


Post-Approval Obligations of Drug Applicants

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Introduction

- Adverse drug experience (ADE) reports
  - 15-day alert reports
  - Periodic ADE reports
- Annual and other reports
- FDA drug safety activities
- Post-approval changes/supplements
- Grounds for withdrawal of approval
- Sale/transfer of NDAs/ANDAs
- Medicare, Medicaid, and reimbursement issues
- Drug Supply Chain Security Act product tracing

ADE Reports

- Any “adverse event” associated with use of a drug in humans, whether or not considered drug-related
- Can be associated with:
  - Normal use
  - Drug overdose or abuse
  - Withdrawal
  - Failure of expected pharmacological action
- Applicants to develop written procedures for handling and submitting ADEs to FDA
- Rx drugs without NDAs covered by 21 C.F.R. § 310.305 (written procedures not required)
- Serious Adverse Event Reporting now required for OTC monograph drugs

ADE Reports - Terms

- "Serious" means:
  - Death
  - Life-threatening adverse experience
  - Hospitalization (or prolonging hospitalization)
  - Persistent or significant disability/incapacity
  - Congenital anomaly/birth defect
  - "Important medical event" that may jeopardize a patient (based on "appropriate medical judgment")

- "Unexpected" means:
  - Not listed in the current labeling
  - May be related to an event listed in current labeling, but more severe or more specific

15-Day Alert Reports

- Applicant must report ADEs that are both "serious" and "unexpected" no later than 15 calendar days after initial receipt of information
  - "whether foreign or domestic"
- Company must promptly investigate and submit follow-up reports to FDA
- Non-applicant named on label (manufacturer, packer, distributor) must report ADEs to applicant within 5 days or directly to FDA
- If Rx, no NDA, notified manufacturer must then report even if not named on label

15-Day Alert Reports (2)

- Based on scientific literature?
  - Only if case report or results of formal clinical trial
  - Submit copy of published article

- Based on postmarketing study?
  - Only needed if “reasonable possibility” that drug caused the adverse experience

ADE Reporting

- MedWatch – [Form FDA 3500A]
  - Now “Individual Case Safety Report” (ICSR) submitted electronically
- Provide as much information as known, but at least:
  - Identifiable patient
  - Identifiable reporter
  - Suspect drug product
  - Adverse event
- Disclaimer permitted
  - Report does not constitute an admission that drug caused or contributed to the adverse event

ADE Proposed Rule

- March 14, 2003 proposed rule
  - Require expedited reporting in more circumstances (*e.g.*, actual and potential medication errors)
  - Change focus to Suspected Adverse Drug Experiences
  - Improve harmonization of international reporting standards
  - Many potential changes to timing and types of reporting
  - Comment period extended; no final action yet (none projected)
- Final rule issued for reporting AEs during clinical trials (compliance date: September 28, 2011)
- Final rule (compliance date: Sept. 8, 2015) – adverse events for Rx and OTC drugs (NDA and monograph) must be submitted electronically

Periodic ADE Reports

- ADEs not considered “serious” and “unexpected” must be reported:
  - Quarterly for 3 years after drug approval
  - Annually thereafter
- FDA may establish more frequent interval
- Report must include:
  - Narrative summary and analysis of 15-day reports submitted;
  - Form 3500A/ICSR for non-15-day ADEs; and
  - History of actions taken in response to ADEs

ADE Enforcement

- Failure to submit 15-day reports
- Failure to submit reports within 15 days
- Failure to conduct follow-up investigation and submit 15-day follow-up
- Failure to submit periodic reports
- Failure to have adequate written procedures for surveillance, receipt, evaluation, and reporting

Quiz – ADE Issues

- What criteria describe “reportable” ADEs?

