The New Drug Approval Process: NDA Submission and Review

Elizabeth Mulkey

April 21, 2021
Roadmap

A. Content and Organization of a Full NDA
B. The Review Process
C. Expedited Programs
D. Responses to FDA Adverse Decision
E. Post-approval Study and Surveillance Requirements
F. Critical Path Innovations
Purpose of an NDA

- Enables FDA to determine:
  - Whether the drug is safe and effective for the proposed indication, and whether the drug’s benefits outweigh the risks
  - Whether the drug’s proposed labeling is appropriate, and what should be included in the package insert
  - Whether manufacturing methods & quality controls are adequate to preserve drug’s identity, strength, quality & purity
Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DEFITELIO safely and effectively. See full prescribing information for DEFITELIO.

DEFITELIO (defibrotide sodium) injection, for intravenous use
Initial U.S. Approval: 2016

—INDICATIONS AND USAGE—
DEFITELIO is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT). (1)

—DOSEAGE AND ADMINISTRATION—
• Administer DEFITELIO 6.25 mg/kg every 6 hours given as a 2-hour intravenous infusion. (2.1)
• Treat for a minimum of 21 days. If after 21 days signs and symptoms of VOD have not resolved, continue treatment until resolution. (2.1)

—DOSEAGE FORMS AND STRENGTHS—
Injection: 200 mg/5.5 ml (38 mg/ml) in a single-patient use vial. (3)

—CONTRAINDICATIONS—
• Concomitant administration with systemic anticoagulant or fibrinolytic therapy. (4)
• Known hypersensitivity to DEFITELIO or to any of its excipients. (6)

—WARNINGS AND PRECAUTIONS—
• Hemorrhage: Monitor patients for bleeding. Withhold or discontinue DEFITELIO if significant bleeding occurs. (2.3, 3.1)
• Hypersensitivity Reactions: If severe or life threatening allergic reaction occurs, discontinue DEFITELIO, treat according to standard of care, and monitor until signs and symptoms resolve. (2.3, 5.3)

—ADVERSE REACTIONS—
The most common adverse reactions (incidence >10% and independent of causality) with DEFITELIO treatment were hypotension, diaphoresis, vomiting, nausea and epistaxis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-866-529-5668 or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch.

—DRUG INTERACTIONS—
• DEFITELIO may enhance the activity of antimicrobials/fibrinolytic drugs. (7)

Set 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSEAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Administration Instructions
2.3 Treatment Modification
2.4 Preparation Instructions
3 DOSEAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hemorrhage
5.2 Hypersensitivity Reactions
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
A. Content & Organization of a Full NDA

**Sources:**

- **FDCA § 505(b)(1)**
  - High level description of NDA elements

- **21 CFR Part 314 (i.e., 21 CFR 314.50)**
  - Detailed description of NDA elements

- **FDA Guidance Documents**
  - Various guidance documents describe the NDA elements in much greater detail
Content of an NDA

• **Cover Letter**
  – Not officially part of the NDA content and format
  – Vitally important
  – Opportunity to give overall strategy and remind FDA of important events that occurred during development

• **Summary**
  – General understanding of the application
  – Annotated labeling text identifying supporting information from technical section of NDA

• **Chemistry, Manufacturing, and Controls (CMC)**
  – Drug substance and drug product
Content of an NDA

• **Non-Clinical Data**
  – *Animal and in vitro studies*
    • Pharmacology/toxicology
    • Statement of compliance with GLPs

• **Pharmacokinetics/Bioavailability**
  – In humans

• **Microbiology**
  – Only for anti-infectives
Content of an NDA

• **Clinical Data**
  – Description and analysis of studies
  – Summary of efficacy and safety
  – Benefits outweigh risks
  – Safety updates

• **Statistical**
  – Description of statistical analysis to evaluate the data
Content of an NDA

• **Pediatric Use**
  – Pediatric rule (requiring pediatric assessment unless waived or deferred)

• **Samples and Labeling (and Packaging, if Requested by FDA)**
  – FDA validation of analytical procedures
  – Labeling (package insert and patient labeling)

• **Case Report Forms**
  – Tabulations of clinical data
  – Case report forms for deaths, adverse events
Content of an NDA

