Pharmacovigilance and the Generic Industry

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Scope of Coverage

• What is Pharmacovigilance?
• Basic Overview of the Regulations
• Spectrum of Pharmacovigilance Practices in the Generic Pharmaceutical Industry
• Overview of Pharmacovigilance Inspections by FDA
• Triggers for Enforcement Action
• Literature Cases
• Future Evolvement of Pharmacovigilance within the Generic Pharmaceutical industry
What is Pharmacovigilance?

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

The aims of PV are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.

*World Health Organization definition*
accessed 10/30/15
What is Pharmacovigilance? (Cont’d)

- A large part of the generic industry has practiced Pharmacovigilance in a reactive manner, i.e., by collecting, documenting and submitting information on Adverse Events to FDA in order to meet the requirements of the applicable regulations.
- Proactive measures such as signal detection have not been widely practiced within the Generic industry because the labeling for generic products, including safety-related aspects, is dictated by innovator labeling.
- Furthermore, the innovator has access to the underlying safety database that formed the basis of approval and is better positioned to decide on safety-related labeling changes in the context of the extensive safety database.
Basic Overview of the Regulations

• 21 CFR 312.32 – IND Safety Reporting
• CFR 320.31 (d)(3) – BA/BE Study Safety Reporting
• 21 CFR 310.305 – Adverse Drug Experience Reporting for Marketed Prescription Drugs Not subject to an Approved Application
• 21 CFR 314.80 – Adverse Drug Experience Reporting for Drugs Covered by an NDA or ANDA
• 21 CFR 329.100- Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application
21 CFR 312.32 – IND Safety Reporting

• Applies to those generic drugs that require an IND as a prerequisite to the conduct of BA/BE studies.
• Requires reporting of serious and unexpected adverse events (AEs) within 15 calendar days.
• Requires reporting of unexpected fatal adverse events or life threatening suspected AEs within 7 calendar days.
• Causality assessment is factored into the decision as to whether to report, i.e., whether there is a reasonable possibility that the drug caused the AE.
• Sponsor must promptly investigate all AEs and submit relevant follow-up information as soon as it is available.
21 CFR 320.31 (d)(3) – Safety Reporting for BA/BE Studies Exempt from an IND

• Person conducting the study must notify FDA of any serious AE within 15 calendar days.
• Person conducting the study, must also notify FDA of any fatal or life-threatening AE within 7 calendar days.
• Unlike studies conducted under an IND, causality is not factored into the reporting decision.
• Relevant follow-up information must be submitted as soon as it is available or within 15 calendar days of a request by FDA.
• Submission of the above is made to the Office of Generic Drugs.
21 CFR 310.305 – Adverse Drug Experience (ADE) Reporting for Drug Products Not to an Approved Application

- Each person whose name appears on the label of a marketed unapproved drug as a packer, manufacturer, or distributor must report all serious and unexpected ADEs within 15 calendar days of initial receipt.
- Person must promptly investigate all such ADEs and submit follow-up reports within 15 calendar days of receipt of new information.
- If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information.
21 CFR 310.305 – Safety Reporting for Drug Products Not to an Approved Application

• To avoid duplication, a packer's or distributor's obligations may be met by submission of the above reports to the manufacturer of the drug product and document this submission as dictated in the regulation.

• The responsibilities of the various parties involved in the manufacturing, packaging, and distribution of a drug product, relative to ADE processing and reporting should be identified in a Quality or Safety Information Exchange Agreement and translated into SOPs to facilitate implementation of agreed on terms.
21 CFR 310.305 – Safety Reporting for Drug Products Not to an Approved Application

• 15-day Alert report Individual Case Study Reports (ICSRs) and any ICSR attachments must be submitted electronically as of September 8, 2015

• Records of adverse events, including raw data must be maintained for a period of 10 years.
21 CFR 314.80 – Postmarketing Reporting of ADEs

