Arnold & Porter

Biologics: Post-Approval Pharmacovigilance

Abeba Habtemariam

March 16, 2022

Agenda

- Postmarket safety reporting
- Risk assessment and risk management
- Post-approval changes

Postmarket Safety Reporting

Postmarket Safety Reporting Requirements

- Postmarket safety reporting requirements for biologics licensed under BLAs are set forth in 21 C.F.R. § 600.80.
- The §600.80 requirements are largely the same as the postmarket safety reporting requirements for NDA drugs (21 C.F.R. § 314.80), but there are some differences, including as pertains to information to include in reports for vaccine biologics.
- BLA-licensed biologics that are vaccines are also subject to additional postmarket safety reporting requirements set forth in the Public Health Service Act ("PHSA") as amended by the National Childhood Vaccine Injury Act of 1986 ("NCVIA").

What Is an Adverse Experience?

- **Adverse Experience:** Defined in § 600.80 as any adverse event associated with the use of a biological product in humans, whether or not considered product related, including e.g.,:
  - An adverse event occurring in the course of the use of a biological product in professional practice;
  - an adverse event occurring from overdose of the product whether accidental or intentional;
  - an adverse event occurring from abuse of the product;
  - an adverse event occurring from withdrawal of the product;
  - and any failure of expected pharmacological action
- 2011 Draft FDA Guidance: "An adverse experience is any *undesirable event* that is associated with the use of a drug or biological product in humans whether or not considered product-related by the applicant." (emphasis added)

What Is a Serious Adverse Experience?

- **Serious Adverse Experience**:
  - Any adverse experience occurring at any dose that results in any of the following outcomes:
    - death,
    - a life-threatening adverse experience,
    - inpatient hospitalization or prolongation of existing hospitalization,
    - a persistent or significant disability/incapacity, or
    - a congenital anomaly/birth defect.
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when:
    - based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of a serious adverse experience.
      - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

What Is an Unexpected Adverse Experience?

- **Unexpected Adverse Experience:**
  - Any adverse experience that is not listed in the current labeling for the biological product.
  - This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity.
    - For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis.
    - Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.
  - "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

What Is an Individual Case Safety Report (ICSR)?

- **Individual case safety report (ICSR):**
  - A description of an adverse experience related to an individual patient or subject.

Postmarket Safety Reporting Requirements

- Procedures
  - BLA sponsors (and others subject to the § 600.80 reporting requirements) are required to:
    - Develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarking adverse experiences to FDA.
- Review
  - Required to promptly review adverse drug experience information pertaining to their product for reportability to FDA.
  - Applies to information obtained or otherwise received by the applicant from any source, foreign or domestic, including:
    - Information derived from clinical marketing experience
    - Postmarketing studies
    - Reports in scientific literature

15-Day Alert Reports

- Reporting Requirements – 15 Day Alert Reports
  - Postmarketing 15-day “Alert reports”
    - Applicants must report each adverse experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant.
  - Postmarketing 15-day “Alert reports” followup
    - Applicants must promptly investigate all adverse experiences reported in a 15-day Alert report and must submit followup reports within 15 calendar days of receipt of new information or as requested by FDA.
      - If not able to complete all applicable elements for an ICSR within 15 calendar days.

Minimal Data Elements for Reporting of an ICSR

- Before considering any clinical incident for submission to the FDA in an individual case safety report, applicants should, at a minimum, have knowledge of the following four data elements:
  1. An identifiable patient
  2. An identifiable reporter
  3. A suspect drug or biological product
  4. An adverse experience or fatal outcome suspected to be due to the suspect drug or biological product
- If any one of these basic elements remains unknown after being actively sought by the applicant, a report on the incident should not be submitted to the FDA.
  - Reports without such information make interpretation of their significance difficult or impossible.
  - The applicant should maintain records of efforts to obtain the basic elements for an ICSR.

15-Day Alert Reports

- Who Is Required to Submit 15-day Alert reports?
  - BLA sponsors *and* any person whose name appears on the label of a licensed biological product as a:
    - manufacturer,
    - packer,
    - distributor,
    - shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing
  - To avoid unnecessary duplication in submission of 15-day Alert reports to FDA, obligations of persons other than the applicant may be met by submission of all reports of serious adverse experiences to the BLA applicant.
    - If a person elects to submit adverse experience reports to the applicant rather than to FDA, the person must submit each report to the applicant within 5 calendar days of initial receipt of the information.
    - The applicant must then comply with the requirement to submit 15-Day reports to FDA.

