BioBootcamp 2016
REGULATORY AFFAIRS for DRUGS and VACCINES

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Part of Public Health Service, within Department of Health & Human Services

PHS consists of FDA, CDC, NIH, and other public health organizations (e.g. IHS)

FDA organized into Offices and Centers

HQ organized into Centers e.g. CDRH, CDER, CBER, CVM

Regional and District offices for inspections, labs, compliance
What is a Drug?

Defined in the 1938 FD&C Act:
- Articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals

Reviewed by:
- FDA’s Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER)
What is a Biologic?

Defined in Public Health Service Act of 1944

- Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man

Regulated by:

- PHS and FD&C Act
- Reviewed by FDA’s Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER)
Biologics

Well Characterized Biologics (review by CDER)
  o Recombinant proteins, antibodies

Allergenics
  o Allergen patch tests, allergenic extracts

Blood
  o Blood, Blood Components, Blood Bank Devices, Blood Donor Screening Tests

Devices
  o Medical devices and tests used to safeguard blood, blood components, and cellular products, blood typing reagents, machines used to collect blood and blood components.

Gene Therapy and Gene Therapy Products
  o Gene–based Treatments, Cell–based Treatments, Cloning

Tissue and Tissue Products
  o Bone, Skin, Corneas, Ligaments, Tendons, Stem Cells, Sperm, Heart Valves

Vaccines
  o Vaccines used for the prevention of infectious diseases, tuberculin testing

Xenotransplantation Products
  o Transplantation of Non–Human Cells, Tissues or Organs Into a Human
Vaccines (1 of 2)

- Definition
  - A substance used to stimulate the production of antibodies and provide immunity against one or several diseases, prepared from the causative agent of a disease, its products, or a synthetic substitute, treated to act as an antigen without inducing the disease.
Examples:
- Traditional (flu, polio, measles, rubella, TB, etc.)
  - Given to a non-infected person with the goal to prevent infection. Not individually tailored.
- Cancer vaccine
  - Treatment of patients with existing diagnosis of cancer
  - Train immune system to recognize damaged, abnormal, or transformed cells such as cancer cells via specific epitopes on the cancer cells. Look for the individual cancer cells hiding in body.
  - Challenging because there is no naturally acquired immunity against cancer cells – they exist because they have evaded detection by the immune system
  - Prepared from the causative agent, i.e. cancer cells, its products, or a synthetic substitute, treated to act as an antigen without inducing cancer and they stimulate an immune response
  - Types of cancer vaccines
    - Individual vaccine for each patient (Dendrion’s Provenge® for prostate cancer)
    - Use of an oncolytic virus, injected into the tumor or given systemically (Amgen’s T-VEC, Talimogene laherparepvec for inoperable melanoma, injected into tumor)
    - Dual-acting cancer vaccine/viral therapy
    - “Off-the-shelf” peptide or protein tailored to population of patients with a given cancer
    - Tissue- specific, tumor-specific, cancer testis, and tumor-overexpressed antigens
- Fecal Microbiota for Transplantation to treat Clostridium difficile infection not responsive to standard therapies
  - FDA Guideline: if use donor bank, must file an IND
Combination Products

- A product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product
  - Combination across at least 2 Centers
  - Reviewing Center is primary mode of action

- Examples:
  - Monoclonal antibody with a therapeutic drug
  - Drug-eluting stent
  - Transdermal patch
  - Biologic in a drug delivery system
  - Pre-filled syringe
Regulatory Basis for Approval:
- An application that contains full reports of investigations of safety and effectiveness, but where at least some of the data/information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (NDA Section 505(b)(2))

Reasons for Popularity:
- Drug already works, acceptable/understood safety profile
- Old dog, new tricks (formerly called “paper NDA”)

Examples:
- New formulation (immediate to extended release)
- New delivery system (SC to nasal spray, IM to transdermal patch)
- New clinical indication (antirejection drug to eye drops for dry eye)
- Literature-based application (long history of use)
- Unapproved medicinal product (“grandfathered”)

Repurposing Old Drugs
Drug Development is...

