Introduction to Drug Law and Regulation

Post-Approval Issues

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Topics

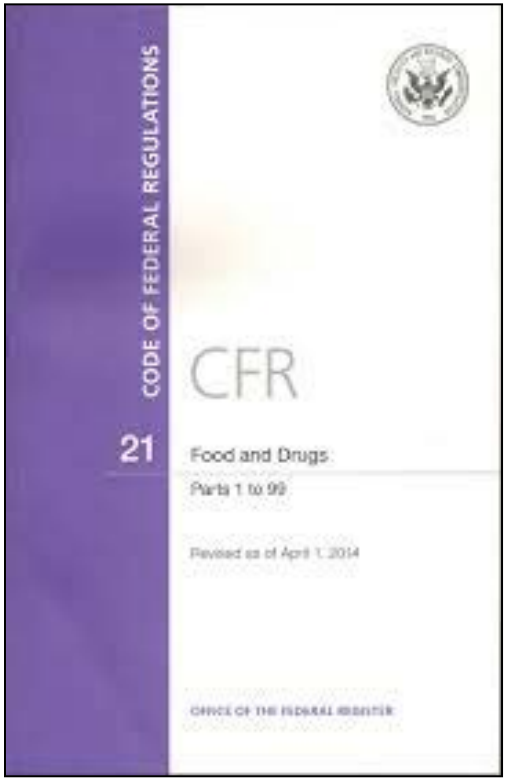
- Adverse Drug Experience (ADE) Reports
- Annual and Other Reports
- Post-Approval Changes and Supplements
- FDA Drug Safety Activities
- Postmarketing Requirements and Commitments
- Grounds for Withdrawal of Approval

Who's Who in the Audience?

- Attorneys?
- Regulatory professionals?
- Industry/trade professionals?
- Manufacturers?
- Government employees?
- The Press?

ADE Reporting - Basic Overview of the Regulations

- 21 CFR 312.32 – IND Safety Reporting
- 21 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 600.80 Biological Products: Postmarketing Reporting of Adverse Experiences



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 and reporting must cover both foreign and domestic cases.
- Scope of surveillance includes commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.

21 CFR 314.80 – Postmarketing Reporting of ADEs (Cont'd)

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.

21 CFR 314.80 – Postmarketing Reporting of ADEs (Cont'd)

- 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 a 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.*

21 CFR 314.80 – Postmarketing Reporting of ADEs (Cont'd)

Periodic Adverse Drug Experience Reports (PADERs)

- Applicant must report each ADE not reported in a 15-Day Alert Report quarterly for three (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 ADEs;

  (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).

- Individual Case Safety Reports (ICSRs) 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)

ICSRs

- 15-day Alert report ICSRs and any ICSR attachments must be submitted electronically.
- PADERs including the ICSRs, any ICSR attachments, and the narrative descriptive information portion must be submitted electronically.
- Records of adverse events, including raw data must be maintained for a period of 10 years.

FDA Guidance for Industry

- Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines; Draft Guidance March 2001

ADE Reporting Question

True or False?

Only ADEs reported from the United States must be reported to FDA.

NDA & ANDA Annual Reports

Regulations

- 21 CFR 314.70(d) [CMC changes]
- 21 CFR 314.81(b)(2)
- 21 CFR 314.98

- FDA Form 2252 (Transmittal of Periodic Reports for Drugs for Human Use) outlines the components required in the submission of annual reports.

NDA & ANDA Annual Reports (Cont'd)

Submit annually, within 60 days of the anniversary of the application approval.

- Summary of significant new information and actions taken
- Distribution data
- Authorized generic drugs
- Labeling
- CMC changes
- Nonclinical laboratory studies (toxicology studies)
- Clinical data
- Status reports of any postmarketing clinical study commitments
- Status reports of any postmarketing CMC study commitments
- Log of outstanding regulatory business (optional)

NDA – Field Alert Reports

Applies to drugs in distribution.

- Report to FDA Field Office within three (3) working days any information concerning:
  - An incident that causes the drug product or its labeling to be mistaken for another article.
  - Any bacteriological contamination.
  - Any significant chemical, physical, or other change.
  - Any failure of a batch of drug product to meet approved specs.

