Post NDA/ANDA Approval Commitments

SNMMI Annual Meeting - June 9, 2014
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PETNET Solutions, Inc. (a Siemens Company)
Session Objectives

• Overview of Post NDA/ANDA Approval Commitments (§ 314.80 and § 314.81)
  – § 314.80 Adverse Event Reporting
  – § 314.81 Other post marketing reports
    • NDA Field Alert Report
    • Annual Report
    • Other (Advertising and Promotion - OPDP)

• Overview of FDA Requirements for Prescription Drug Promotion
314.80 Adverse Event Reporting

• PHARMACOVIGILANCE:

Pharmacovigilance (PV or PVG) is the science associated with detection, assessment, understanding and prevention of adverse effects of drugs. *(WHO)*
314.80 Adverse Event Reporting

• Postmarketing Reporting of Adverse Drug Experience

  – 314.80(a) Definitions
  Understanding the definitions is critical in making a correct determination of whether an ADE is required to be reported in 15-days VS reported in annual report
314.80 Adverse Event Reporting

(a) Definitions

- Adverse Drug Experience
  - Any adverse event associated with the use of a drug in humans, **whether or not considered drug related**
  - An ADE occurring in the course of the use of a drug product in professional practice
  - An adverse event occurring from drug overdose whether accidental or intentional (RAM reporting?)
  - [an adverse event occurring from drug abuse]
  - [an adverse event occurring from drug withdrawal]
  - any failure of expected pharmacological action (e.g., unusual or unexpected biodistribution)
314.80 Adverse Event Reporting

(a) Definitions

- **Disability**: A substantial disruption of a person's ability to conduct normal life functions.
- **Life-threatening ADE**: Any ADE that places the patient, in the view of the initial reporter, at *immediate* risk of death from the ADE as it occurred, *i.e.*, it does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
314.80 Adverse Event Reporting

(a) Definitions

• **Serious adverse drug experience** - Any adverse drug experience occurring at any dose that results in any of the following outcomes:
  
  – Death
  – a life-threatening adverse drug experience
  – inpatient hospitalization or prolongation of existing hospitalization
  – a persistent or significant disability/incapacity
  – a congenital anomaly/birth defect
314.80 Adverse Event Reporting

(a) Definitions

• **Unexpected ADE** - Any adverse drug experience that is not listed in the current labeling (PI) for the drug 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.
  
  - "Unexpected," as used in this definition, refers to an adverse drug 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.
314.80 Adverse Event Reporting

(b) Review of adverse drug experiences

• Any person subject to the reporting requirements under paragraph (c) of this section shall also develop **written procedures** for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.
314.80 Adverse Event Reporting
(c) Reporting Requirements
(MedWatch)

• The applicant shall report to FDA adverse drug experience information, as described in this section
  – The applicant shall submit two copies of each report to:
    FDA Central Document Room
    5901-B Ammendale Rd.
    Beltsville, MD 20705-1266.
314.80 Adverse Event Reporting
(c) Reporting Requirements (3500A)

• (1)(i) *Postmarketing 15-day "Alert reports".*
  – The applicant **shall report each ADE that is both serious and unexpected**, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

• (ii) *Postmarketing 15-day "Alert reports"—follow-up.*
  – The applicant shall promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and shall submit follow-up reports within 15 calendar days of receipt of new information or as requested by FDA.
• (iii) *Submission of reports*
  – The requirements concerning the submission of postmarketing 15-day Alert reports, shall also apply to any person other than the applicant (nonapplicant) whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor
  • If CMO, coordinate with application sponsor to avoid duplication
314.80 Adverse Event Reporting
(c) Reporting Requirements

• (2) *Periodic Adverse Drug Experience Reports (PADER)* (in EU PSUR = periodic safety update report)
  – (i) The applicant shall report each adverse drug experience not reported under paragraph (c)(1)(i) of this section (15-day Alert)
  – at quarterly intervals, for 3 years from the date of approval of the application,
  – and then at annual intervals.
  – The applicant shall submit each quarterly report *within 30 days of the close of the quarter* (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application.
314.80 Adverse Event Reporting
(c) Reporting Requirements

• (ii) Each periodic report is required to contain:

(a) a narrative summary and analysis of the information in the report and an analysis of the 15-day Alert reports submitted during the reporting interval;

(b) a FDA Form 3500A (Adverse Reaction Report) for each adverse drug experience not reported under paragraph (c)(1)(i) of this section; and

(c) a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).
314.80 Adverse Event Reporting
(f) Reporting Requirements (3500A)

(1) Except as provided in paragraph (f)(3) of this section, the applicant shall complete FDA Form 3500A for each report of an adverse drug experience.

