FDA Regulation of the New Drug And Device Approval Process

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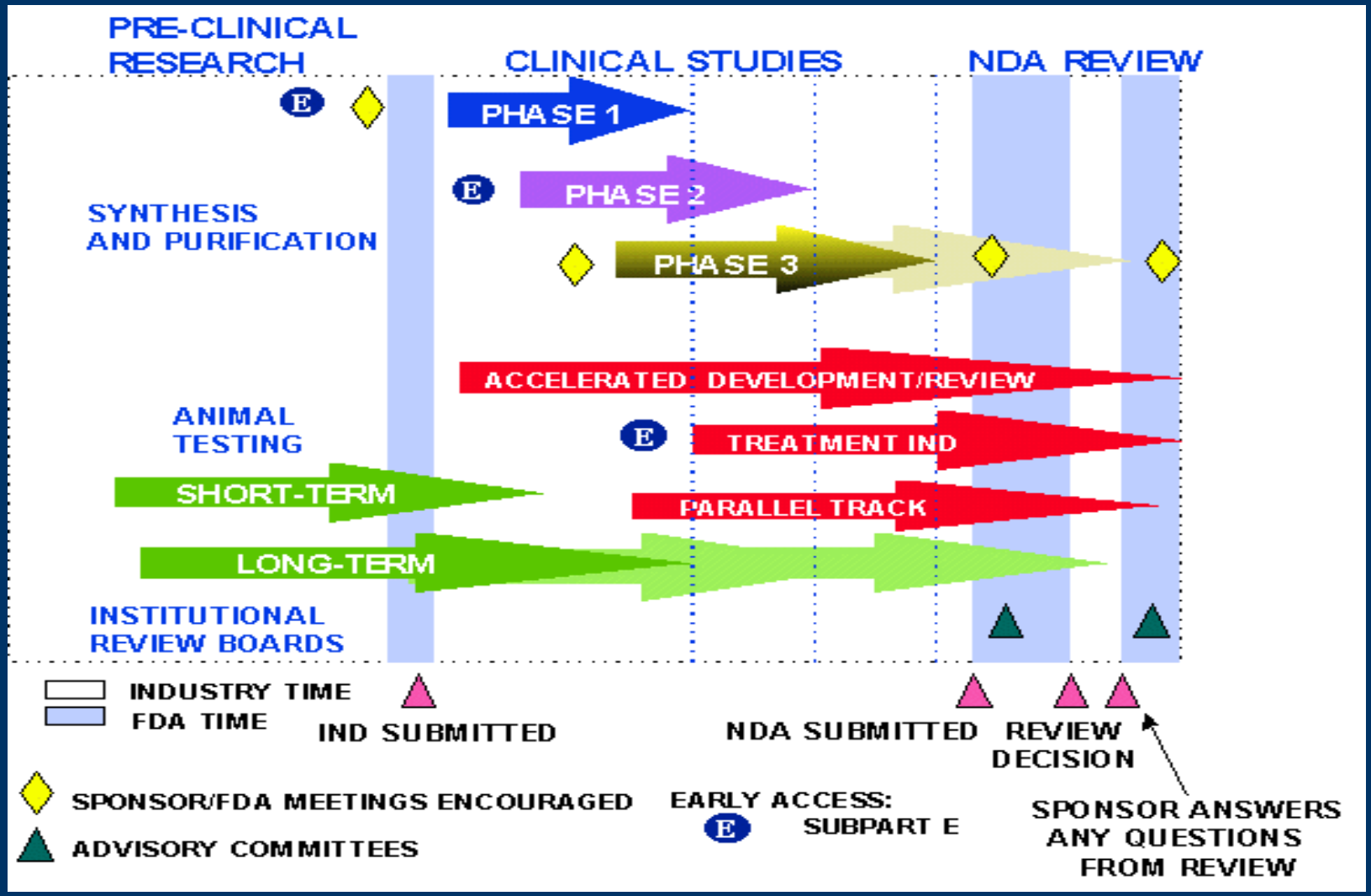
Agenda

- Classifying your Product
- Testing your Product
- Pathways to Market
- Filing an Application
- Expediting Approval
- “Generic” drugs
- Hot Topics