• **Patent Information**
  – Information for Applicant’s own patents (21 CFR 314.54)
  – Certification for other patents (21 CFR 314.50(h))
  – No process patents
  – *Note:*
    • NDA patent information is provided in FDA’s “Approved Drug Products with Therapeutic Evaluations” (i.e., the “Orange Book”)

• **Disclosure/Certification**
  – Investigator financial certification
  – Debarment certification
  – Claimed exclusivities
  – Compliance with clinical trial disclosure requirements
Drug Master Files (DMFs)

• Submission to FDA of information concerning facilities, processes, or ingredients for a drug

• Method for supplying information in a confidential manner

• May be referenced by “DMF holder” or others (with permission) in an application (e.g., IND, NDA, or ANDA)

• DMF Types:
  – Type II: Drug substance
  – Type III: Packaging materials
  – Type IV: Inactive ingredients
  – Type V: FDA-Accepted Reference Information

Website: https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs
Guidance: https://www.fda.gov/drugs/guidances-drugs/drug-master-files-guidelines
Regulation: 21 CFR 314.420
Use of the Common Technical Document (CTD)

- CTD is a set of specs for regulatory applications & related submissions
- Harmonizes technical documentation for US, Europe, and Japan
- Int’l Conference on Harmonization (ICH)
- Five main modules:
  - (1) Administrative Information
  - (2) Overviews and Summaries
  - (3) Quality (pharmaceutical documentation)
  - (4) Non-Clinical Reports (pharmacology/toxicology)
  - (5) Clinical Study Reports (clinical trials)
The 5 CTD Modules
Electronic Common Technical Document (eCTD)

• Electronic submission
  – eCTD format is required
  – FDA eCTD Web Page:
B. The Review Process

• User Fees and Goals (PDUFA)
• The Review Clock and Impact of PDUFA
• Interacting with FDA
• Pre-Approval Inspections (PAIs)
• Complete Response and Approval Letters
Overview of the NDA/BLA Review Process and Major Steps for Completing the Review

1. Pre Submission Activities
2. Process Submission
3. Plan Review
4. Conduct Review
5. Take Official Action
6. Post Action Feedback

Note: The timeline for review of NMEs/BLAs under PDUFA V’s “Program” Review extends the Conduct Review Phase by two months. See Appendix A for a timeline diagram for PDUFA V.
User Fees and Goals (PDUFA)

• Prescription Drug User Fee Act (PDUFA) was enacted in 1992
  – Intended to address U.S. “drug lag”
  – Reauthorized every 5 years
  – Last reauthorized in 2017 as part of FDARA (PDUFA VI)

• Leading up to PDUFA reauthorization, FDA and stakeholders negotiate goals

• PDUFA outlines the “user fees” drug sponsors must pay for FDA activities related to prescription drug reviews
  – Application Fees
  – Program Fees

• FDA agrees to user fee “goals” for review timelines and additional goals or programs (e.g., patient-focused drug development meetings)
  – During the COVID-19 pandemic, FDA has continued to publish updates on its ability to meet these goals
# PDUFA VI User Fees (FY 2021)

<table>
<thead>
<tr>
<th>Fee category</th>
<th>Fee rates for FY 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application:</strong></td>
<td></td>
</tr>
<tr>
<td>Requiring clinical data</td>
<td>$2,875,842</td>
</tr>
<tr>
<td>Not requiring clinical data</td>
<td>1,437,921</td>
</tr>
<tr>
<td><strong>Program:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>336,432</td>
</tr>
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</table>
### PDUFA VI User Fee Goals (FY18-22)

#### Table 1: Original and Resubmitted Applications and Supplements:

<table>
<thead>
<tr>
<th>SUBMISSION COHORT</th>
<th>STANDARD</th>
<th>PRIORITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>NME NDAs and original BLAs</td>
<td>90% in 10 months of the 60 day filing date</td>
<td>90% in 6 months of the 60 day filing date</td>
</tr>
<tr>
<td>Non NME NDAs</td>
<td>90% in 10 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
<tr>
<td>Class 1 Resubmissions</td>
<td>90% in 2 months of the receipt date</td>
<td>90% in 2 months of the receipt date</td>
</tr>
<tr>
<td>Class 2 Resubmissions</td>
<td>90% in 6 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
<tr>
<td>Original Efficacy Supplements</td>
<td>90% in 10 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
<tr>
<td>Class 1 Resubmitted Efficacy Supplements</td>
<td>90% in 2 months of the receipt date</td>
<td>90% in 2 months of the receipt date</td>
</tr>
<tr>
<td>Class 2 Resubmitted Efficacy Supplements</td>
<td>90% in 6 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
</tbody>
</table>

