Drug Development and “Incrementally Modified Drugs”: Regulatory Perspective

American Association of Pharmaceutical Scientists
October 27, 2015

Larissa Lapteva, M.D., M.H.S.,
Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Incrementally Modified Drugs

• Known Active Pharmaceutical Ingredient with modifications made to the drug product

• Increased effectiveness
• Reduced side effects
• Reduced or more predictable drug-drug interactions
• Improved dosing regimen and increased compliance
• New patient population
• Other
Modification of Pharmaceutical Products

• **Chemical or Molecular modification**
  • Polar functional groups to improve water solubility or lipid solubility
  • Acidic and basic groups to form different salts
  • Aromatic acid group to enhance anti-inflammatory activity

• **Drug Delivery modification**
  • Permeability enhancement
    » Intestinal membrane permeation enhancers
    » P-glycoprotein inhibitors
    » Surfactant vehicles
    » Ion pairing
  • Solubility enhancement
    » Particle size reduction
    » Solid dispersion and co-crystallization
    » Complexation
  • Modified release
    » Delayed, sustained, extended, pulsatile
  • PEGylation to delay drug clearance
  • Targeted delivery and local delivery
Modification and Repurposing of Pharmaceutical Products

- Modification and repurposing of pharmaceutical drug products are common
  - Off-target effects
  - Multiple mechanisms of action
  - Newly understood product’s effects
  - Recently discovered disease mechanisms

- A product may be modified and repurposed at any stage
  - Investigational product in ongoing development
  - Investigational product from a discontinued program
  - Approved product repurposed for another indication or reformulated for a target effect
  - Dietary supplement showing promise as a treatment for a disease
Overview of Drug Development

NIH/ Academia

Basic Science

Translational

Pre-IND

Clinical/IND phases

FDA Interactions

Drug Developers

Ph 1

Ph 2

Ph 3

NDA/BLA Review

Post-marketing

Ph 4

undefined

~5-10 years

~5-10 years

ongoing

Courtesy of Larry Bauer, RDP/FDA
Regulatory Mechanisms for Review and Approval of Pharmaceutical Products with Available Information

- IND application exemptions
  - IND applications for botanical products
- Pre-IND
- IND application
- NDA or BLA application
- Approval
- Post-Marketing
- Generic drugs
- Reference to previously submitted technical information from another IND application
- 505 (b)(2) pathway
- 505 (j) pathway
IND APPLICATION EXEMPTIONS
Exemptions from IND Application Requirements

A study may be exempt from the IND application requirements if the study:

- Involves a lawfully marketed in the US pharmaceutical product AND
  - Conditions for exemption described under 21 CFR 312.2 (b) are met

OR

- Is a bioavailability or bioequivalence study with a copy of an approved drug product AND
  - Conditions for exemption described under 21 CFR 320.31(b) and (d) are met

OR

- Involves radioactive drugs that are generally recognized as safe and effective for the proposed use AND
  - Conditions for IND exemption described in 21 CFR 361.1 are met
Clinical Investigation with an Approved Drug Product Repurposed for Another Use

Criteria for exemption from the IND regulations (21 CFR 312.2(b)):

- There is **no intent** to report the investigation to FDA as a *well-controlled study in support of a new indication* and no intent to use it to support any other significant change in the **labeling** of the product.

- The investigation is **not intended** to support a significant change in the **advertising** of the product.

- The investigation does **not involve a route of administration, dose, patient population, or other factor that significantly increases the risk** (or decreases the acceptability of the risk) associated with use of the drug product.

- The investigation is conducted in compliance with the requirements for review by an **IRB** (21 CFR 56) and **Informed Consent** (21 CFR 50).

- The investigation is **not intended to promote or commercialize** the drug product (21 CFR 312.7).
Exemptions from IND Application Requirements


Two more categories:
- Cold Isotopes
- Dietary Supplements
DIETARY SUPPLEMENTS AND BOTANICAL PRODUCTS
Dietary Supplements (DS)

Under the Dietary Supplement Health and Education Act (1994), a dietary supplement is not a drug
  - DS may include: vitamins, minerals, herbs, amino acids, concentrates, metabolites, and combinations of ingredients

If the clinical investigation is intended to evaluate DS’s effect on the structure or function of the body, an IND application is not required

If the clinical investigation is intended to evaluate DS’s ability to diagnose, cure, mitigate, or prevent a disease, an IND application is required
IND Applications with Botanical Products

- Botanical products are finished labeled products that contain vegetable matter as ingredients.