New Drug Development Timeline



Classifying Your Product

FDA Regulated Therapeutic Products

- Drugs (CDER)
  - Rx
  - OTC
- Biologics (CBER & CDER)
- Medical Devices (CDRH)
  - Restricted
  - Not restricted
- HCT/Ps (CBER, CDRH, CDER)

Drugs v. Medical Devices

- Type of product:
  - DEVICE: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory
  - DRUG: An "article" (other than food, for S/F claims)
- Intended to:
  - diagnose, cure, mitigate, treat, or prevent disease, or
  - affect the structure or any function of the body
- Mechanism of Action (Device):
  - does not achieve its primary intended purposes through chemical action within or on the body, and
  - which is not dependent upon being metabolized for the achievement of its primary intended purposes

Classification of Devices

- Class I – Least Risk
  - Most are exempt from premarket review
  - Subject to "general controls"
- Class II – Intermediate Risk
  - Most require clearance of a premarket notification (510(k))
  - General + "Special" controls" (e.g., standards, guidances)
- Class III – Highest Risk
  - Require premarket approval application (PMA)
  - Can be "restricted" device

How Do I Find My Device Classification?

- FDA Classification Database
- 16 "Panels" w/individual regulations

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 866 -- IMMUNOLOGY AND MICROBIOLOGY DEVICES

Subpart C--Microbiology Devices

Sec. 866.2560 Microbial growth monitor.

(a) *Identification.* A microbial growth monitor is a device intended for medical purposes that measures the concentration of bacteria suspended in a liquid medium by measuring changes in light scattering properties, optical density, electrical impedance, or by making direct bacterial counts. The device aids in the diagnosis of disease caused by pathogenic microorganisms.

(b) *Classification.* Class I. With the exception of automated blood culturing system devices that are used in testing for bacteria, fungi, and other microorganisms in blood and other normally sterile body fluids, this device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter.

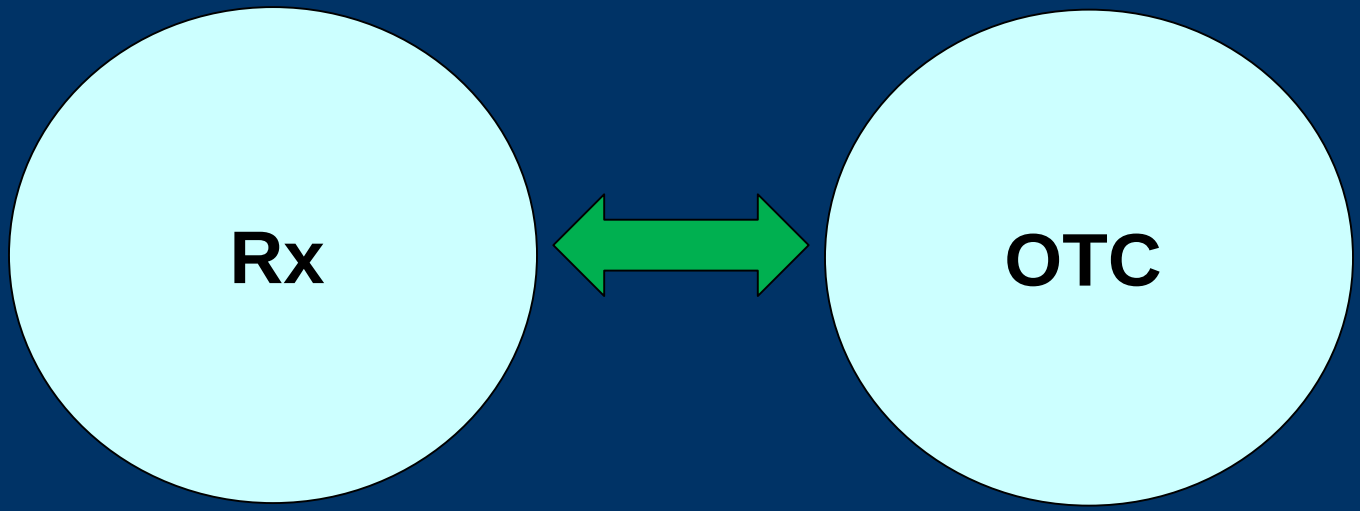
[47 FR 50823, Nov. 9, 1982, as amended at 60 FR 38482, July 27, 1995]

Can I Change a Device's Classification?