- The process of obtaining information for inclusion in the Package Insert for a drug or biologic intended for the cure, mitigation, treatment or prevention of disease

- “Target Product Profile” is a list of desired attributes for the drug, and is a useful roadmap for the drug development process
End Product of Drug Development

FULL PRESCRIBING INFORMATION/PACKAGE INSERT

- Boxed Warning
- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations (pregnancy, labor and delivery, nursing mothers, pediatric, geriatric)
- Drug Abuse and Dependence
- Overdosage
- Description
- Clinical Pharmacology
- Nonclinical Toxicology
- Clinical Studies
- References
- How Supplied/Storage and Handling
- Patient Counseling Information

(21CFR 201.56, FDA Jan 2006 Guidance Documents)
Stages in Drug Development: Preparing for IND Application

- Identification of Target Molecule
- In Vitro/In Vivo Models
- Clinical Supply Manufacture (CMC)
  - GMP regulations
- Nonclinical (IND-enabling in vivo/vitro studies, animal safety studies, genotoxicity, PK/ADME)
  - Some under GLPs
- Clinical Protocol, Site and Investigator Selection
  - GCP regulations
- Pre-IND Meeting
- IND Preparation and Submission
GxPs in Drug Development*

GLP
Pre-clinical Tox/ADME

GMP for Clinical Products
Phase I Safety

Full GMP
Phase II Efficacy

FDA Approval
Phase III Pivotal

Full GMP
Commercial Manufacturing

Pre-IND
IND
NDA/BLA
Phase IV Commitments

* The arrows overlap
CMC Tasks (GMPs)

- Proof of Structure
- Analytical method development and assay
- Formulation, dosage form
- Stability, forced degradation, real-time ICH, methods
- Process Development and Scale-up
- Technology Transfer
- Manufacturing Facility (API, final dosage form, contract vs in-house)
- Specification Development
- Manufacture Clinical Trial Supplies (GMP, quality systems, validation)
- Supply Chain (vendor selection, qualification)
- Matching Placebo
- Packaging, Shipping and Labeling
IND Enabling Nonclinical Studies

- Animal models (in vitro and in vivo efficacy studies, preliminary safety information)
- ADME and PK studies
- Animal toxicology (GLP)
- Genotoxicity (GLP)
- Safety pharmacology (GLP)
- Bioanalytical methods (GLP, validated)
- FDA and ICH guidances available
Animal Safety Studies

- Same route of administration as the intended clinical route
- Test article should be as close to clinical material as possible (drug and impurity profile), but GMP not required
- Goals:
  - Identify potential toxicities in humans (target organ), plans for human safety monitoring
  - Safety margin for human dosing (x-fold above top human dose)
  - Identify target blood levels for efficacy modeling
  - Potential biomarkers for safety or efficacy
  - Qualify the impurities in the clinical material
Seeking FDA Advice: Pre–IND Meeting

- Opportunity to discuss initial clinical study, adequacy of the nonclinical program to support study, and development plan
- Pre–IND is the first time to discuss program with FDA, so not necessarily always first-in-human
- Strongly recommended where there are potential issues
- Make good use of this meeting. The next one is at the end-of-phase 2 (unless special designation)

Logistics
- From submission of meeting request = approximately 8–10 weeks. Meeting Information Package due 30 days before meeting
- Structured meeting, ~60 minutes (rarely 90 minutes). Could be face-to-face or teleconference. FDA is trending towards Written Response Only (WRO) for pre–IND meetings
- FDA will issue preliminary comments (>24 hours before meeting) and final, non-binding meeting minutes (approx. 30 days after meeting)
Requirement for IND Submission

- Required to study unapproved drugs (not approved in the US) in humans
- May be required to study approved drugs for new indications, or approved drugs in a new dosage form
- INDs may be opened for first in human studies or for drugs in later stages of clinical development (if clinical studies initiated ex-US)
- FDA has issued other IND requirements for specific situations
IND Application to FDA

- Compilation of CMC, nonclinical data, and clinical plans
  - Rationale for clinical indication (disease models, description of indication)
  - Results from nonclinical studies, safety margin, and rationale for why studies support intended clinical use (animal species, receptors)
  - CMC data, drug substance, drug product (CofA for clinical lot)
  - Rationale for initiating clinical program and clinical trial design
  - Clinical protocol, Investigator Brochure, clinical investigator qualifications, outline of first year’s clinical trials

- Paper (until May 2018) or electronic filing
  - First-in-human IND = equivalent of 10–14 volumes ~ 300 pages each.

