Statutory Framework for Drug Regulation

Drugs

- Investigational Use
  - Investigational New Drug Application (IND)

- Pre-Market Approval Applications
  - §505(b)(1) NDA
  - §505(b)(2) NDA
  - §505(j) ANDA

- Over-the-Counter (OTC) Non-Rx Drugs
  - Monograph
Legal Standard for Drug Approval

• §505(d) of the FD&C Act:
  • adequate tests of safety by all methods reasonably calculated to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling;
  • results of such tests that show that the drug is effective for the intended use;
  • substantial evidence that drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling;
  • manufacturing, processing and packing is adequate to assure identify, strength, quality and purity.

• “substantial evidence” (§505(d)(7))
  • Adequate and well-controlled investigations (including clinical) by trained experts qualified to evaluate effectiveness for the intended use.
Adequate Tests of Safety

- **Policy:** risk/benefit ratio determination

- **Considers**
  - Dosage (amount and form)
  - Intended use
  - Patient population
  - Route of Administration (ROA)

- **Procedure**
  - Animal Pharmacology studies
  - Animal Toxicology studies
  - Human pharmacokinetics and bioavailability
  - Clinical data and adverse event reports (AERS)
“Substantial Evidence” of Effectiveness

- Adequate and well-controlled studies (21 CFR 314.126)
  - Clear protocol (clear objective and design)
  - Control (placebo or alternative treatment or both)
  - Careful selection of subjects (selection criteria)
  - Minimize bias (blinding)
  - Means of assessing effectiveness (endpoint)
  - Standardized product (id, strength, quality, purity, dosage form)
  - Comply with IRB and informed consent regulations (21 CFR 56)
  - Comply with Good Clinical Practice rules (21 CFR 50 and 54)
“Substantial Evidence” of Effectiveness

- What quantity of evidence is required to meet the “substantial evidence” threshold?
  - Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998) (p.3): “at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.”
  - 505(d) of the FD&C Act (enacted by the FDA Modernization Act of 1997) allows Agency to consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence.”
- Rationale: Independent substantiation, but flexibility
Investigational New Drug Application (IND)

- IND is the exemption from the bar on interstate transport of an unapproved new drug;
  - Submitted after drug sponsor has evaluated pharmacological activity and acute toxicity in animals and chemical entity is ready for therapeutic benefit for humans;

- Three types
  - Investigator (typical model for new drug approval)
  - Emergency Use IND (investigational product)
  - Treatment IND (initial studies show benefit for serious or life-threatening condition)
IND

- Under 21 CFR 312.23, IND (Form 1571) must contain three broad categories of information:
  - Animal pharmacology and toxicology studies ((a)(8));
  - Manufacturing information ((a)(7));
  - Clinical protocols ((a)(6)) and investigator information ((a)(3) and (5)).

- 30-day notice period for FDA to review before clinical trials may proceed
IND

Exceptions to the IND requirement:

- 21 CFR §312.2(b)(1): Clinical investigation of a drug product that is legally marketed in the U.S. if:
  - Not intended to be reported as an adequate and well-controlled clinical trial;
  - Not intended to support change in advertising;
  - Does not involved route of administration, dosage level, or patient population that significantly increases the risks (or decreases the acceptability of the risks) of use
  - IRB (21 CFR 56) and Informed Consent (21 CFR 50); and
  - No promotion of the investigational or off-label use (21 CFR 312.7)
IND

- Exceptions to the IND requirement (cont.):
  - Blood-related IVD of another IVD is confirming test (21 CFR 312.(b)(2))
  - Drug intended for *in vitro* or animal use (21 CFR 312.2(b)(3))
Meetings with FDA

- Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants (2009)
  - Type A:
    - Necessary for stalled effort (dispute, clinical hold, Special Protocol Assessment (21 CFR 10.75, 312.48, and 314.103; see also Formal Dispute Resolution Guidance)
  - Type B
    - Pre-IND, End Phase 1 (21 CFR 312.82)
    - End Phase 2/Begin Phase 3, Pre-NDA/BLA (21 CFR 312.47)
  - Type C
    - Other
  - Process: request, scheduling, meeting package, questions, meeting, minutes

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3 Phases of Clinical Trials

- **Studies must be adequate and well-controlled** (21 CFR 314.126)

- **Pre-IND Consultation Program** (21 CFR 312.82(a))

- **Phase I** (21 CFR 312.219(a))
  - Initial introduction in humans
  - Number of Participants: 20-100 participants
  - Length: Several months
  - Purpose: study safety (metabolism, pharmacologic activity, PK, PD information)
  - 70% success rate at Phase I (across all classes)
3 Phases of Clinical Trials

- **Phase II** (21 CFR 312.20(b))
  - Number of Participants: several hundred
  - Length: several months to years
  - Purpose: mainly effectiveness, but some safety (short-term side effects)
  - 33% success rate at Phase II (across all classes)