__ Serious

__ Inconvenient

__ Unexpected

__ Painful

Quiz – ADE Issues

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✓ Serious

___ ~~Inconvenient~~

✓ Unexpected

___ ~~Painful~~

NDA Field Alert Reports

- Mandatory reporting of:
  - Any incident causing a product or its labeling to be mistaken for, or applied to, another article
  - Any bacteriological contamination, or significant chemical, physical, or other change or deterioration in a distributed product
  - Any failure of a distributed product to meet specifications
- Notify FDA District Office within 3 working days after receiving information
- 21 C.F.R. § 314.81(b)(1)

Annual Reports

- 21 C.F.R. § 314.81(b)(2)
  - Summary of significant new information that might affect safety, effectiveness, or labeling
  - Distribution data
  - Current labeling
  - Chemistry, manufacturing, and control changes
  - Nonclinical lab studies
  - Clinical data
  - Status report on postmarketing studies

Other Information

- Submission of promotional materials
  - Representative copies at time of initial dissemination
  - April 2015 – draft FDA guideline on electronic submission
- Withdrawal of approved drug from sale
  - Notify FDA within 15 working days
  - Sole manufacturer of drug that is life supporting, life sustaining, or intended to prevent serious disease or condition - must notify FDA at least 6 months before discontinuing manufacture
  - [Existing regulation; also part of FDASIA]
- Establishment registration (electronic)
  - Update annually
- Drug product listing (electronic)
  - Update every 6 months

FDA Drug Safety Activities

- Drug Safety Oversight Board
  - 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
  - Includes representatives of two FDA Centers and eight other federal agencies

- CDER Office of Surveillance and Epidemiology
  - monitors and evaluates safety profiles of drugs post-approval, via:
    - MedWatch program
    - Managing Risk Evaluation and Mitigation Strategies (REMS) programs (>60 as of November 2021)
    - Sentinel® System

FDA Drug Safety Activities (2)

- 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 obligations
  - "Postmarketing commitment" – study sponsor has agreed to do (usually as a condition of approval)
  - "Postmarketing requirement" – study FDA requires the sponsor to perform post-approval
  - Status available to public
    - https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

Post-Approval Changes/Supplements

- NDA/ANDA holder must notify FDA about any "change in a condition established in an approved application beyond the variations already provided for" in application
- Assess whether advance approval is needed to implement change
- Fact-specific analysis
- 21 C.F.R. § 314.70

Post-Approval Changes/Supplements (2)

- "Prior approval" (major)
  - Most changes in formulation, manufacturing process, packaging materials
- "Changes being effected" (moderate)
  - 30 days: packaging change that doesn't affect drug quality
  - Immediate: addition of specification; labeling change to reflect "newly acquired information" if there is "sufficient evidence of a causal association"
- "Annual report" (minor)
  - E.g., delete color; adopt compendial change
  - Final FDA Guidance (March 2014)

Quiz – Post-Approval Changes

- Which of the following would require a PAS?

__ New manufacturing site for the API

__ New manufacturing site for secondary packaging

__ Change in sterilization method

__ Change to imprint code on solid oral dosage form

__ Addition of a stability protocol

__ Extension of shelf-life based on existing stability protocol

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Withdrawal of Approval

- FDC Act § 505(e)
  - 5 Mandatory bases ("shall")
  - 3 Discretionary bases ("may")
- 21 C.F.R. § 314.150(b)
  - Additional "regulatory" bases not in statute
- Formal process requires administrative hearing (substantial effort by FDA)
- Statutory basis for reinstating approval when "the facts so require"
  - FDC Act § 505(f)

Withdrawal - Mandatory

- Safety - clinical or other evidence shows drug is unsafe
- Safety - based on new clinical evidence not in NDA or known to FDA that drug “is not shown to be safe”
  - E.g., Seldane (following Allegra approval)
  - E.g., Avastin for breast cancer (2011)
  - E.g., >325 mg acetaminophen in Rx drugs (2014)
- Effectiveness - new evidence shows lack of substantial evidence of effectiveness
  - Generics not effective - methylphenidate ER (proposed October 2016)
  - Postmarket study (ineffective) – Makena (2020)
- Failure to file required patent information
- Application includes untrue statement of material fact
  - KV Pharmaceutical (1998)
  - Concerns about Able Labs (2005)

Withdrawal - Discretionary

- Failure to have system for maintaining required records, to permit access to records, or to file required reports
- New information: serious manufacturing deficiencies and not corrected within a reasonable time after written notice
- New information: labeling is false or misleading and not corrected within a reasonable time after written notice
  - Generic MiraLax (Rx/OTC marketing) (October 2008)
    - Four companies requested hearings on withdrawal
    - FDA denied requests on April 2, 2018
    - ANDA approvals withdrawn on November 2, 2018