#### Table 2:

<table>
<thead>
<tr>
<th></th>
<th>PRIOR APPROVAL</th>
<th>ALL OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing Supplements</td>
<td>90% in 4 months of the receipt date</td>
<td>90% in 6 months of the receipt date</td>
</tr>
</tbody>
</table>
Interacting with FDA

- Premarket Review/Good Review Management Principles
- Special Protocol Assessment (SPA)
- Approval Meetings; Product Application Meetings
- Advisory Committees
Premarket Review/
Good Review Management Principles

• Clarify roles and responsibilities of review staff in managing the review process

• Identifies principles and time goals for review and action on drug applications
  – 1. Filing Determination & Review Planning Phase
  – 2. Review Phase
  – 3. Advisory Committee Meeting Phase
  – 4. Action Phase:
    • Wrap-Up, Labeling, Signatory Review Documentation, Regulatory Action
  – 5. Post-Action Phase

Guidance: https://www.fda.gov/media/72259/download
Reviews and Review Clocks

- Drug Sponsor
- Application Fileable?
- Yes: Review by CDER
- No: Submit NDA
- 60 Days
- Refuse to File Letter

Fileable?

60 Days

No

Yes

Refuse to File Letter

Submit NDA
Reviews and Review Clocks

- Filed Application
  - Medical
  - Biopharmaceutical
  - Pharmacology
  - Statistical
  - Chemistry
  - Microbiology

- Advisory Committee Meeting
- Meetings with Sponsors

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Reviews and Review Clocks

CDER Reviews

Reviews Complete & Acceptable?

Sponsor Amendments

CDER Reviews

No

Sponsor Revises

Labeling Acceptable?

Pre-Approval Inspection Acceptable?

FDA Action

Pending Satisfactory Results
Special Protocol Assessment (SPA)

- **Mechanism for requesting feedback from FDA on:**
  - Protocols
    - I.e., animal carc., final product stability, Phase 3 clinical trials
  - Whether protocols are adequate to meet scientific and regulatory requirements identified by the sponsor

- **45-day PDUFA review clock**

- **SPA agreement may be rescinded**
  - “FDA may rescind an SPA agreement when the division director or senior management determines that a substantial scientific issue essential to determining the safety or efficacy of the product has been identified after the trial has begun.”
  - FDA states that less than 1% (of 1,000+) have been rescinded
Approval Meetings; Product Application Meetings

- Sponsors may request meetings with FDA
  - FDA grants meetings unless “clearly unnecessary” or “premature”
- Meeting types (Face-to-Face/TC/VTC or Written Response Only)
  - **Type A**: Dispute resolution, clinical hold, protocol assessment, post-action/RTF
  - **Type B**: Pre-IND, Pre-NDA, REMS, BT, pre-EUA
  - **Type B (EOP)**: End-of-Phase 2, certain EOP1
  - **Type C**: Other than Type A, B, or B (EOP)
- Pre-meeting submissions (request & briefing/meeting package)
- Preliminary responses from FDA
- Memorandum of meeting
Table A: Meeting Management Procedural Goals

<table>
<thead>
<tr>
<th>Meeting Type</th>
<th>FDA Response to Request</th>
<th>FDA Receipt of Meeting Package</th>
<th>FDA Preliminary Responses to Requester (if applicable†)</th>
<th>Requester Preliminary Response to FDA Preliminary Responses (if applicable†)</th>
<th>FDA Scheduled Meeting Date (days from receipt of request)</th>
<th>FDA Meeting Minutes to Requester (if applicable†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>14 days</td>
<td>With meeting request</td>
<td>No later than 2 days before meeting</td>
<td>--</td>
<td>Within 30 days</td>
<td>30 days after meeting</td>
</tr>
<tr>
<td>B</td>
<td>21 days</td>
<td>No later than 30 days before meeting</td>
<td>No later than 2 days before meeting</td>
<td>--</td>
<td>Within 60 days</td>
<td>30 days after meeting</td>
</tr>
<tr>
<td>B (EOP)*</td>
<td>14 days</td>
<td>No later than 50 days before meeting**</td>
<td>No later than 3 days after receipt of preliminary responses</td>
<td></td>
<td>Within 70 days</td>
<td>30 days after meeting</td>
</tr>
<tr>
<td>C</td>
<td>21 days</td>
<td>No later than 47 days before meeting***</td>
<td>No later than 3 days after receipt of preliminary responses</td>
<td></td>
<td>Within 75 days</td>
<td>30 days after meeting</td>
</tr>
</tbody>
</table>

