic medical centers capturing more inpatient data, as well as tracking product NDCs through integrated EHR

⁷ Baker, M. (2013). Developing Systems to Support Pharmacovigilance of Biologic Products: Blood Safety Continuous Active Surveillance. Retrieved February 24, 2014, from <http://www.brookings.edu/~media/events/2013/11/20%20system%20support%20biologics/biosimilar%20slide%20deck.pdf>.

⁸ Centers for Medicare and Medicaid Services (2012). Healthcare Common Procedure Coding System (HCPCS) Level II Coding Procedures. Retrieved June 19, 2014 from <http://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/Downloads/HCPCSLevelIICodingProcedures7-2011.pdf>.

⁹ Baker, M. (2013). Developing Systems to Support Pharmacovigilance of Biologic Products: Blood Safety Continuous Active Surveillance. Retrieved February 24, 2014, from <http://www.brookings.edu/~media/events/2013/11/20%20system%20support%20biologics/biosimilar%20slide%20deck.pdf>.

systems. A possible solution discussed in the workshop was to incorporate data streams from inpatient pharmacy and blood banks into EHR, and to work towards harmonization between health systems.

Participants proposed several solutions to support FDA's claims-driven pharmacovigilance efforts, particularly for products administered in the inpatient setting. One suggestion was to record NDCs, which are product-specific, along with the HCPCS code in claims forms. This is already required in Medicaid claims for calculating drug rebates, and existing Medicaid claims forms have a field to record this data. Participants noted that a Medicare requirement to record NDCs could drive the private sector to adopt the same standards. Stakeholders also suggested that product-specific HCPCS codes could be assigned earlier in a product's market lifecycle. While progress has been made to expedite the assignment of unique codes, participants also cautioned against creating thousands of unique HCPCS codes for biologic products, given the objectives of the coding system.

Product Naming

Both trade and nonproprietary product names are used extensively by health care providers, pharmacists, and patients in communication about medications, but product naming also has the potential to impact pharmacovigilance efforts, commercialization, reimbursement, and clinical perception and usage. Nonproprietary naming strategies have been a major point of contention in the discussions around the regulation of biosimilar products. The European Medicines Agency, which was the first regulatory agency to develop a biosimilars approval pathway, allows for the use of the same international nonproprietary name (INN) for both biosimilar and innovator products, while Japan and Australia require products to have distinguishable nonproprietary names.¹⁰

While some stakeholders felt that products being approved as biosimilar or interchangeable should share the same nonproprietary name to reflect their similarity, others felt that it could promote confusion about the therapeutic equivalence of these products since biosimilars cannot be considered identical. These issues may also have implications for the commercial success of both innovator and biosimilar biologic products, although stakeholders noted that experiences had been mixed. Participants reiterated that the entry of biosimilars onto the market is intended to increase access to high quality, safe, and affordable medicines, and pointed to some notable successes, particularly in the European market where biosimilars have increased utilization overall. On the other hand, in cases where a unique INN has been used in Europe, participants described how some products have failed to achieve the same market penetration in certain EU nations and have struggled to compete with other products when they don't share an INN (e.g., in tendering).

Some have expressed concerns that using the same nonproprietary name for biosimilar products has the potential to negatively impact pharmacovigilance efforts, particularly for adverse event reporting. Patients and providers often use nonproprietary names in adverse event reporting, but may not always report definitive identifying information such as a brand name, manufacturer, or NDC when voluntarily submitting adverse event reports to FAERS. This could pose major challenges for identifying the relevant medical product in pharmacovigilance investigations. Because FAERS data quality and completeness is highly variable, some have expressed concern that it may be difficult to distinguish biosimilar products from one another and the reference product in FAERS if they share the same nonproprietary name, and

¹⁰ Alexander, E.A. (2014). The biosimilar name debate: what's at stake for public health. *Generics and Biosimilars Initiative Journal* 3(1). Retrieved February 25, 2014, from <http://gabi-journal.net/the-biosimilar-name-debate-whats-at-stake-for-public-health.html>.

if the brand name, manufacturer, or NDC are not included in adverse event reports. Others also fear that if an interchangeable biologic product is substituted at the pharmacy and an adverse event occurs, the prescriber may incorrectly attribute the event to the reference product. Currently, a number of states have introduced legislation that would require pharmacies to notify physicians of any biologics substitutions in order to address this problem, but such measures have been controversial.

Participants noted that some similar biologic products, such as human growth hormone, epoetin, and others, have been widely used and studied for years without any major pharmacovigilance challenges, and some developers felt that their ability to monitor and track safety was not impeded by the use of the same INN. Some expressed concerns that imposing unique demands on biosimilar manufacturers that do not confer any safety benefits could put manufacturers at a commercial disadvantage and discourage development. Others felt that there are no serious downsides to giving biosimilars unique INNs and that distinguishable names will support accurate product identification in FAERS reports, even if the report is incomplete. In addition, some participants cited a need for redundancy, confidence in and accountability for the quality and safety of biosimilars, and a globally harmonized approach in support of distinguishable nonproprietary names.