(2) Each completed FDA Form 3500A should refer only to an individual patient or a single attached publication.

(3) Instead of using FDA Form 3500A, an applicant may use a computer-generated FDA Form 3500A or other alternative format.

(4) FDA Form 3500A and instructions for completing the form are available on the Internet at http://www.fda.gov/medwatch/index.html
314.80 Adverse Event Reporting (f) Reporting Requirements (3500A)

- 3500A used for both drugs and devices
  - Read instructions carefully for appropriate completion
  - Some sections apply to both drugs and devices
  - Some sections only to drugs and others only for devices
314.80 Adverse Event Reporting

(f) Reporting Requirements

Form 3500A
§ 314.81 Other postmarketing reports

(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) NDA/ANDA—Field alert report
(2) Annual report
(3) Other reporting requirements
§ 314.81 Other postmarketing reports

(1) **NDA—Field alert report:** The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written follow-up.* The report and its mailing cover should be plainly marked: “NDA—Field Alert Report.”

- (i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.
- (ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

*Form FDA 3331 has a sheet that contains contact information including email addresses specifically for rapid submission of reports to FDA.
## Field Alert Form FDA 3331

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**NDA-FIELD ALERT REPORT**

In accordance with Section 314 B1(b)(1)(i) and (ii) of the New Drug Application Regulations (21 CFR 314) promulgated under the Federal Food, Drug and Cosmetic Act, as amended, the following information is herewith submitted:

1. **NDAMDA:**  
   2. **NDC No.:**

3. **GENERIC NAME OF DRUG PRODUCT:** Fiducial glucose F-18 injection  
   4. **TRADE/BRAND NAME(S) OF DRUG PRODUCT:**

5. **FIRM NAME AND ADDRESS WHERE PROBLEM OCCURRED:**

6. **RECEIPT:**

7. **DOSEAGE FORM, STRENGTH AND PACKAGE SIZE(S):**

8. **LOT NUMBER(S):**

9. **EXPIRATION DATE(S) OF DRUG PRODUCTS:**

10. **DATE WHEN NOTIFIED OF PROBLEM(S) OR WHEN PROBLEM(S) FIRST BECAME KNOWN TO APPLICATION HOLDER:**

11. **HOW WAS PROBLEM DISCOVERED:**

12. **STATE PROBLEM(S):**

13. **ROOT CAUSE(S) OF PROBLEM(S):**

14. **CORRECTIVE ACTION(S) TAKEN (IF ANY) TO PREVENT RECURRENT OF PROBLEM(S):**

15. **REMARKS:**

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**NOTE: SEPARATE NARRATIVE REPORTS MAY BE ATTACHED IF DESIRED:**

**REPORTING ESTABLISHMENT**

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**Coalition for PET Drug Approval**
§ 314.81 Other postmarketing reports

Annual Report

• ADVICE
  – Develop systems and processes to mine data for annual report.
Annual Report

(2) Annual report: The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application.

Each annual report is required to be accompanied by a completed transmittal Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date.
§ 314.81 Other postmarketing reports

Annual Report

The report is required to contain in the order listed:

(i) **Summary.**

A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study.
§ 314.81 Other postmarketing reports

Annual Report

(ii) (a) Distribution data.

Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors.

(ii) (b) Authorized generic drugs.  (NOT APPLICABLE TO PET)

If applicable, the date each authorized generic drug (as defined in §314.3) entered the market, the date each authorized generic drug ceased being distributed, and the corresponding trade or brand name.
§ 314.81 Other postmarketing reports

Annual Report

(iii) Labeling.

(a) Currently used professional labeling, patient brochures or package inserts (if any), and a representative sample of the package labels.

(b) The content of labeling required under §201.100(d)(3) of this chapter (i.e., the package insert or professional labeling), including all text, tables, and figures, must be submitted in electronic format.

(c) A summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.
§ 314.81 Other postmarketing reports

(iv) Chemistry, Manufacturing, and Controls changes.

(a) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.