- Applies to all NDAs and ANDAs for both Prescription and OTC products.
- Applicant must have SOPs in place for surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.
- Written procedures must cover cases that are both foreign and domestic.
- Scope of surveillance includes commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.
15-Day Alert Reports

- Applicant must submit ADEs that are both serious and unexpected to FDA within 15 calendar days of initial receipt.
- Applicants must promptly investigate ADEs that are subject to 15-Day reporting and submit relevant follow-up information within 15 calendar days of receipt.
- If additional information is not obtainable, applicant must keep written records of unsuccessful steps to obtain additional information.
• 15-Day reporting requirements also apply to any person other than the applicant whose name appears on the label as a manufacturer, packer, or distributor of the drug product.

• To avoid duplication; obligations of a nonapplicant may be met by submission of all serious ADEs to the applicant, provided that records of the transition are maintained in accordance with 21 CFR 314.80(c)(iii) (A-D).

• The responsibilities of the various parties involved in the manufacturing, packaging, and distribution of a drug product, relative ADE processing and reporting should be identified in a Quality or Safety Information Exchange Agreement and translated into SOPs to facilitate implementation of agreed-on terms.
Periodic Adverse Drug Experience Reports (PADERs)

- Applicant must report each ADE not reported in a 15-Day Alert Report quarterly for 3 years from the date of approval; and annually, thereafter, in a PADER. PADERs must contain:
  1. A narrative summary and analysis of the information in the report;
  2. An analysis of the 15-Day Alert Reports submitted during the reporting period;
  3. A history of actions taken since the last report because of ADE’s;
  4. A line listing of the patient identification code, and ADE term(s) for all non 15-Day Alert cases (i.e., serious/expected and nonserious cases).

- ICSR’s pertaining to item 4 can be submitted individually or in one or more batches during the relevant reporting period.
21 CFR 314.80 – Postmarketing Reporting of ADEs (Cont’d)

• 15-day Alert report ICSRs and any ICSR attachments must be submitted electronically as of September 8, 2015
• PADERs including the ICSRs, any ICSR attachments, and the narrative descriptive information portion must be submitted electronically as of September 8, 2015
• Records of adverse events, including raw data must be maintained for a period of 10 years.
21 CFR 329.100- Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application

- Applies to those drug products that are marketed pursuant to OTC monographs under 21 CFR 330.
- No requirement to report ADEs for these products prior to the Dietary Supplement and Nonprescription Drug Consumer Protection Act signed into law on December 22, 2006.
- Regulation at 21 CFR 329.100 defines reporting requirements
- Final Guidance for Industry issued July 2009 provides further detail.
• Responsible person (defined as manufacturer, packer or distributor whose name appears on the label) must submit reports of **serious** ADEs to FDA within 15 **business** days of receipt, along with a copy of the label from the retail package.

• Responsible person should make and document reasonable follow up attempts to obtain complete information for case assessment.

• Responsible person must submit follow-up reports containing any new medical information within 15 **business** days of receipt.
• Reports under this section are referred to as Section 760 Reports
• 15-day ICSRs and any ICSR attachments for section 760 reports must be submitted electronically as of September 8, 2015
• Records of adverse events, including raw data must be maintained for a period of 6 years.
Basic Overview of Regulations

The preceding slides cover the basics. Firms should consult relevant guidance documents for more detail:

• March 2001 Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines.

• July 2009 Final Guidance for Industry: Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed without an Approved Application

• December 2012 Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies
Spectrum of Pharmacovigilance Practices in the Generic Pharmaceutical Industry

There is a very wide spectrum of Pharmacovigilance practices across the generic industry.

• Many firms have very sophisticated systems, procedures, and methods of processing/evaluating ADE case information similar to branded companies.

• Others have very basic systems and procedures that handle ADEs in the same manner as product quality complaints with little or no medical coding, medical review, etc.

• Some firms outsource their complete Pharmacovigilance Program.