Withdrawal - Regulatory

- Legal authority uncertain (but not challenged)
  - Failure to submit bioavailability or bioequivalence data
    - E.g., FDA concerns about data generated by contract research organizations
    - ANDA holders requested multiple times to submit new data, holders did not, ANDA approvals withdrawn
      - 9/16/19: urisidol capsules (CorePharma)
      - 8/3/20: oxycodone HCl and ibuprofen combination (Watson Labs)
  - Failure to explain omission of investigation or other information pertinent to evaluation of the drug (omission itself not a basis for withdrawal)
  - Good laboratory practice violations
  - Informed consent/Institutional Review Board (IRB) violations
  - Refusal to permit inspection (applicant or contract research organization)

Withdrawal – "Voluntary"

- Product no longer marketed – sponsors ask FDA to withdraw approval
- Product pulled from market based on safety reports
  - Redux (pulled 1997; approval withdrawn 2007)
  - OraFlex (1982; 2013)
  - Vioxx (2004 – still technically approved)
  - Zecuity (2013; 2019 (claimed "commercial reasons"))
- Postmarket trial - efficacy not shown
  - *E.g.*, Iressa, one indication for Celebrex
- Postmarket trial - safety issues
  - *E.g.*, Mylotarg, Meridia

Withdrawal – "Voluntary" (2)

- Postmarket trial – not completed
  - *E.g.*, Bexxar, Oforta
- Generic not effective
  - Buproprion HCl ER (final April 2014)
  - Propranolol HCl ER (final August 2017)
- Withdrawing indication for co-administration (label statement re no additional benefit) (April 2016)
  - Niacin extended-release and fenofibric acid ER
  - Advicor (niacin ER and lovastatin fixed combination)
  - Simcor (niacin ER and simvastatin fixed combination)

Withdrawal – Others

- Citizen petition
  - Raising alleged safety concerns
    - *E.g.*, Crestor, Xenical, Avandia, Propecia
  - Confusion over product names
- "Imminent hazard" to public health
  - Summary suspension with opportunity for expedited hearing
  - HHS Secretary's decision - only used once
    - Phenformin HCl (diabetes treatment) (concern: lactic acidosis)
    - FDA started withdrawal process in May 1977
    - HHS issued "order of suspension" on July 25, 1977
    - Formal NDA approval withdrawn November 15, 1978

Withdrawal – Others (2)

- Advisory Committee recommendation
- Darvon/Darvocet (propoxyphene) (1/2009)
  - AdCom voted to withdraw approval based on safety issues
  - FDA (July 2009): no withdrawal – strengthened label, Medication Guide, additional safety study
  - FDA (Nov. 2010): based on new data, requested withdrawal, manufacturer agreed
  - March 10, 2014: Notice of withdrawals of approvals
- Vicodin, Percocet (narcotics + acetaminophen) (6/2009)
  - AdCom voted to withdraw approval
  - March 27, 2014: Notices of withdrawals of approvals

Withdrawal – Others (3)

- Advisory Committee recommendation
- Opana ER (oxymorphone HCl) (June 2017)
  - Drug originally approved in 2006
  - Reformulated in 2012 to make resistant to manipulation to allow snorting or ingestion
    - Lack of data to justify including abuse-deterrent information in labeling
  - AdCom voted (March 2017) 18-8 that benefits no longer outweighed risks
  - June 8, 2017: FDA asked Endo Pharmaceuticals to withdraw product from market voluntarily
    - If Endo declines, “the agency intends to take steps to formally require its removal by withdrawing approval”
    - July 2017: Endo agrees to remove product from the market

Withdrawal – Others (4)

- "Administrative Reconsideration"
- Spear Pharmaceuticals – fluorouracil ANDA approved April 11, 2008
  - Valeant Citizen Petition (denied), lawsuit against FDA
  - FDA announced reconsideration May 14 due to "outstanding questions regarding this approval"
  - Approval stayed until May 30, 2008 (Spear agreed to stay)
  - No indication of what issues were uncovered
  - No additional delay in approval beyond May 30

Withdrawal – Agency "Mistake"?