BLA Reports

- Annual Reports
  - CMC changes : 21 CFR 601.12(d)
  - Labeling changes : 21 CFR 601.12(f)(3)
  - Postmarketing Pediatric Studies : 21 CFR 601.28
  - Progress Reports of Postmarketing Studies : 21 CFR 601.70

- Biologic Product Deviation Reports (BPDRs)
  - 21 CFR 600.14
    - Biologics version of Field Report
    - Report via Form FDA-3486
- Distribution Reports (every six (6) months)
  - 21 CFR 600.81

Annual Report Question

True or False?

Distribution data is reported annually in the Annual Report.

Advertisements and Promotional Labeling

- Submit at the time of dissemination.
- Include FDA Form 2253 and a copy of the current Package Insert.

Notification of Discontinuance

Report at least six (6) months prior to discontinuance of manufacturing, if:

- You are the sole manufacturer, and
- The drug is life-supporting, life-sustaining, or it prevents a serious disease or condition.
- See 21 CFR 314.81(b)(3)(iii)(b) for reporting process.

Withdrawal of Approved Drug Product from Sale

- Report within 15 working days of withdrawal of product from sale.
- Include FDA Form 2657 (Drug Product Listing).
- See 21 CFR 314.81(b)(3)(iv) for process.

Post-Approval Changes and Supplements

The Regs:

- For NDAs & ANDAs – 21 CFR 314.70
- For BLAs – 21 CFR 601.12

FDA Guidances (not all inclusive):

- Changes to an Approved NDA or ANDA; April 2004
- Changes to an Approved NDA or ANDA; Questions and Answers; January 2001
- Scale-Up and Post-Approval Changes – multiple dependent on dosage form
- CMC Postapproval Manufacturing Changes to be Documented in Annual Reports; March 2014
- Postapproval Changes to Drug Substances; Draft Guidance, September 2018
- PAC-ATLS: Postapproval Changes-Analytical Testing Laboratory Sites; April 1998

Post-Approval Changes and Supplements (Cont'd)

Three (3) types of supplements:

- Prior-Approval Supplements (PAS).
- Changes Being Effected in 30 days (CBE-30).
- Changes Being Effected Immediately (CBE / CBE-0).

Prior-Approval Supplements (PAS)

- For changes that have a substantial potential to have an adverse impact on the quality (identity, strength, quality, purity, or potency) of the product.
  - e.g., new manufacturing facility, new manufacturing process.
- Changes to the labeling except those allowed under a lower supplement category.
  - e.g., new clinical indication, change in dose or delivery route.

Changes Being Effected in 30 days (CBE-30)

- For changes that have a moderate potential to have an adverse impact on the quality of the product.
  - e.g., move to a different manufacturing site for primary packaging of modified-release solid oral dosage form drug products.

Changes Being Effected immediately (CBE-0)

- For changes that have a moderate potential to have an adverse impact on the quality of the product.
  - e.g., move to a different manufacturing site for manufacture or processing of the final intermediate.

Review Clocks for Supplements for NDAs & BLAs

For CMC Supplements & Labeling Supplements –

- PASs – four (4) months
- CBE-30s & CBEs – six (6) months

For Efficacy Supplements (always a PAS)

- Non-Priority – ten (10) months
- Priority –six (6) months

Review Clocks for Supplements for ANDAs

Type	Priority?	Inspection?	PFC?	Goal (mo.)
PAS	No	No	N/A	6
PAS	No	Yes	N/A	10
PAS	Yes	No	N/A	4
PAS	Yes	Yes	Yes	8
PAS	Yes	Yes	No	10
CBE-30/CBE	N/A	N/A	N/A	6

PFC = Pre-submission Facility Correspondence

Question on Post-Approval Supplements

True or False?

A CBE-30 may be implemented 30 days after FDA approval of the supplement?

FDA Drug Safety Activities

- MedWatch – The FDA Safety Information and Adverse Event Reporting Program
  - https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
- PADERS
- Drug Safety Oversight Board (505-1(j))
  - https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082129.htm
- Supply-Chain Integrity
  - https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/default.htm
- Drug Safety Communications
  - https://www.fda.gov/Drugs/DrugSafety/ucm199082.htm

Drug Safety Oversight Board

- Mandated by the FDA Amendments Act of 2007.
- Advises the CDER Center Director on the handling and communicating of important drug safety issues and the impact of safety decisions on the various Federal healthcare systems.
- Composed of representatives from two FDA Centers and eight other federal government agencies, including:
  - Agency for Healthcare Research and Quality (AHRQ),
  - Centers for Disease Control and Prevention (CDC),
  - Centers for Medicare and Medicaid Services (CMS),
  - Department of Defense (DOD),
  - Health Resources and Services Administration (HRSA),
  - Indian Health Service (IHS),
  - National Institutes of Health (NIH), and
  - Department of Veterans Affairs (VA).