†Not applicable to written response only.

* EOP = end of phase

** If the scheduled date of a Type B (EOP) meeting is earlier than 70 days from FDA receipt of the meeting request, the requester’s meeting package will be due no sooner than 6 calendar days after FDA response time for issuing the letter granting the meeting (see Table 1 in section VI.B., Meeting Granted).

*** If the scheduled date of a Type C meeting is earlier than 75 days from FDA receipt of the meeting request, the meeting package will be due no sooner than 7 calendar days after FDA response time for issuing the letter granting the meeting. Note that for Type C meetings that are requested as early consultations on the use of a new surrogate endpoint to be used as the primary basis for product approval in a proposed context of use, the meeting package is due at the time of the meeting request.
Examples – What Type of Meeting?

[Survey: Type A / Type B / Type C]

- A sponsor has completed Phase 2 studies and is planning for Phase 3
- There is a clinical hold in place, and FDA and the sponsor agree that a new path forward should be discussed
- A sponsor wants to discuss the appropriate endpoints to be used in a rare disease trial
Advisory Committees

• FDA generally has discretion to call advisory committee meetings

• FDA seeks advice for specific scientific & medical questions (e.g., re data in NDA)
  – Advisory committees hear testimony (usually from FDA & stakeholders), discusses, and votes
  – FDA is not bound by advisory committee’s vote

• Pediatric Advisory Committee dispute resolution is the only required AdCom mtg

• FDCA § 505(n) describes appointment process and membership criteria

• Federal Advisory Committee Act (FACA)
  – Meetings must be open to the public
  – Materials supplied to committee are public
  – Exceptions: (FOIA) trade secrets, etc.

Website: www.fda.gov/AdvisoryCommittees/Laws, Regulation, and Guidance:
www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/LawsRegulationsGuidance/default.htm
Advisory Committees

View of the Dec. 20, 2012 Meeting of the Arthritis Advisory Committee
The Great Room, White Oak Conference Center, Food & Drug Administration, Silver Spring, Maryland

Source: Solve CFS
Pre-Approval Inspections (PAIs)

• **Goals:**
  – Ensure drug establishment is ready to manufacture the drug
  – Verify that the conformance of drug manufacturing to application specifications
  – Check the integrity of application data (data audit)

• **Application Recommendations:**
  – Withhold or Approve

• **Compliance Policy Guide 7346.832**

• **During COVID-19**
  – FDA has issued guidance on availability of remote interactive evaluations
Complete Response & Approval Letters

• **Complete Response (21 CFR 314.110)**
  – Possible reasons to refuse to approve outlined in 21 CFR 314.125 (e.g.,
    inadequate evidence of effectiveness & safety, inadeq. CMC, inadeq. labeling)
  – **Sponsors can:**
    • Resubmit with new PDUFA review goals
    • Withdraw the marketing application
    • Request an opportunity for hearing

• **FDA Approval Letter (21 CFR 314.105)**
  – If none of the reasons to refuse to approve outlined in 21 CFR 314.125 applies
  – Marketing application may be approved if there are minor labeling deficiencies
C. Expedited Programs

- Expedited programs:
  - Fast track
  - Priority review
  - Breakthrough therapy designation (also RMAT)
  - Accelerated Approval

- These programs are intended to speed the development and approval of therapies to treat serious, life-threatening diseases and conditions

- Competing interests:
  - Ensuring safety & effectiveness vs. avoiding undue delay

- Development program may be eligible for multiple expedited programs
Fast Track & Priority Review