- *American Therapeutics* (1990)
  - ANDA approved on 6/23/89, revoked on 8/3/89
  - FDA official not aware of cGMP deficiencies identified during inspection completed on 6/23
  - Court: FDA acted quickly and in good faith to correct error

- *Ranbaxy v. FDA* (March 2015)
  - Nov. 2014, FDA withdrew two tentative approvals issued in 2008
  - Substantial cGMP issues existed at time of TAs (only later discovered), still ongoing
  - Court:
    - "A series of [FDA] errors combined with [Ranbaxy's] malfeasance led to the tentative approval[s]"
    - FDA "has the inherent authority to correct its mistakes" even though Agency acted "belatedly"
  - [Ranbaxy lost first-filer exclusivity]

Withdrawal – Agency "Mistake"? (2)

- Sun Pharma Advanced Research Company
  - NDA approved in March 2015
  - Complete response letter received in September 2015
  - Sun press release: Approval rescinded because "compliance status of the manufacturing facility was not acceptable on the date of approval"
  - Trade press report:
    - FDA transitioning to new computer system
    - Compliance status of Sun facility not accurately displayed or assessed in new system
    - NDA approved by mistake
  - Sun apparently not challenging FDA's action

Withdrawal – Agency "Mistake"? (3)

- Lannett Company
  - ANDA approved in March 23, 2016
  - FDA letter to Lannett dated May 17, 2016 "rescinding" the approval
    - FDA's April 1, 2016 letter said approval was issued in error
    - Inspection of Chinese API manufacturer found cGMP issues
    - Information about API status was "not adequately conveyed to the FDA officials making the final decisions about the ANDA approval"
  - Lannett sued FDA in DC District Court; decision issued on October 25, 2017
    - ANDA rescission is not "final agency action"
    - Lannett failed to exhaust administrative remedies before suit (options under 21 CFR 314.110(b))
    - Court cited *American Therapeutics* approvingly

Quiz – Withdrawal of Approval

- Which of the following are bases for withdrawing approval?

__ New information shows drug is not safe

__ New information shows drug is not effective

__ Failure to file required reports

__ Bad attitude during FDA inspection

Quiz – Withdrawal of Approval

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✓ New information shows drug is not effective

✓ Failure to file required reports

__ ~~Bad attitude during FDA inspection~~

Sale/Transfer of NDA/ANDA

- Notify FDA at time of transfer
- Letter from former owner confirming transfer of rights
- Letter from new owner:
  - Providing commitment to meet conditions of application
  - Confirming effective date of transfer
  - Certifying possession of full copy of application
- 21 C.F.R. § 314.72

Post-Approval Safety Issues

- FDA authority to require:
  - Postmarket studies
  - Change in label safety information
- Risk Evaluation and Mitigation Strategy (REMS)
- Penalties for noncompliance:
  - Misbranded drug
  - Civil money penalties

Medicare, Medicaid, and Reimbursement

- Medicare: federal health insurance program for:
  - People who are 65 or older
  - Certain younger people with disabilities
  - People with End-Stage Renal Disease (permanent kidney failure requiring dialysis or a transplant, sometimes called ESRD)
- Medicare Parts:
  - Part A (Hospital Insurance)
  - Part B (Medical Insurance)
  - Part D (prescription drug coverage)

Medicare, Medicaid, and Reimbursement (2)

- Medicaid: health insurance program for:
  - Eligible low-income adults; children; pregnant women; elderly adults; and people with disabilities
- Jointly funded by states and federal government

- Medicare drug coverage issues:
  - Network/preferred pharmacies
  - List of covered prescription drugs (formularies) – will vary by plan
  - Coverage rules (examples):
    - Prior authorization
    - Step therapy
    - Quantity limits

Track-Trace

- Guard against counterfeits/poor quality
  - FDA Counterfeit Drug Task Force formed July 2003
  - Task Force report issued February 2004
- FDA Amendments Act of 2007:
  - FDA to develop standards for “effective technologies” to secure drug supply chain
  - FDA developed “standardized numerical identifier” to identify drug and allow track/trace (March 2010 guidance)
- October 2011 – final guidance on “physical-chemical identifiers” in solid oral dosage forms to prevent counterfeiting

Drug Quality and Security Act (2013)

- Drug Supply Chain Security Act (Title II)
- Elements
  - Product tracing – 1/1/15
    - FDA to establish standards for information to be exchanged
  - Product verification – 1/1/15
  - Product identification – 11/27/17 through 11/27/20
  - Wholesaler and third-party logistics provider licensing standards – 11/27/15
  - Enhanced system – electronic package tracing (11/27/22)
  - Penalties – failure to comply results in adulterated and misbranded product
  - National uniformity - preempts state laws

Thank you!

Questions? Please contact:

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