- Reclassification Petition
  - Formal mechanism to reclassify a device type
  - Historically lengthy process
  - Changes as a result of FDASIA
- De Novo Process
  - Post-FDASIA, two routes
    - After receipt of an NSE letter; or
    - Applicant can directly submit a de novo request
  - Historically lengthy, but now 120-day clock

Combination Products

Drug Classifications



- “Drug” v. “new drug”
- NDA’d versus monograph OTCs

Drug v. Biologic

Biological Product (PHSA § 262(i)): "A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide) or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

- Overlap with definition of drug
- Many biologics regulated by CDER, not CBER

Testing Your Product

The IND/IDE

- Generally illegal to introduce a medicinal product into “interstate commerce” w/o FDA clearance/approval
- But clinical trials often required for product approval
- Statute includes special exemption
  - Drugs/Biologics = IND
  - Devices = IDE
- Permits shipment in interstate commerce for sole purpose of conducting required testing

Good Clinical Practice (GCP)

- Required for all drug clinical trials
- GCP exists in many places, e.g.
  - Part 312 -- IND requirements, e.g.
    - Selecting investigators
    - Monitoring ongoing investigations
    - Communicating with investigators
    - Control of investigational drug
    - Recordkeeping and reporting (e.g., safety)
  - Part 50 -- Informed consent
  - Part 54 -- Financial disclosure by clinical investigators
  - Part 56 -- Institutional Review Boards (IRBs)
  - Guidance (e.g., ICH E6)
- No GCP can mean no "substantial evidence"
  - But FDA may use results for safety

Risk Categories for Medical Devices

- "Significant Risk" (SR) Device
  - Presents a potential for serious risk to the health, safety, or welfare of a subject, and:
    - Is an implant;
    - Supports or sustains life;
    - Is for a use of substantial importance in diagnosis, mitigation, or treatment, or otherwise prevents impairment of health; or
    - Otherwise presents a potential for serious risk
- "Nonsignificant Risk" (NSR) Device
  - Does not meet SR criteria

Requirements for Device Studies

- SR Device Study
  - IDE application must be approved by FDA
  - IRB approval of investigational plan, etc.
  - Informed consent from study subjects
  - Full IDE requirements for reporting and recordkeeping
- NSR Device Study
  - IRB approval of investigational plan, protocol, informed consent
  - IRB must make affirmative determination that device is NSR
  - Informed consent from study subjects
  - Abbreviated IDE requirements (recordkeeping, reporting, labeling)

Hot Topics in Clinical Testing

- Clinical trials disclosure/transparency
- Subsequent testing on biospecimens
- Pre-approval promotion
- Expanded access

Pathways to Market

Medical Device Pathways

- Exempt Devices
  - Must have an exempt classification regulation
  - Subject to “general controls” but no premarket review
- 510(k) Notification
  - Show “substantial equivalence” to a “predicate device”
  - Generally subject to general and special controls
- Premarket Approval Applications (“PMAs”)
  - Must prove device is safe and effective through “well controlled” investigations
  - Can be “restricted” devices

"Least Burdensome"

- FDA must require "the least burdensome means" of demonstrating:
  - Substantial equivalence for 510(k) device
  - Effectiveness for PMA device
- Where clinical data are needed, FDA should consider alternatives to randomized controlled trials
- Concept is to be applied throughout device development process

Drug & Biologic Pathways

DRUGS

- **NDA:** New Drug Application
  - "Substantial evidence" of effectiveness
  - Safety via "adequate tests by all methods reasonably applicable"
- **ANDA:** Abbreviated New Drug Application
  - "Same as" the RLD
- **"505(b)(2)"** Application

BIOLOGICS

- **BLA:** Biologics License App.
  - "Safety, purity, and potency"
  - But standard similar to drugs
- **Biosimilar** Application
  - "Highly similar" to the RLD
- No equivalent?