Adverse Event Reporting: Periodic Reports

- Periodic Reports
  - Applicants must report each adverse experience not reported in a 15-day Alert report at quarterly intervals, for 3 years from the date of issuance of the BLA, and then annually.
    - (all serious, expected and nonserious adverse experiences)
  - Upon written notice, FDA may extend or reestablish the requirement for quarterly reports, or require submission of reports at different intervals.
  - Each periodic report is required to contain: (not exhaustive)
    - An analysis of the 15-Day alert reports submitted during the reporting interval
    - A history of actions taken since the last report because of adverse experiences
      - e.g., labeling changes, studies initiated
    - ICSRs for serious, expected, and nonserious adverse experiences
      - i.e., for those adverse drug experiences not reported in a 15-day Alert report

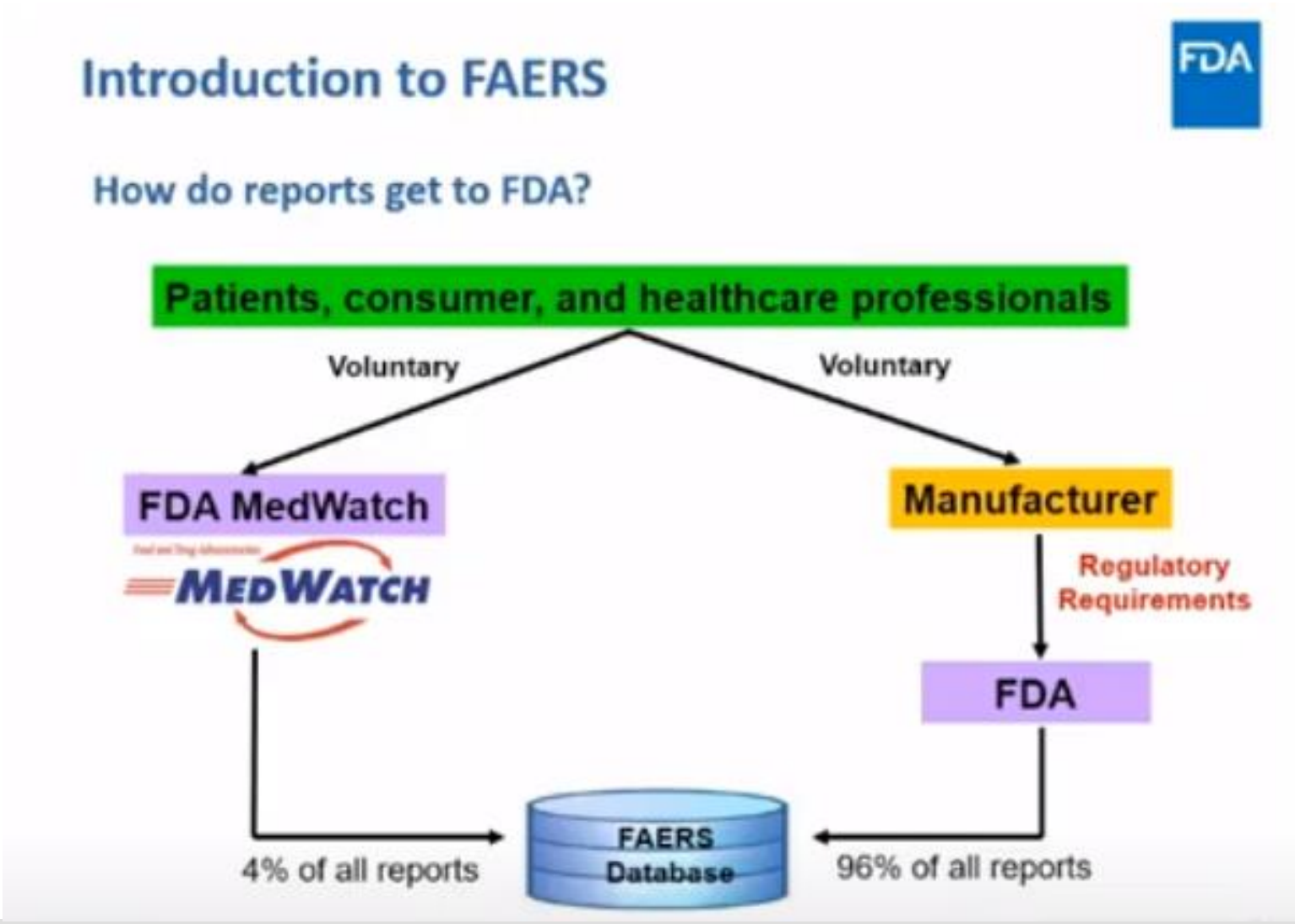
Individual Case Safety Reports

- An individual case safety report describes an adverse experience(s) for a patient or subject.
- Information to be reported in an ICSR is described in §600.80(f) (for non-vaccine biological products).
- Includes information relating to:
  - the patient
  - the adverse experience
  - the suspected medical product
  - initial reporter information
  - applicant information
- Information to be reported n an ICSR for a vaccine products is described in §600.80(g).

FDA Adverse Event Reporting System (FAERS)

- 21 C.F.R. § 600.80 requires that safety report submissions, including ICSRs, and the descriptive information in periodic reports, be in an electronic format that FDA can process, review, and archive.
- Two options for electronic submission:
  - (1) Direct submission through the Electronic Submission Gateway (ESG)
  - (2) Submission through the Safety Reporting Portal (PSP)
- Electronic submissions are processed into the FDA Adverse Event Reporting System (FAERS) database.
  - FAERS is FDA's postmarketing safety surveillance database for drugs and therapeutic biologic.
  - FAERs contains adverse event reports that were submitted to FDA.
    - Healthcare professionals, consumers, and manufacturers submit reports to FAERS.
- Link to FAERS public dashboard: https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis

FDA Adverse Event Reporting System (cont'd)



FDA Adverse Event Reporting System (cont'd)

- FDA uses the information in FAERS for activities such as:
  - looking for new safety concerns that might be related to a marketed product
  - evaluating a manufacturer's compliance to reporting regulations