• And…..there are some firms that mistakenly believe that generic products are exempted from ADE surveillance, receipt, evaluation and reporting requirements.
The practices within a given firm are often based on the following:

• Whether the firm markets products globally
• Whether the firm owns NDAs in addition to ANDAs
• The size of the firm in terms of the number of marketed products and revenues
• The outcome of previous, targeted Pharmacovigilance inspections by FDA
There are multiple ways to “skin the cat”. Here are some tips for success:

• Employees should be trained to recognize potential ADEs and promptly forward them to the appropriate functional area for processing.

• Systems, procedures and controls should be designed to promptly capture ADEs that may come into the company via various means (paper, electronic, phone live call, phone voicemail, etc.)

• Systems, procedures, and controls should be designed to comply fully with the applicable regulations.

• Written procedures should reflect the fine points that are captured in the applicable guidances.
• Firms should establish documented approaches for handling “gray areas” pertaining to case processing, classification and reporting, so that recurring examples are handled consistently.
• Pharmacovigilance and Quality Units should interact effectively to ensure that ADEs are evaluated for potential product quality issues and vice versa.
• Firms should maintain appropriate levels of oversight of Pharmacovigilance contractors, and establish SOPs, which link the functions of the company and contractor.
• Firms should establish and report key PV performance metrics to management on a regular basis
• Firms should perform periodic internal audits of its PV program
Overview of Pharmacovigilance

Inspections by FDA

• **Surveillance Inspection** – FDA reviews ADE reporting at a relatively high level. Focus is on appropriate classification of ADEs and timely reporting. This approach is often taken with manufacturers who are not the holders of approved applications and/or manufacturers who hold a modest number of approved applications.

• **Targeted PhV Inspection** - Entire focus of inspection is on ADE surveillance, receipt, evaluation and reporting. Involves a deeper dive into systems, procedures and controls, as well as a detailed review of selected case files.
Overview of Pharmacovigilance
Inspections by FDA (Cont’d)

• **For cause inspection** – May focus on a specific product and/or Pharmacovigilance systems. May be prompted by concerns identified by OSE during review of submitted cases; a potential emerging safety concern associated with a product and/or as a result of unsatisfactory findings from previous inspections that covered pharmacovigilance.
Triggers for Enforcement Action

A Review of Warning Letters issued to firms over the last 10 years, including Generics, revealed the following common themes:

• Failure to develop adequate written procedures for surveillance, receipt, evaluation, and reporting of postmarketing ADEs as required by 21 CFR 314.80(b).
• Failure to submit timely 15-Day Alert Reports for serious and unexpected ADEs.
• Failure to submit timely and/or complete PADERs.
Triggers for Enforcement Action
(Cont’d)

4/3/2015 Warning Letter to Galena BioPharma* - Inadequate SOPs for the detection, identification, assessment and reporting of ADEs.

- Procedures lack mechanisms for detecting/identifying potential ADEs embedded in product quality complaints
- Procedures not clear on responsibilities and links between call center and company in respect to handling of certain types of ADEs
- Procedures lack appropriate steps/detail for ADE follow-up
- Procedures lack detail regarding requirements for submission of PADERs
- PADERs not submitted in accordance with regulations - failure to submit quarterly reports for first three years of marketing

*http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm442577.htm accessed 10/30/15
Triggers for Enforcement Action

(Cont’d)

5/10/2012 Warning Letter to Acorda Therapeutics Inc.*

• Failure to submit serious and unexpected ADEs within 15 calendar days - repeated observation from previous inspections
• Corrective action involved change in contractor, but infractions continued after the change
• Failure to establish procedures and administer effective training to specialty pharmacies re: ADE reporting for Abstral® (Fentanyl Citrate Sublingual Tablet), which is covered by a REMS
• Failure to maintain source documentation related to individual ADE cases
• Failure to submit lack of effect complaints as ADEs

*http://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm303979.htm accessed 10/30/15
Recent Untitled Letters to Generic Companies have included the following types of citations:

- SOPs do not squarely address how ADEs received after normal business hours are handled
- SOPs do not squarely address how Day 0 is identified when ADEs are received outside of normal business hours
- SOPs do not specifically state that causality must not be a factor that impacts reporting decisions for literature cases
- Failure to submit literature cases that specifically identified another manufacturer’s product as the suspect drug
- SOPs do not address how notifications to management will address issues related to receipt, evaluation and reporting of ADEs
- Failure to submit PADERs on time
Triggers for Enforcement

- We have observed that FDA is checking ANDA Annual reports during Pharmacovigilance inspections and will cite firms on failure to submit these reports on time.
- Repeated instances of the above have, in some cases, led to further enforcement measures.
Global Companies:

• Must ensure that serious and unexpected cases from foreign sources be reported as 15-Day Alert Reports, even if formulation is different from U.S., marketed product. Expectedness must be assessed in accordance with U.S. labeling.

• EMA regulations and guidances are very comprehensive albeit more lenient than U.S. in specific areas. Exercise caution in evaluation of literature cases in particular!!
Pharmacovigilance Contractors

- Often represent a very reasonable solution for small firms that do not have sufficient internal capacity/capability to handle ADE related activities.

- However, firms must ensure that they exercise appropriate levels of oversight - at a minimum auditing as a CRO selection criterion and periodic auditing thereafter.
Pharmacovigilance Contractors

• Firms must develop contracts that specifically define the roles and responsibilities of the contractor and the firm.

• Written procedures must be developed to implement the provisions of the contract and to ensure appropriate linkage between functions to be performed by the firm and functions to be performed by the contractor.
Pharmacovigilance Contractors

• Firms should develop, monitor, and report to management, key metrics associated with the operation of the Pharmacovigilance function.
• This is especially important when contractors are used, but is highly recommended for internal Pharmacovigilance operations as well.
• Recommended metrics include on time reporting of 15-Day Alerts and follow-ups; on-time reporting of PADERs. CAPAs should be developed and corrective actions should be monitored for effectiveness when infractions occur.
Watch Outs (Cont’d)

Literature Cases:

- 21 CFR 314.80 (b) and (d) requires firms to report serious and unexpected ADEs from the literature as 15-Day Alert Reports.
- FDA does not require that firms perform structured literature searches. However, FDA expects that firms will have suitable written procedures and training to ensure conformance with the regulation, i.e., reporting of qualifying literature cases which any employees have knowledge of.
- Conduct of structured searches may be the “lesser of two evils”.
Watch Outs (Cont’d)

Literature Cases:

If structured searches are performed, firms must process the output in accordance with U.S. FDA expectations, recognizing that there are fine, but substantive differences between FDA and EMA requirements. For example:

• FDA expects submission of serious and unexpected literature cases irrespective of the author’s conclusion regarding causality.

• The above applies even when the ADE described in the article is from a clinical trial.

• FDA expects submission of serious and unexpected literature cases even when the article specifically identifies another manufacturer’s product as the suspect drug.
Two potential events could warrant a significant change in the way that generic firms practice Pharmacovigilance:

1. FDA’s 11/13/2013 Proposed Rule resulting from Mensing preemption, which would give ANDA applicants the authority to make safety-related changes to their labeling without FDA’s prior authorizations if progressed to a final rule.

   - Would mandate more proactive PV activities including, but not limited to structured literature searches, signal detection, etc. to identify ADE information that may quality for inclusion in labeling
   - Would also require the capability to distinguish between ADEs that warrant inclusion in labeling versus those that do not
Future Evolvement of Pharmacovigilance within the Generic Pharmaceutical Industry

- FDA’s 3/14/2003 Proposed Rule (“Safety Tome”)
  - Would introduce onerous ADE intake, evaluation, coding and medical review requirements and thus warrant a substantive upgrade of ADE handling infrastructure for many Generic firms.
Thank You

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