- If a botanical product is intended for use in diagnosing, mitigating, treating, or curing a disease, it is considered a drug under section 201(b)(1)(B) of the FDCA and would be subject to the IND application submission requirements.

- Chemistry, manufacturing and controls information needed to support initial trials under IND applications with legally available botanical products with no safety issues may be markedly reduced compared to other investigational products.

Guidance for Industry: Botanical Drug Products
REFERENCE TO AVAILABLE INFORMATION
Right of Reference to Available Information for Investigational New Drug (IND) Applications

- **21 CFR 312.22**
  - An investigator who uses for their research an investigational new drug that is already a subject to a manufacturer’s IND or marketing application may, if authorized by the manufacturer, refer to the manufacturer’s IND or marketing application in providing the technical information to support the proposed investigation.

- For example, a Letter of Authorization may be obtained from the product’s manufacturer for reference to materials submitted to FDA, such as:
  - Pharmacology Toxicology (PT) studies
  - Chemistry, Controls, and Manufacturing (CMC) information

- Product’s manufacturer may be holding an IND application, and/or the marketing authorization, and/or the product’s Drug Master File* on file with FDA.

*http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm
Reference to Available Information for New Drug Applications (NDA) 505(b)(2) Pathway

- A 505(b)(2) application is an application submitted under section 505(b)(1) for which the investigations the applicant relied on for approval were not conducted by or for the applicant and the applicant has not obtained a right of reference or use for the investigations (21 U.S.C. 355(b)(2))

- Section 505(b)(2) expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant - such as published literature or FDA’s finding of safety and/or effectiveness of a previously approved drug product
Examples of 505(b)(2) applications

- New dosage form
- New route of administration
- Substitution of an active ingredient in a combination product
- New dosing regimen
- New indication
- New active ingredient (same active moiety but reformulated as a different salt, ester, complex, etc.)

Draft Guidance for Industry: Applications Covered by Section 505(b)(2)
# New Drug Applications Approved in 2011-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>All Approved Applications *</th>
<th>Applications Approved under 505(b)(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>105</td>
<td>51 (49%)</td>
</tr>
<tr>
<td>2013</td>
<td>94</td>
<td>40 (43%)</td>
</tr>
<tr>
<td>2012</td>
<td>94</td>
<td>48 (51%)</td>
</tr>
<tr>
<td>2011</td>
<td>93</td>
<td>56 (60%)</td>
</tr>
</tbody>
</table>

* Excluding tentative approvals

Drug and Biologic Approval Reports
Communications with FDA

- Advice for development of a repurposed (incrementally modified) product could be obtained from FDA at any stage of development:
  - Pre-IND consultation
  - IND application and related communications
  - End-of-Phase 2 meeting
  - Pre-NDA (pre-BLA) meeting

- Communication with FDA at early stages and throughout the product development is recommended

Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants
Making Generic Drugs Available

- Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) -- 1984
- Today, 86% of all prescribed medicines in the US are generic drug products
- Generic Drug User Fee Act (GDUFA) -- 2012

Generic Drug Product Substitutability

• In relation to the Reference Listed Drug, generic products are expected to be:
  • Pharmaceutically Equivalent
    • The same active ingredient, dosage form, strength, route of administration and meet the same compendial Standards (strength, quality, purity, and identity)
  • Bioequivalent
    • No significant difference in the rate and extent of absorption of the active ingredient
  • Therapeutically Equivalent
    • The same safety and efficacy when used in the indicated population according to the labeling recommendations
21 CFR 320.24