  - responding to outside requests for information
- FDA staff (CDER and CBER) regularly examine the FAERS database as part of routine safety monitoring.
- The Food and Drug Administration Act of 2007 (FDAAA) requires FDA to conduct regular, bi-weekly screening of the FAERS database and post a quarterly report of any new safety information or potential signal of a serious risk identified.
  - Link to quarterly reports: https://bit.ly/3kUBv6w
- If new safety information or potential safety signal is identified, FDA evaluates the need for regulatory action.
  - E.g., label change, additional studies or analyses, revocation of product approval

Recordkeeping Requirements

- 21 C.F.R. § 600.80(k)
  - Applicants must maintain records of all adverse experiences known to the applicant for a period of 10 years.
    - including raw data and any correspondence relating to the adverse experiences

Postmarket Safety Reporting for Vaccines

- Vaccine products marketed pursuant to approved BLAs are subject to the general 21 C.F.R. § 600.80 adverse event reporting requirements for biological products.
- Vaccines are also subject to additional vaccine-specific adverse events reporting requirements set forth in the PHSA as amended by the NCVIA.
  - Some of those additional vaccine-specific adverse event reporting requirements turn on whether a vaccine is included in what is known as the Vaccine Injury Table.
- 21 C.F.R. § 600.80 reports and the additional NCVIA required reports are reported through the Vaccine Adverse Event Reporting System (VAERS).
  - VAERS is the national vaccine safety monitoring system.

Postmarket Safety Reporting for Vaccines (cont'd)

- The NCVIA (42 U.S.C. § 300aa-10 et seq.) established a Federal compensation program for persons thought to be injured by vaccines.
- NCVIA also established certain vaccine-related reporting requirements, including adverse event reporting requirements.
  - One of those vaccine adverse event reporting requirements turns on whether a vaccine is included in the Vaccine Injury Table.
    - Requires each healthcare provider and vaccine manufacturer to report the occurrence of any event set forth in the Vaccine Injury Table that occur within 7 days of administration of any vaccine set forth in the table or within a longer period specified in the table.
  - A second vaccine-specific adverse event reporting requirement does not turn on a vaccine's inclusion in the Vaccine Injury Table.
    - Requires each healthcare provider and vaccine manufacturer to report the occurrence of any contraindicating reaction to a vaccine which is specified in the manufacturer's package insert.