- **Phase III** (21 CFR 312.20(c))
  - Number of Participants: several hundred to thousands
  - Length: 1-4 years
  - Purpose: effectiveness, safety and dosage
  - 25% success rate at Phase III (across all classes)
Stages of Drug Development

Phase 1
21 CFR 312.219(a)
Safety

Phase 2
21 CFR 312.20(b)
Efficacy
Safety
Dose-Ranging

Phase 3
21 CFR 312.20(c)
Efficacy
Safety

NDA Submission
Data to support safety and efficacy determination

NDA Supplement
Efficacy, some safety

Phase 4/ Post-marketing
Safety
Efficacy

Clinical Studies Completed Under IND

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Basic Drug Requirements

- Establishment registration, annually (21 CFR 207.21(a))
- Product listing (21 CFR 207.21(b))
- Labeling is not False and Misleading (21 CFR 201)
- Drug Adverse Event Reporting (21 CFR Part 310)
§505(b)(1) NDA

- §505(b)(1) of the FD&C Act
  - Full scale application after 3-phase Investigation of drugs safety and efficacy
  - New Drug Application (NDA)

- 21 CFR 314.50 (Content and Format):
  - Chemistry, Manufacturing and Controls (CMC) data
  - Non-clinical pharmacology and toxicology
  - Human pharmacokinetics and bioavailability
  - Clinical data
  - Statistical analysis
  - Pediatric data (*)
§505(b)(1) NDA

- 21 CFR 314.50 (Content and Format, continued):
  - Labeling
  - Case report forms and tabulations
  - Any right of reference obtained
  - Patent information re: article subject of the application
  - Any claim of marketing exclusivity under 21 CFR 314.108 for
    - New Chemical Entities (NME) = active moiety not previously approved
§505(j) ANDA

  - Created abbreviated approval pathway at 505(j) for generic versions of approved (“reference”) drugs.
  - Abbreviated New Drug Application (ANDA)
    - ANDA approval for bioequivalent copies of innovator drugs without costly clinical trials
    - reduced clinical portfolio = lower cost medications
    - greater competition with innovator = lower cost medications
505(j) ANDA

- A “generic” drug is therapeutically equivalent to and substitutable for the approved brand-name, or “innovator” drug.

- 505(j) requires applicant to demonstrate therapeutic equivalence:
  - pharmaceutically equivalent (same active ingredient, dosage form, route of administration, strength, conditions of use) and
  - bioequivalent to the listed drug (the rate and extent of absorption of the drug do not show a significant difference from that of the listed drug)
505(j) requirements (cont.)
- Identical labeling as listed drug
  - Patent not filed;
  - Patent expired;
  - Date of patent expiration;
  - Patent is invalid and will not be infringed by mfr., use or sale of drug for which ANDA is submitted. (“Paragraph IV Certification”)
- Application must include bioequivalence data, CMC data, and labeling.
- Petition may be made for changes in route of administration, dosage form, strength, etc.
- 6 Month Marketing Exclusivity for 1st to Successfully Challenge Innovator Patent
505(b)(2) NDA

- Added by Hatch-Waxman, like (b)(1) NDA, but:
  - based on “investigations...relied on by the application for approval of the application [that] were not conducted by or for the applicant and for which the applicant has not obtained a right of reference.” (§505(b)(2) of the FD&C Act; see also Guidance for Industry: Applications Covered by Section 505(b)(2))

- May rely on any combination of the following:
  - New clinical data;
  - Published literature; or
  - FDA’s prior safety and efficacy determination for the listed drug (“follow-on approach” to reference product).
505(b)(2) NDA

- Application ideal for variations on an innovator product that require additional clinical study;
- For “follow-on” (b)(2) applications, applicant “may rely on FDA’s finding only to the extent that the proposed product in the 505(b)(2) application shares characteristics [examples removed] with the listed drug.” (5/30/06 Omnitrope Citizen Petition Response)
- To extent innovator and follow-on are different, sufficient data must be provided to demonstrate safety and efficacy (21 CFR 314.54(a))
The following are examples of changes to approved drugs which would fall under the 505(b)(2) mechanism, as included in the FDA’s 1999 Draft Guidance on 505(b)(2) applications:

- Changes in dosage form, strength, formulation, dosing regimen or route of administration
- A new combination product, including substitution of an active ingredient
- A modified active ingredient (i.e. – salt, chelate, ester, complex, etc.)
- New indications for previously approved drugs
- Over-the-counter switch of an approved prescription drug.
505(b)(2) NDA

- Patent certifications required as in ANDA scenario;
- Applicant can earn 3 (clinical investigations) or 5 years of marketing exclusivity (new chemical entity);
- **Benefits**: reduced clinical trial portfolio, costs and time to market;
- **Risks**: challenge to determine the data required to demonstrate safety and efficacy and required close collaboration with FDA.
  - 21 CFR 314.54: “application need contain only that information needed to support the proposed modification(s) to the listed drug.”