As described above, divergent opinions on the importance of unique nonproprietary names to pharmacovigilance and other factors have already driven several naming strategies in the countries that have developed biosimilar regulations. Participants discussed the merits and shortcomings of using the same or distinguishable INNs as they relate to pharmacovigilance. Some felt that interchangeable products should share a nonproprietary name, with unique names reserved for products that have distinct clinical applications in order to prevent medication errors and confusion. Participants noted that NDCs and brand names were already useful in distinguishing different manufacturers' products, but acknowledged that incomplete FAERS reports did present a significant challenge that may need to be addressed through higher reporting standards or other measures.

Participants generally indicated that distinct but related nonproprietary names could address some of the challenges cited above. Distinct but related names, such as a common stem plus a qualifier, was a more intuitive approach than unrelated names and could help communicate to the health care community the therapeutic class to which a product belongs. This approach could also facilitate information collection for pharmacovigilance, prevent inadvertent substitutions and errors, and may be a viable solution over the long term as the biosimilars landscape evolves.

As previously mentioned, the use of FAERS to identify safety signals is limited by incomplete and inaccurate reports. However, some participants suggested that the utility of FAERS could be strengthened through the implementation of distinct but related names. For example, if a patient completed a FAERS report for a biosimilar with a distinct but related name that identified the manufacturer (e.g., with a suffix), pharmacovigilance investigators might feel more confident of the product's identity, even if the patient did not fill in the manufacturer and NDC fields in their report. Stakeholders stressed that whatever naming convention becomes standard, it needs to work internationally and across practice settings.

Lot-Level Variation and the Need to "Track and Trace"

One of the major challenges cited in discussions of pharmacovigilance for biologics has been the potential for lot-level differences in products, even from the same manufacturer. Workshop participants noted that while distinguishable names and codes could help identify the right product, the sensitivity of biologic products to environmental and manufacturing changes may require collecting more granular

information to conduct effective pharmacovigilance. Specialty pharmacies are equipped to track lot numbers, and as was noted by participants, dispense about half of all biologics by revenue. However, most existing systems outside of specialty pharmacy are not equipped to track lot-level differences or may not do it optimally and biologics may become more widely used in primary care or outpatient settings in the future. While the FAERS reporting form does include a field for the product lot, this information often does not reach the administering physician or patient, and this may be an important reason why most FAERS reports do not include lot numbers. That said, participants noted that reports for biologics include lot numbers at a much higher rate than reports for small-molecule drugs.

Mechanisms to support the traceability of certain prescription drugs as they are distributed within the United States are expected to be implemented over the next decade. In November 2013, Congress passed the Drug Quality and Security Act, which, under Title II, outlines the regulatory path to build an electronic tracking system and creates new requirements for supply chain members over the next decade.¹¹ In four years, manufacturers will be required to serialize packages and homogenous cases of prescription drugs with product identifiers composed of the NDC, unique serial number, lot number, and expiration date. In ten years, members of the supply chain—from the manufacturer down through the dispenser—will be required to exchange specified transaction documentation in an interoperable, electronic manner (with some exceptions) to prevent product diversion and counterfeiting and improve detection and removal of potentially dangerous drugs from the drug supply chain.

Participants noted that while track and trace initiatives are geared towards securing the medical product supply chain, they have the potential to support improved pharmacovigilance efforts over the long term once they are fully implemented. Several major challenges remain, however, including that track and trace information is not linked to patient dispensing or EHRs and will need to be made available to pharmacovigilance investigators. Additionally, participants noted that medical product tracking has not been standardized globally.

Conclusions

Several guiding principles emerged from the workshop discussion. First, participants stressed the need for redundant systems that can rapidly identify the relevant biologic product in pharmacovigilance applications and help reduce “class-level” regulatory action, particularly in the case of manufacturer-specific or lot-level safety issues. Recognizing that incomplete reporting is a reality, stakeholders commented that multiple identifiers could facilitate the identification of biologic products, and that related but distinguishable INNs could support accurate product tracking. Participants were also conscious of burdens being imposed on providers and the need to ensure that reporting and accurate product tracking are easily integrated into routine care and workflow. Workshop participants also felt that additional training, education, information sharing, and responsibility could support better data capture and reporting by providers, as could prescribing software, clinical decision-making support tools, and meaningful use efforts.

Finally, stakeholders reiterated the need to keep patients in mind when considering efforts to improve pharmacovigilance and data collection. Workshop participants indicated that they frequently observe switching between biologic products for a number of acute and chronic conditions, often due to side effects and other factors that are not always captured in the patient’s medical record. To address these

¹¹ “Drug Quality and Security Act.” (PL 113-54, 27 November 2013). Retrieved February 25, 2014, from <http://beta.congress.gov/113/plaws/publ54/PLAW-113publ54.pdf>.

issues, they highlighted the need to integrate patient-centered and patient-reported outcomes into pharmacovigilance systems and evaluations of comparative effectiveness. Workshop participants felt that there was an opportunity to provide patients and patient caregivers better information – including usable and accessible barcodes and serial numbers – that could help them report adverse events easily and accurately.