(b) A full description of the manufacturing and controls changes not requiring a supplemental application under §314.70 (b) and (c), listed by date in the order in which they were implemented.
§ 314.81 Other postmarketing reports

Annual Report

(v) Nonclinical laboratory studies.
Copies of unpublished reports and summaries of published reports of new tox findings in animal and in vitro studies conducted by or obtained by the applicant.

(vi) Clinical data.
Published clinical trials of the drug conducted by or obtained by the applicant.

(viii) **Status of other postmarketing studies.**
Status report of each study required by FDA or committed to by the applicant

(ix) **Log of outstanding regulatory business.**
List of any open regulatory business with FDA concerning drug product
(3) **Advertisements and promotional labeling.**

The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product.

Each submission is required to be accompanied by a completed transmittal Form FDA–2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA–2253 is available on the Internet at [http://www.fda.gov/opacom/morechoices/fdaforms/cder.html](http://www.fda.gov/opacom/morechoices/fdaforms/cder.html).
§ 314.81 Other postmarketing reports

- Other Reporting: Form FDA 2253
Overview of FDA Requirements for Prescription Drug Promotion
Office of Prescription Drug Promotion (OPDP)

- Formerly the Division of Drug Marketing, Advertising and Communications (DDMAC)
- Reviews prescription drug advertising and promotional materials to ensure not false or misleading
- Provides written advisory comments to pharmaceutical sponsors on proposed promotional materials
- Initiates enforcement actions on promotional materials that are false or misleading
OPDP Continued...

- Far greater resources than CDRH dedicates to advertising/promotion
- Formerly divided into 2 divisions: Consumer Drug Promotion and Professional Drug Promotion
- March 2013, OPDP announced reorganization into Division of Advertising and Promotion Review I & II by therapeutic areas:
  - Division I: Neurology/Psychiatry; Hematology/Oncology (blood cancer); Oncology (solid tumors); and Analgesics, Anesthetics, Antivirals
  - Division II: Osteoporosis, Reproductive, Urology; Dental, Dermatology, Metabolic & Endocrine; Allergy, Gastroenterology, Pulmonary, Rheumatology; and Anti-Infective, Cardiovascular, Medical Imaging, Ophthalmology, Renal, Transplant
OPDP Interactions

- Can utilize assigned reviewer to request “advisory comments” on new promotional campaigns
- Be prepared to implement recommendations

- Submit all advertising and labeling to OPDP via a Form 2253 on initial publication or dissemination (only needed for first use of advertisement)
Misbranding

Drug is deemed misbranded under the Federal Food, Drug, and Cosmetic Act if:

- labeling false or misleading;
- label fails to include required information;
- required information not prominently displayed;
- generic or established name not displayed at required size; or
- adequate directions for use not included.

~Sec. 502 FDCA (21 USC 352)
Labels vs. Labeling

Labels

Display of written, printed or graphic matter upon the immediate container of any article.

~21 U.S.C. 321(k)

Labeling

All labels and any written, printed or graphic matter upon an article . . . or “accompanying such article.”

~21 U.S.C. 321(m)
Advertising vs. Labeling

Labeling includes:

- Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published for use by medical practitioners containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor

- Can include oral statements made in presentation of the above

~(21 C.F.R. § 202.1(l)(2))
Advertising includes:

- Advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communications systems
- Includes Internet (advertising/labeling line is blurred with Internet)
- Can also include testimonials by spokespeople, endorsers

~(21 C.F.R. § 202.1(l)(1))
Select Legal Authorities


- § 331(a) and (d): Prohibits introduction of misbranded or unapproved drug into interstate commerce
- § 321(n): Drug misbranded if labeling or advertising includes misleading representations or fails to reveal material facts
- § 352(f): Drug or device misbranded unless labeling bears adequate directions for use and adequate warnings
- § 352(n): Drug or device misbranded unless advertisement or other printed matter includes true statement of name and formula and brief summary of side effects, contraindications, and effectiveness

FDA regulations

- 21 C.F.R. § 201.100 (c)(1) and (d)(1): implements 21 U.S.C. § 352(f)
- 21 C.F.R. § 314.81(b)(3): Requires submission of advertisements and promotional labeling to FDA on Form 2253 at time of initial publication or dissemination
- 21 C.F.R. § 312.7: Prohibits pre-approval promotion or commercialization of investigational drugs but permits full exchange of scientific information concerning drugs, including dissemination of scientific findings in scientific or lay media
- 21 C.F.R. § 201.6: Says false or misleading representation of one drug versus another drug or device can misbrand drug
Guiding Principles

- Claims must be supported by substantial evidence: adequate and well-controlled clinical trials
  
  Except for “health care economic information” presented to formulary committees: lower FTC standard of “competent and reliable scientific evidence” (21 U.S.C. § 352(a))

- Claims must not be false or misleading (directly or indirectly)

- Advertising and labeling must maintain fair balance

- Advertising must contain brief summary of approved prescribing information (unless reminder ad)

- No pre-approval promotion
Guiding Principles (cont.)