- FDA has 30 days to review (primarily safety)
- Negative veto system, IND is NOT approved by FDA
  - No news is good news. May receive an IND May Proceed Letter.
IND Maintenance

- Clinical
  - New Protocols, new investigators, and amendments to protocols
  - Clinical safety reports (7- and 15-day expedited reports)
  - Clinical updates, revised Investigator’s Brochure

- CMC updates
  - Stability
  - Manufacturing changes and scale up
  - Analytical method development and validation
  - Improved/final dosage form for market
  - Phase 3 material – should be comparable to planned market supplies
  - Identify commercial manufacturer

- Nonclinical updates
  - New nonclinical reports (longer dosing, repro tox, carcinogenicity, etc.)

- Annual reports
Phase 1 First in Human (FIH)

- Healthy subjects or patients (depending on potential toxicities)
  - Chemotherapy agents tend to have FIH in patients
  - If genotox signal, only single dose allowed in healthy subjects
- Starting dose defined by animal toxicity studies
- Phase 1a – Single escalating doses (SAD) given until Maximum Tolerated Dose (MTD) or Maximum Feasible Dose is reached
- Phase 1b – multiple escalating doses (MAD) given to define maximum tolerable dose for repeated administration
Phase 1 (Safety)

- Objective: investigate the safety and tolerability profile of the drug, **not efficacy**
- Pharmacokinetic information on the absorption, distribution and clearance of the drug (systemically absorbed drugs)
- Defines the safe range of doses for future studies (MTD)

- Additional Phase 1 studies may be required later in development: eg, DDI, PK in special populations (elderly, pediatrics, hepatic or renal impairment), TQT, food effects, etc.
Phase 2: Safety, Dose Ranging, Preliminary Efficacy

- Performed in patients/target population
- Starting dose and dose range defined by Phase 1 SAD/MAD study
- Goals of Phase 2
  - Identify target population
  - Dose ranging to define regimen
  - Collect safety information in the target patient population
  - Clinical effects that will be used to design pivotal studies
    - Dose/response
    - Onset time
    - Duration of effect
    - Endpoints: disease endpoint or biological marker to predict response
- Study Designs
  - Controlled (placebo or active) and randomized
    - To collect statistically significant efficacy data
    - Potential support for efficacy package
  - Non-controlled (no placebo or active control, open-label)
    - Proof-of-concept data but usually not used to support regulatory approval
    - Could compare to historical controls (e.g., a similar population treated with current standard of care)
Agreement that company and study design are ready for Phase 3

Clinical Questions
- Clinical population
- Dose, dosing regimen, trial design, endpoints
- Statistical analysis plan, sample size, stats power
- Number of pivotal studies
- Total number of patients for NDA (safety and efficacy populations)
- Other planned clinical studies (pediatric plan due 60 days after EOP2 meeting)

Nonclinical Questions
- Complete nonclinical data package to support Phase 3 and for NDA

CMC Questions
- Plans to supply Phase 3
- Initial plans for market supplies

* Could be EOP1 Meeting if product received special FDA designation (Breakthrough, Fast Track, etc.) and agreement that can submit marketing application after Phase 2.
Pivotal Clinical Studies