"361" HCT/Ps

- An HCT/P is regulated solely under PHSA section 361 if all of the following apply:
  1. It is "minimally manipulated"
  2. It is intended for "homologous use"
  3. It is not combined with "another article"; and
  4. Either
     a) No systemic effect and not dependent upon metabolic activity of living cells for primary function; or
     b) It does but is for
        - » autologous use
        - » allogeneic use in close blood relative; or
        - » reproductive use
- Otherwise regulated as drug, biologic, or device

Filing an Application

New Drug Applications (NDAs)

- Statute and regulations
  - Section 505; Part 314
- Contents of an NDA, e.g.
  - Clinical/statistical
  - Chemistry, manufacturing, and controls (CMC)
  - Labeling
  - Pediatric assessments/REMS
  - Patents
- Common Technical Document (CTD)

NDA Approval Standards

- Adequate tests by all methods reasonably applicable
- Safe for all conditions of use

- "Substantial evidence"
- Adequate and well-controlled studies

NDA Approval Standards (Cont.)

- Chemistry, Manufacturing & Controls
  - Identity, strength, quality
- Labeling
  - Not false/misleading
  - Adequate directions for use
  - Warnings
  - Labeling negotiations can be critical
- Approval is product specific

PDUFA: User Fees

Industry pays $$ to support drug review
- Applications/supplements
- Annual product
- Annual establishment

- FDA financial triggers
- FDA performance goals
  - In “side letter”
- MDUFMA, GDUFA, BsUFA, etc.

FDA Review (cont.)

CDER Reviews

Reviews Complete & Acceptable?

NO

Sponsor Amendments

Advisory Committee Meeting?

Labeling Acceptable?

NO

Sponsor Revises

YES

Pre-Approval Inspection Acceptable?

NO

Pending Satisfactory Results

FDA Action

REMS

- Risk Evaluation and Mitigation Strategies
  - FDA may require pre-approval to ensure benefits > risks
- REMS Elements
  - Timetable for assessments (all REMS)
  - Medication guide
  - Elements to assure safe use
  - Implementation plan
- REMS assessments must be submitted periodically
- Statutory provision for drugs, not devices

Expediting Approval

Four Expedited Programs

- Accelerated approval
  - Approval pathway
- Priority Review
  - Shorter PDUFA clock
- Fast Track
  - "Unmet medical need" standard
- Breakthrough Therapy Designation
  - "Preliminary clinical evidence" standard
  - Intensive & high level FDA guidance

Accelerated Approval: The Basics

- **Available to drugs that:**
  1. Are intended to treat serious/life-threatening disease; and
  2. Provide a meaningful therapeutic benefit over existing therapies
- **Allows FDA to approve based on:**
  1. Surrogate endpoint "reasonably likely" to predict clinical benefit; or
  2. "Intermediate clinical endpoint"
- **In exchange, FDA gets:**
  1. Confirmatory clinical trials
  2. Streamlined withdrawal procedures; and
  3. Pre-review of promotional materials
  4. Labeling

Endpoints

- Surrogate endpoint
  - "Marker" "reasonably likely" to predict clinical benefit
    - E.g., tumor shrinkage, PFS(?), short-term suppression of viral load
  - Fully validated surrogate endpoints not eligible for AA
    - E.g., LDL cholesterol, blood pressure
    - 197/84/18 (between 2010 and 2014)
- "Intermediate Clinical Endpoint"
  - Clinical endpoint
    - that can be measured earlier than irreversible morbidity or mortality, that is *reasonably likely* to predict an effect on irreversible morbidity or mortality or other clinical benefit

Case Study: Avastin for MBC

- 1st line MBC granted accelerated approval in 2008
- E2100 Study as basis for accelerated approval
  - Avastin + paclitaxel v. paclitaxel alone
  - **FDA:** E2100 demonstrated 5.5 month difference in median PFS v. paclitaxel alone with no OS benefit
- Confirmatory clinical trials showed lower magnitude of PFS
  - FDA concerns with benefit-risk assessment
- FDA withdraws accelerated approval in 2011