Noncompliance with Postmarket Reporting Requirements

- If an applicant fails to report adverse events, FDA can take advisory or enforcement actions such as issuance of a Warning Letter.
- If necessary, the agency also has authority to revoke an applicant's BLA
  - If an applicant fails to maintain records and make reports as required by §600.80, FDA may revoke the biologics license for subject to specified procedural requirements. (See 21 C.F.R. §601.5)

BLA Revocation

- BLA Revocation
  - FDA can also move to revoke a BLA for other reasons, including if FDA finds:
    - The manufacturer failed to report a change as required by §601.12.
    - The manufacturing establishment, or the product for which the license has been issued, fails to conform applicable requirements designed to ensure the continued safety, purity, and potency of the manufactured product,
    - The establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the requirements established in this chapter in order to protect the public health, or
    - The licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use.

Risk Assessment and Risk Management

Risk Evaluation and Mitigation Strategies

- FDA has the authority to require risk evaluation and mitigation strategies (REMS) for a drug when the agency determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.
  - (section 505-1 of the FDCA (21 U.S.C. 355-1) as added by FDAAA and later amended by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA))
- REMS can include one or more elements:
  - Medication guide
  - Patient package insert
  - Communication plan
  - Elements to assure safe use (ETASU)

Elements to Assure Safe Use

- ETASU may include one or any combination of the following requirements:
  - Healthcare providers who prescribe the drug have particular training or experience, or are specially certified
  - Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
  - The drug be dispensed to patients only in certain health care settings, such as hospitals
  - The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
  - Each patient using the drug be subject to monitoring
  - Each patient using the drug be enrolled in a registry

Postmarketing Studies and Trials

- FDA can require postmarketing studies or clinical trials upon approval or post-approval based on new safety information.
- 21 U.S.C. § 505(o)(3)
  - Postmarking studies and clinical trials may be required for any or all of the following three purposes:
    - To assess a known serious risk related to the use of the drug
    - To assess signals of serious risk related to the use of the drug
    - To identify an unexpected serious risk when available data indicate the potential for a serious risk
  - Clinical Trials vs Postmarketing Studies:
    - *Clinical Trial:* Any prospective investigations in which the applicant or investigator determines the method of assigning the drug(s) or other interventions to one or more human subjects.
    - *Postmarketing Studies:* All other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.
- Pediatric research required postmarketing studies
- Accelerated approval required postmarketing studies

Section 505(o)(4) Safety Labeling Changes

- FDA has authority to require safety labeling changes for prescription drug products and biological products based on new safety information that becomes available after approval of the product.
- New Safety Information
  - Information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), peer-reviewed biomedical literature, data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by FDA about:
    - "A serious risk or an unexpected serious risk associated with use of the drug that [FDA] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy (REMS) was required, or since the last assessment of the approved [REMS] for the drug," or
    - "The effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS]."

Post-Approval Changes

Overview of Reporting Categories

- Post-approval changes to a BLA-approved product are governed by 21 C.F.R. § 601.12.
- Applicants are required to notify FDA about each change in each condition established in an approved BLA beyond the variations provided for in the BLA.
- The type of FDA notification required depends on the reporting category in which a change falls.
- **Reporting Categories:**
  - Major Change
    - Requires a "Prior Approval Supplement" ("PAS").
  - Moderate Change
    - Requires either a:
      - Changes Being Effected ("CBE") Supplement, or
      - Changes Being Effected in 30-Days ("CBE-30") Supplement
  - Minor Change
    - Requires reporting in the next annual report for the BLA.
      - Does not require a PAS, CBE Supplement, or CBE-30 Supplement.

Overview of Reporting Categories (cont'd)

- **What is a Major Change?**
  - A change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.
  - A major change requires a PAS.
- **What is a Moderate Chang?**
  - A change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.
- **What is a Minor Change?**
  - A change that has minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of the product as these factors may relate to the safety or effectiveness of the drug product.