CDER Office of Surveillance and Epidemiology

- The Office of Surveillance and Epidemiology (OSE) monitors and evaluates the safety profiles of drugs post-approval, via:
  - MedWatch program
  - Managing REMS
  - Sentinel® System

OGD Clinical Safety and Surveillance Staff

- Monitors:
  - Drug Quality Reporting System (DQRS)
  - FDA Adverse Event Reporting System (FAERS)
  - Market Data from IMS and Symphony®
- Focus is on potential differences between Brand and Generic or between Generics.

Postmarketing Commitments (PMC) and Postmarketing Requirements (PMR)
Federal Food, Drug, and Cosmetic Act (FFDCA)
Sections 506B and 505(o)

- **Postmarketing Commitment** is a study that the sponsor has agreed to do (usually as a condition of application approval).
- **Postmarketing Requirement** is a study that the FDA requires the sponsor to perform post-approval.

PMR & PMC Progress Reports

- 21 CFR 314.81(b)(2)(vii) & 601.70
- Annual Status Reports
  - FDA Guidance for Industry: Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997; February 2006

PMC & PMR Public Reporting

The FDA provides information to the public regarding the status of PMCs and PMRs at the following URL:

www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

Postmarketing Studies & Clinical Trials; Labeling – FFDCA Section 505(o)

- The Secretary can notify a sponsor that new safety information should be included in the product labeling.
- The sponsor must submit a supplement proposing revised labeling within 30 days of such notification.
- Discussion of the labeling proposal may ensue for no longer than 30 days.
- Within 15 days of the conclusion of the discussions, the Secretary may issue an order directing the sponsor to make the change.
- The sponsor must submit a labeling supplement within 15 days after the issuance of the order.
- If the sponsor wishes to appeal the order, this must be done via Dispute Resolution within 5 days of issuance of the order.

Violation of FFDCA Section 505(o)

- If one fails to perform the studies required by the Secretary within the specified timelines or fails to make the required safety labeling changes, Section 303(f)(4)(A) allows for monetary penalties of up to $250,000 per violation.
- The penalty doubles every 30 days of non-compliance and can reach $10MM for all violations.

FDA Guidance for Industry

- Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act; April 2011

Risk Evaluation and Mitigation Strategy (REMS) Assessments (FFDCA Section 505-1(g))

- With respect to each goal in the strategy:
  - Assess the extent to which the strategy is meeting the goal, and
  - Whether the goals need to be modified.
- Submit reports at timepoints approved in the REMS
  - Usually at 18 months, 3 years, and 7 years post-approval.

Grounds for Withdrawal of Approval

FFDCA Section 505(e) and 21 CFR 314.150(a)

- Imminent hazard to the public health.
- Data show that the drug is unsafe under the approved conditions of use.
- Lack of substantial evidence that the drug will be effective for its approved use.
- The application contains any untrue statement of material fact.
- Patent info prescribed by 505(c) has not been submitted within 30 days of written notice from FDA.

Grounds for Withdrawal of Approval

21 CFR 314.150(b)

- Failure to establish a system for maintaining required records (ref. 505(k), (507(g), 314.80, 314.81, 314.98).
- Manufacturing is inadequate to ensure identity, strength, quality, & purity.
- Labeling is false or misleading.
- Failure to submit biannual drug listings in accordance with 510(j)(2).
- Failure to submit bioavailability or bioequivalence data required by Part 320.
- Failure to explain an omission of a report of any investigation of the drug product.
- Failure to conduct nonclinical studies under GLPs or if the results don't support the validity of the study.
- Failure to adequately protect the rights of subjects in a clinical study.
- Refusal to permit inspection of a BA or BE site or refusal to submit reserve samples of the Drug Product.
- Labeling of a generic drug that is no longer consistent with the RLD (w/exceptions).

Withdrawal of Approval Question

True of False?

FDA may withdraw approval of an application if the applicant submits an Annual Report later than sixty (60) days after the approval anniversary date.

Wrap-up

- Adverse Drug Experience (ADE) Reports
- Annual and Other Reports
- Post-Approval Changes and Supplements
- FDA Drug Safety Activities
- Postmarketing Requirements and Commitments
- Grounds for Withdrawal of Approval

Thank you!

Questions?

Thank you for attending!

Contact Us Below For More Information

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