Avastin Case Study: Lessons Learned

- Characterizations of endpoints not always clear
  - Disagreement within ODAC re PFS
- FDA has significant flexibility within AA program
- Physicians continued to use off-label
  - Impediment to FDA expansion of accelerated approval?
- FDA doesn't like hearings

Orphan Drug

- Conditions exist in < 200,000 people in the U.S.
- Or no way to recover cost

Orphan Drug Designation

Office of Orphan Product Development

FDA Assistance

- Grants
- Study Design Asst.
- User Fee Waiver

7 Year Exclusivity

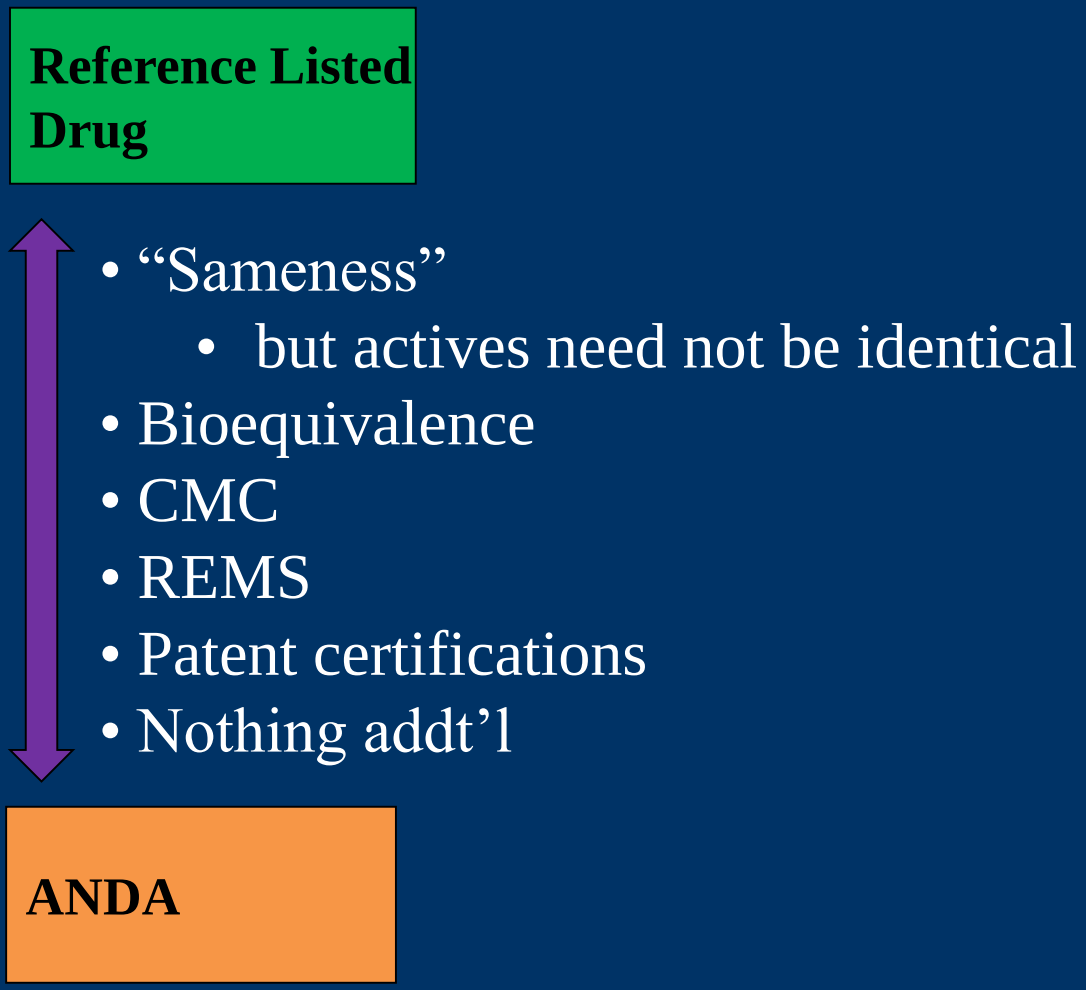
Generics

Hatch-Waxman Exclusivity

- Protects against ANDAs and section 505(b)(2) applications, but not full NDAs
- **5 year NCE exclusivity:** for new chemical entities, blocking submission of applications (4 years in certain cases)
- **3 year exclusivity:** ANDA/505(b)(2) cannot be approved for three years after NDA or sNDA approval; protection limited to innovation. Requirements:
  - Clinical investigations other than BA studies
  - Investigations are essential to approval
  - Investigations are conducted or sponsored by the applicant

Generic Drug Approval Process

- ANDAs: FD&C Act § 505(j)
  - Does not apply to biologics!