- **Fast Track** (FDCA § 506(b))
  - For serious conditions and demonstrated potential to fill unmet medical need
  - Also available to sponsors of drugs designated by FDA as Qualified Infection Disease Products (QIDPs)
  - More FDA meetings and interactions & rolling review of application

- **Priority Review** (PDUFA)
  - For serious conditions and demonstrated potential for significant improvement in safety or effectiveness
  - Also available to sponsors that redeem priority review vouchers (tropical disease, rare pediatric disease, medical countermeasure priority review vouchers, FDCA §§ 524, 529, 565A)
  - FDA reviews application within 6 months (rather than 10 months)
Breakthrough Therapy Designation

- For **serious condition** and **preliminary evidence** indicates that the drug **may demonstrate substantial improvement** on a **clinically significant endpoint(s)** over available therapies

- Intensive guidance on efficient drug development; organizational commitment; rolling review; other actions to expedited review (including a potentially shorter review time)

- FDCA § 506(a)
Regenerative Medicine Advanced Therapy (RMAT) Designation

- Established by 21st Century Cures Act (FDCA § 506(g)), a drug is eligible for RMAT designation if:
  - The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and CFR Part 1271;
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; AND
  - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

- Features:
  - Expedited development and review, including early interactions with FDA to discuss surrogate or intermediate endpoints to support accelerated approval; also eligible for priority review
Accelerated Approval/Subpart H

- Unlike Fast Track, Priority Review, Breakthrough, and RMAT which reduce FDA’s review time, Accelerated Approval shortens the Sponsor’s clinical development time

- For serious conditions with a meaningful advantage over available therapy

- Permits the use of a “surrogate endpoint” that is likely to predict clinical benefit (e.g., viral load, tumor shrinkage)

- Sponsors required to conduct post-marketing studies to confirm benefit (i.e., confirmatory trials)

- FDCA § 506(c); 21 CFR 314.500
<table>
<thead>
<tr>
<th>Designation</th>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>At submission of IND through pre-NDA/pre-BLA meeting</td>
<td>At submission of IND or later (preferably before EOP2 meeting); must have prelim. clinical data</td>
<td>No formal process; discuss with FDA during development, including use of planned endpoint and confirmatory studies</td>
<td>At time of submission of NDA or BLA</td>
</tr>
<tr>
<td><strong>Eligibility</strong></td>
<td>1. Serious condition, AND Potential to fill unmet medical need</td>
<td>1. Serious condition, AND Preliminary data → may have substantial improvement over existing therapies on clinically significant endpoint</td>
<td>1. Serious condition, AND 2. <strong>Meaningful advantage</strong> over existing therapies, AND 3. <strong>Surrogate or intermediate endpoint</strong> reasonably likely to predict clinical benefit</td>
<td>1. Serious condition, AND 2. <strong>Significant improvement</strong> over existing therapies on safety or efficacy</td>
</tr>
<tr>
<td><strong>Type of Data</strong></td>
<td><strong>Preclinical data</strong> is acceptable as is clinical data</td>
<td>Must have <strong>clinical data</strong></td>
<td>Must have <strong>clinical data</strong> with a surrogate or intermediate endpoint</td>
<td>-</td>
</tr>
</tbody>
</table>
Examples – What Expedited Program?

[Survey – Fast Track / BTD / AA]

• This program involves use of a surrogate endpoint or intermediate clinical endpoint
• This designation may be granted on the basis of preclinical data
• This program is intended for a drug that treats a serious/life-threatening condition and preliminary clinical evidence indicates that it may demonstrate improvement over available therapies
D. Responses to FDA Adverse Decisions

• **Administrative Matters**
  – Consumer safety officer
  – Ombudsman

• **Scientific & Medical Disputes**
  – End-of-review meeting
  – Appeal within hierarchy under the regulations
  – Formal dispute resolution
  – Right to advisory committee review
Responses to FDA Adverse Decisions

• **Right to a Hearing on Refusal to Approve an Application**
  – Applicants have a right to an administrative hearing if FDA refuses to approve an application
  – FDCA § 505(d)

• **Judicial Review of Refusal to Approve an Application**
  – Applicants have a right to judicial review in U.S. Court of Appeals
  – Deference to scientific determinations
  – Rarely invoked
  – FDCA § 505(h)

• **Judicial Review of Approval of a Competitor’s Application**
  – Extremely uncommon (if at all)
E. Post-Approval Study & Surveillance Reqs