- FDA may require in vivo or in vitro testing, or both, to establish the bioequivalence of specific drug products. The method used must be capable of establishing bioequivalence, as appropriate, for the product being tested...
  - In vivo test in which the concentration of active ingredient in a biological fluid is measured as a function of time
  - In vitro test that has been correlated with and is predictive of in vivo bioavailability
  - In vivo test in which the urinary excretion is measured as a function of time
  - In vivo test where an acute pharmacological effect of the active moiety is measured as a function of time
  - Well-controlled clinical trials to demonstrate bioequivalence
  - A currently available in vitro test acceptable to FDA
  - Any other approach deemed adequate by FDA to establish bioequivalence
Determination of Generic Drug Product’s Equivalence to its Reference Listed Drug

- It is expected that manufacturers conduct testing using the most accurate, sensitive, and reproducible approach.
- The choice of methodology used for establishing and ensuring Therapeutic Equivalence throughout product’s lifecycle will involve considerations for:
  - Formulation design
  - Product composition
  - Site of action
  - Mechanism of drug delivery and release
  - Ability to measure drug’s availability at the site of action
  - Expected and measured therapeutic effects and their relationship to drug concentration
  - Other factors related to patient-product interaction
When It May be Challenging to Demonstrate Therapeutic Equivalence

- Locally-acting
- Drug-device combos
- Unspecified mixtures, naturally derived API
- Products with specific mechanisms of release or target delivery
- Nano-products
- Other products as new technologies emerge

- Skin
- Ophthalmic
- Otic
- GI tract
- Implants
- Periodontal

- Oral Inhalers
- Nasal Sprays and Aerosols
- Injectables
- Transdermal Delivery Systems

- Peptide products, unspecified mixtures, naturally derived products

- Prodrugs
- Osmotic pumps
- Delayed release systems
- Liposomes Microspheres

- Nanoemulsions
- Nanocrystals
- Nanotubes
- Gold and silver colloids
- Protein-drug complexes
Identification and Measurement of Factors Influencing Patient-Product Interaction

- Identification of the formulation and manufacturing factors that are critical to interaction with the specific tissues
  - lung, eye, GI environment, skin, muscle, etc.
- Finding and validating adequate measurements
  - PD parameters, clinical endpoints, cellular markers, microdialysis, artificial and in vitro created organoid systems, SNPs in GI transporter systems
- Improving specific drug delivery systems
  - liposomal delivery: retaining drug inside liposomes, rapid clearance of liposomes by mononuclear phagocytes, delivery to intracellular sites
- Clinical endpoint studies to demonstrate BE have to fit for purpose
  - Adequately chosen endpoint
  - Effect of change in inactive ingredients
Regulatory Pathways For Generic Drug Product Development

- Controlled Correspondence
- Pre-ANDA Meetings
- Product-Specific Recommendations
- INDs for bioequivalent studies outside of the exemption rules
Controlled Correspondence (CC)

- Guidance for Industry: *Controlled Correspondence Related to Generic Drug Development*

- Specific questions about individual product development programs
  - Evaluation for eligibility for BE study waivers
  - Product composition
  - Study design issues
  - Any aspect of a new generic drug development program

- 60 day response time for each CC
Product-Specific Recommendations For Generic Drug Development

- Recommendations on programs and strategies for generic drug product formulation development and bioequivalence demonstration
Pre-ANDA meetings

- Relatively new practice for Office of Generic Drugs
- Meeting requests may be granted with a face-to-face communication, a teleconference, or written responses
- Multidisciplinary team approach to managing meetings
- Submit a request with a meeting package to GenericDrugs@fda.hhs.gov
FDA’s Office of Generic Drugs Regulatory Science Program (RSP)

• Research grants awarded on a competitive basis every year
• Funds allocated under GDUFA to stimulate innovation and growth in the generic drug field
  • Identify, study, and implement new methodologies and tools to be used in development and evaluation of quality and equivalence of new generic drug products in all therapeutic areas and various product categories
• FDA holds an annual public meeting with multiple stakeholders to provide an opportunity for public input on research priorities in generic drug development and regulation

http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm
In Summary...

- Incremental innovation is common in all industries and is intended to improve products and services.
- Pharmaceutical Industry knows many examples where “second mover’s advantage” has been shown to be beneficial.
- There is a number of regulatory pathways in place for development and approval of incrementally modified and repurposed pharmaceutical products.
- Early communications with FDA on the intent of product development and design help streamline testing strategies, shorten development time, and make review and approval more predictable.
Thank you!