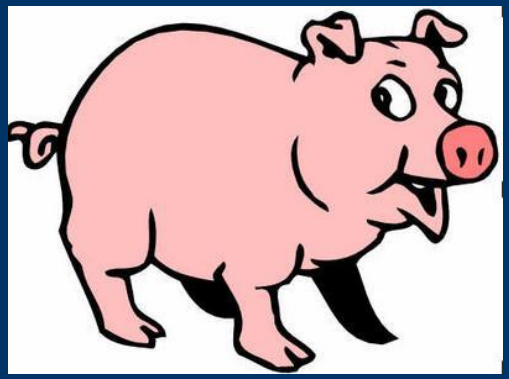


ANDA Process

- When can you file an ANDA?
  - Any time after expiry of 5-year Hatch-Waxman exclusivity
    - Or after four years if paragraph IV certification
- Can I file an ANDA for a drug that isn't "the same"?
  - Yes, if FDA approves a suitability petition
- What do I get?
  - A/B-rated approval w/o clinical trials
  - 180-day exclusivity?
- Is there an equivalent process for devices?
  - Technically, 6-year data exclusivity for PMA

"Sameness" Case Study: Enoxaparin

- Lovenox® (enoxaparin) most widely sold LMWH (anticoagulant)
- Pig gut → heparin → depolymerization → LMWH
- Changes to time/temperature of reaction = changes to LMWH
  - Process makes the product
- Not fully "characterized"
- Sanofi files CP: Can't know ANDA has the "same" active w/o
  - Clinical testing; or
  - Same manufacturing process
- FDA requires immunogenicity testing
- Ultimately adopts a "close enough" approach
  - Same ≠ identical



Biosimilars: Statutory Standards

- Created by the BPCIA in 2009
- "Biosimilar" to reference product (RP), i.e.,
  - highly similar notwithstanding minor differences in clinically inactive components and
  - no clinically meaningful differences in safety, purity, or potency
- Same mechanism of action, if known for RP
- Proposed conditions of use were approved for RP
- Same route of administration, dosage form, and strength
- Facilities meet standards designed to assure product safety, purity, and potency

Contents of a Biosimilar Application

- Application must contain data from:
  - Analytical studies demonstrating "highly similar" to the RP
  - Animal studies
  - Clinical studies (including PK, PD, and immunogenicity) sufficient to demonstrate safety, purity, and potency for one or more RP indications
- FDA may waive any "unnecessary" data requirements
- FDA Guidance: "Selective and targeted approach"?

Biosimilars: Key Issues

- **Interchangeability**
  - Not automatic
  - Separate application?
  - Higher standard than biosimilarity?
- **Naming**
  - FDA August 2015 draft guidance
  - Use of proper name with distinguishing suffix for non-interchangeable products
- **Foreign Comparable Products**
- **Extrapolation**

Hot Topics

Mobile Medical Apps

- FDA Guidance on MMAs – risk based system
  - MMAs are devices that (a) are accessories to medical devices, or (b) "transform the mobile platform into a regulated device"
  - FDA focus on MMAs whose "functionality could pose a risk to a patient's safety if [it] were not to function as intended"

HCT/Ps – *Regenerative Sciences v. U.S.*

- Regenexx Procedure
  - MSCs isolated from patient's bone marrow
  - Grown to greater numbers in cell culture media
  - Placed back in patient for regeneration of injured or degenerated areas
- No IND or product approval
- FDA alleges new drug, misbranding, and adulteration violations
- Regenerative Sciences sues in federal court
  - Court sides with FDA

Questions?

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