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# Regulation of Biological Product Development

**Christopher M. Mikson, M.D.**
*Partner*

DLA Piper LLP (US)

1650 Market Street
Philadelphia, PA 19130

500 Eighth Street, NW
Washington, DC 20004

T +1 215 656 3380
M +1 215 530 0569
*christopher.mikson@dlapiper.com*
*dlapiper.com*

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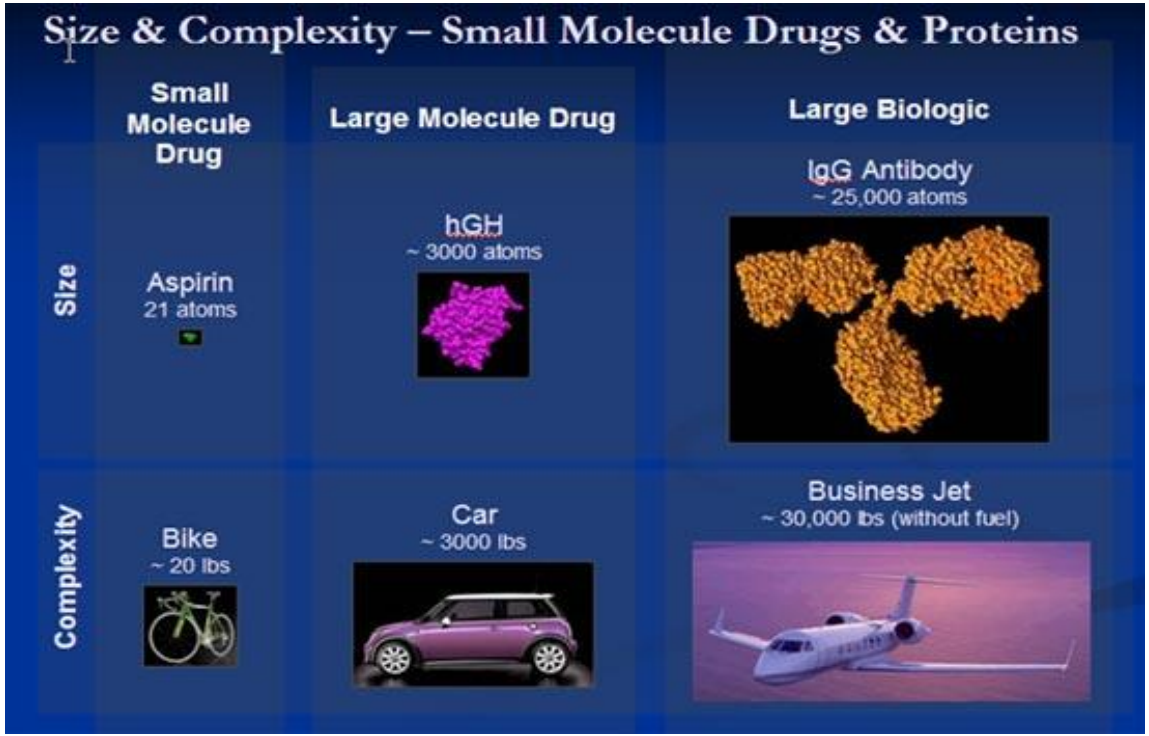
# FDA APPROVAL OF BIOLOGICS FOR MARKETING

# Drugs and Biological Products



# Drugs and Biological Products

| BIOLOGICS | DRUGS |
| --- | --- |
| • Large molecules | • Small molecules |
| • Difficult to characterize | • Easier to characterize |
| • Complex to manufacture | • Easier to manufacture |
| • Manufactured from a living system | • Manufactured through chemical synthesis |
| • Alteration of manufacturing process may change compound | • Can alter manufacturing process without changing compound |
| • FDA approval through Biologics License Application | • FDA approval through New Drug Application |

# Drug and Biological Products Legislation

| BIOLOGICS | | | FOOD, DRUGS, DEVICES |
|---|---|---|---|
| Biologics Control Act | 1902 | | |
| | | 1906 | Pure Food and Drug Act |
| | | 1938 | Food Drug and Cosmetic Act |
| Public Health Service Act | 1944 | | |
| | | 1962 | Kefauver-Harris Amendments |
| | | 1984 | Drug Price Competition and Patent Term Restoration Act (“Hatch-Waxman”) |
| Biologics Price Competition and Innovation Act (BPCIA) | 2010 | | |

# Statutory Definitions

**Drug (FDC Act)**

- articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;
- articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- articles intended for use as a component of any article specified above.

**Biological Product (PHS Act)**

- "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"

# Biologics Are Also Drugs

- Biological products are also drugs under the FDCA in that they are “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease”
- Biological products include blood-derived products, vaccines, *in vivo* diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products
- Hormones such as insulin, glucagon, and human growth hormone have been regulated as drugs under the FDCA, not biological products under the PHS Act, but that is changing

# Marketing Application for Drugs Under the FDC Act

- Two Types of New Drug Applications (NDAs)
  - "Full" NDA – FDC Act Section505(b)(1)
    - Includes "full reports" of studies to prove safety and effectiveness
  - "505(b)(2)" NDA – FDC Act Section 505(b)(2)
    - NDA where applicant does not have rights to some of the "full reports" necessary for approval
- Abbreviated New Drug Application (ANDA) – FDC Act Section 505(j)
  - No requirement for "full reports"
  - Approval based on showing of similarity to previously approved drug product, including bioequivalence