- Risk Evaluation and Mitigation Strategies (REMS)
- Safety Labeling Changes
- Post-Approval Study Requirements
- FDAAA (Post-Approval Surveillance)
REMS

• REMS are **required risk management plans** that use risk minimization strategies **beyond the professional labeling** to ensure that the **benefits** of certain prescription drugs **outweigh** their **risks**

• Essentially, a REMS is a **safety strategy** to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their **safe use**
REMS

• **FDA may require REMS for a drug:**
  – To ensure benefits outweigh risks (new & marketed drugs) (FDCA § 505-1(a)); **or**
  – If “new safety information” causes FDA to determine a REMS is necessary to ensure benefits of the drug outweigh the risks (FDCA § 505-1(a)(2))

• **Information sources include:** clinical trials; epidemiological studies; adverse event reports; literature; FDA monitoring system. (FDCA § 505-1(b)(3))
REMS

- REMS must address "serious risks" (e.g., death, immediate risk of death, hospitalization, incapacity, birth defects)
- REMS can be required for a single drug or a class of drugs
- FDA will generally inform a company that REMS are required; companies then submit a proposed REMS (FDCA § 505-1(a)(1))
- Disagreements are handled through a dispute resolution procedure (FDCA § 505-1(h))
- FDA can enforce REMS as statutory violations (FDCA § 505(p))
REMS

• Companies must submit written assessments to FDA at predefined intervals (FDCA § 505-1(d)-(g))

• REMS may be modified, added, or removed (FDCA § 505-1(g)-(h))

• Existing REMS apply to generic versions, with limitations (FDCA § 505-1(i))
REMS Elements

• Medication Guide to Patients (FDCA § 505-1(e)(2))

• Communications to Health Care Professionals (FDCA § 505-1(e)(3))

• Elements to Assure Safe Use (ETASU) (FDCA § 505-1(f)(3))
  – For drugs with “inherent toxicity” or potential harmfulness
  – ETASU “elements” must be commensurate with the specific, serious risk & not unduly burdensome on patient access
  – May include:
    • Physician training programs; pharmacy certification; central pharmacy distribution; restrictions on use settings; patient registry enrollment; specific patient monitoring
Safety Labeling Changes

• FDA may require safety labeling changes for already approved drugs (FDCA § 505(o)(4))
  – **Criterion:**
    • Whether new safety info “should be included” in the labeling
  – Sponsors are notified by FDA
  – Sponsors submit labeling changes in a supp’l appl’n
  – Failure to comply is a statutory violation
Post-Approval Study Requirements

• FDA may require post-approval safety studies
  – FDA may only require post-approval safety studies if adverse event reporting and active post-market risk identification and analysis system are inadequate to assess drug risks
  – FDCA § 505(o)(3)(D)

• Purpose of studies
  – Assess known, serious risk; signals of serious risk; or identify an unexpected serious risk when available data indicates the potential for a serious risk
  – FDCA § 505(o)(3)(D)

• FDA may impose post-approval study requirements on basis of “new safety information”
  – FDCA § 505(o)(3)(C)
Post-Approval Surveillance

- **FDA Sentinel Initiative**
  - Public/private effort led by FDA & Center for Medicare & Medicaid Services (CMS)
  - **Goal**: Create “Sentinel System,” an integrated, national, electronic system, for proactively tracking reports of adverse events linked to use of med. products

- **Drug Safety Website**
  - FDAAA required publicly-available labeling information, access to adverse event reports and summaries, and online submission of adverse event reports
F. Critical Path Innovation Meetings

- Developed as means by which CDER and investigators from industry, academia, patient advocacy groups & govt can communicate to improve efficiency & success in drug dev’t.

- Goals:
  - (1) To discuss a methodology or technology proposed by the meeting requester; and
  - (2) for CDER to provide general advice on how this methodology/tech might enhance drug dev’t.

- Potential topics:
  - Trial design (e.g., natural history study designs)
  - Biomarkers
  - Clinical endpoints (e.g., patient-reported outcomes)
  - Emerging technologies or new uses of existing technologies

- Stakeholders may submit a request for CPIM

Guidance: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/critical-path-innovation-meetings
Thank You

Questions?
EMulkey@goodwinlaw.com