- Claims must be **consistent with FDA-approved labeling**

  Off-label information may be provided only in response to unsolicited requests for information/data; in objective reporting of study results in company press releases or securities filings (no conclusions); in “scientific exchange” at scientific meetings/seminars; under FDA’s “Good Reprint Practices” guidance; or if “substantial evidence”

- **Certain exceptions:**
  - Disease awareness communications
  - Reminder advertising and labeling (but not if combined with help-seeking ad)
  - “Coming soon”/institutional promotion
Key FDA Guidance Documents

- Presenting Risk Information in Prescription Drug and Medical Device Promotion (DRAFT – May 2009)
- “Help-Seeking” and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms (DRAFT – Jan. 2004)
- Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (DRAFT – Dec. 2011)
- Consumer-Directed Broadcast Advertisements (FINAL – Aug. 1999)
- Office of Prescription Drug Promotion (OPDP) Frequently Asked Questions (Updated regularly on FDA Website)
PhRMA Industry Guidelines

- PhRMA Revised Code on Interactions with HCPs
  - Much overlap with AdvaMed Code
- PhRMA Direct-to-Consumer (DTC) Advertising Guidelines
Buzzwords

- **New, now approved, introducing** (use of these terms beyond the first 6 months following approval, clearance or introduction not appropriate)

- **Gold standard, standard of care, next-generation** (unless substantiated, terms can misleadingly imply superior efficacy in product class)

- **Novel, breakthrough, only, unique, different** (terms can imply product superiority or greater efficacy than demonstrated to FDA; be careful of claims that use these terms to inappropriately link the mechanism of action (MOA) to clinical significance)

- **Rapid** (term can misleadingly represent that product works faster than it is approved or cleared to work)

- **Potent** (can misleadingly represent greater product efficacy than demonstrated to FDA or superiority in product class)
Buzzwords (cont.)

- **Preferred** (product preference claims can be implied superiority claims; FDA has said that patient preference claims require support from well-designed and controlled head-to-head studies using well-developed instruments)

- **Convenient, easy, simple** (terms can minimize product directions and recommendations for use and administration, as well as minimize risks associated with product use)

- **Well-tolerated** (term should not be used for boxed warning product or in combination with adverse event spread; according to FDA, doing so would be misleading)

- **Quality of Life** (can broaden approved use; measurement instrument should be disclosed and validated)
OPDP Surveillance

- Review of 2253 submissions
- Conference attendance
- Bad Ad Program (deputizing HCPs)
  - When HCPs recognize misleading drug promotion, they can help put a stop to it by reporting it to FDA:
    - Call 855-RX-BadAd
    - E-mail BadAd@fda.gov
- Competitor complaints
Enforcement Activities

- Untitled & Warning Letters (decreasing)
  - 52 (2010): 39 untitled, 13 warning
  - 31 (2011): 26 untitled, 5 warning
  - 28 (2012): 25 untitled, 3 warning

- Injunction (consent decree), seizure, civil monetary penalties (for false and misleading DTC ads), criminal prosecution

- Federal and state prosecutions (criminal and civil)
  - Federal Anti-kickback Statute
  - False Claims Act (off-label promotion)
OPDP: Most Common Violations

- Omission/lack of prominence of risk information
- Misleading efficacy claims
- Misleading superiority claims
- Unsubstantiated Claims
- Promotion of unapproved uses (broadening of indication)
- Failure to submit Form 2253
OPDP Future Plans

- Revising current draft guidance
  - Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements
  - Presenting Risk Information in Prescription Drug and Medical Device Promotion

- Exploring and discussing other areas of interest
  - Health care economic information/formularies
  - Medical practice guidelines
  - Comparative claims
  - Scientific exchange (FR Notice seeking comments)

- Working on Internet/social media promotion
Thank You