- Pivotal = principal demonstration of efficacy and safety for NDA/BLA
  - Phase 3 studies
  - Could be Phase 2 studies (with FDA negotiation)
- FDA usually asks for minimum of 2 randomized, controlled studies in the target population (“2 adequate and well-controlled”)
- Large studies comparing the investigational drug to standard of care or placebo.
- Size of the safety population depends on the seriousness of the disease (eg, orphan diseases require fewer patients than vaccine studies)
  - Chronic, non-life threatening require ≥1,500 overall, 300–500 for 6 months to observe events of 0.5–5%, 100 ≥1 year to observe events of 3% in one year
  - Orphan Diseases could be approved with only a few hundred total exposed. Ultra-orphans: a few dozen exposed.
- During Phase 3 – also complete rest of development program (DDI, special populations, CMC development final dosage form, etc.)
Pivotal Studies: Sample Size/Power Calculations

- Sample size = total number of patients in efficacy trial(s) and safety databases
- Sample size based on anticipated effect size
  - i.e., statistically superior or non-inferior clinical effect of your product compared to the effect of placebo/active control.
  - Understand the response rate of comparator/control (FDA may have strong opinions about activity of chosen control)
  - Don’t underestimate the effect size of your placebo! (Heisenberg Uncertainty Principle)
- The effect size is predicted from
  - Animal disease model studies
  - Previous human experience (e.g., effect of your drug in Phase 2, reported effect of comparator/control, same drug in another indication, same class/related drugs in the same indication)
Seeking FDA Advice:
Pre–NDA/Pre–BLA Meeting

- **Clinical**
  - Pivotal studies
    - efficacy results (meeting statistical endpoint)
    - safety results
  - Results from other studies
  - Completeness of data package (sample sizes for efficacy and safety)
  - Draft Package Insert

- **Nonclinical**
  - Data package for NDA

- **CMC**
  - Data package for NDA, any plans to bridge between manufacturing processes

- Agreement from FDA that NDA is acceptable
  - “Review issue”

- Phase 4 commitments
Expedited Programs
  ◦ Accelerated Approval
    • surrogate endpoint with Phase 4 commitment
  ◦ Fast Track
    • unmet medical need (can be from nonclinical data)
  ◦ Breakthrough Therapy Designation
    • likelihood of clinical benefit (patient data required)
  ◦ Priority Review
    • 6 months vs 10 months for regular NDA review)
FDA Programs (2 of 2)

- **Orphan Drug Designation**
  - <200,000 prevalence (total cases) in the US
  - Advantages
    - Smaller patient numbers (tradeoff = recruitment)
    - Waiver of PREA requirements
    - Waiver of NDA submission fees (> $2.4 million in 2016)

- **Special Protocol Assessment (SPA)**
  - Binding agreement on approvable Phase 3 studies

- **Pediatric Plan (PREA)**

- **Generating Antibiotics Incentives Now (GAIN) Act, QIDP (Qualified Infectious Disease Products)**
US Market Application (NDA/BLA)

- Modular CTD format
  - Accepted in ICH regions (US, EU, Japan) and other regions (Canada, Australia, etc.)
  - Approval in a western country may be used to import drug in other regions
  - Electronic filing preferred
- Review process can take 6–18 months
- Opportunities for expedited review
- Frequent interactions with FDA
- Label (package insert) negotiations critical
  - What you are allowed to promote
- May have Advisory Committee meeting
- Fee with some opportunities for waivers (2016, >$2.6M)
- GMP and GCP inspects during review
After Approval

- On-going clinical safety reporting (pharmacovigilence)
- Annual report
- CMC Supplements (AR vs CBE vs CBE–30 vs PAS)
- Phase 4 commitments
- Registries
- Drug registration, labeling
- Advertising and promotion
- GMP inspections
- License renewals (in some countries)

- New indications, new presentations, new formulations
Some Ideas for Success

- Plan your development program (dynamic documents)
  - Drug Development Plan
  - Target Product Profile

- Hundreds of millions of dollars to get to NDA/BLA
  - Many companies plan for demonstration of proof-of-concept (Phase 2a)
  - Focus your approach. Understand the competition

- Define your “exit strategy”
  - Understand who is your audience for the results
    - FDA or the due-diligence team?
  - How much data are needed in order to sell product advantageously?