# Marketing Application for Biologics Under PHS Act

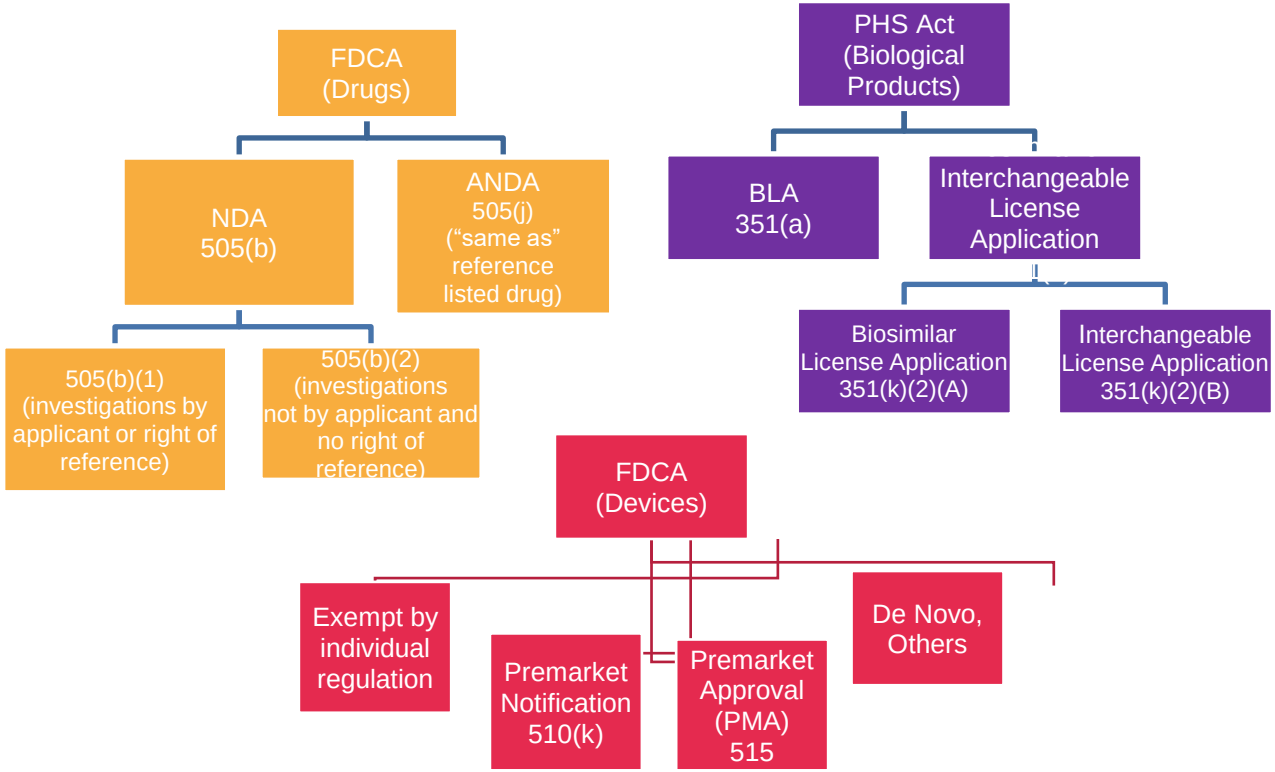
- Biologic License Application (BLA)
  - Analogous to NDA
  - Biological product is safe, pure, and potent, and
  - Facilities where biological product is manufactured, processed, packed, or held (manufacturing facilities) meet standards designed to assure that the biological product continues to be safe, pure, and potent
- Biosimilar
  - Biological product is “highly similar” to the reference product notwithstanding minor differences in clinically inactive components, and
  - No clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product
- Interchangeable
  - Biosimilar that may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product

# Product Approval Standards

- **FDC Act: Safety and Effectiveness**
  - Effectiveness must be established by “Substantial Evidence.”

    “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”
- **PHS Act: Safety, Purity, and Potency**
  - Purity
    - Absence of extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product
  - Potency
    - Ability of the product to yield a given clinical result

# Comparing the Marketing Pathways



# Question/Discussion

Given the differences in the applicable statutes, product definitions, and approval (or licensing) standards,


Would you expect FDA's requirements development, testing, and approval to differ significantly between small molecule drugs and biological products?

# Question/Discussion

As it turns out,


- FDA interprets “potency” to include “effectiveness
- FDA also generally considers “substantial evidence” of effectiveness” necessary to support a biological licensure

# RESEARCH AND DEVELOPMENT PROCESS

# Preclinical Development

- Preclinical studies (studies of investigational product in animals)
  - Provides evidence that drug is “reasonably safe” for clinical trials
  - Also provides evidence establishing safety for approval
- No FDA authorization required to perform preclinical studies
  - Agency will conduct retrospective review
  - Acceptability of study is governed by adherence to Good Laboratory Practice (GLP) regulation [21 CFR Part 58]

# ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

- Selection of animal species and dose for studies
- Immunogenicity
- Reproductive and developmental toxicity
- Carcinogenicity
- Nonclinical exposure should support anticipated dose and duration of use in humans
- For biologics, GLP toxicology in NHP is often key to establish first in human dosing

# Clinical Trials: Investigational New Drug Exemption (IND)

- Investigational New Drug application (21 CFR Part 312 for both small molecules and biologics)
- Essentially “permission” to conduct human clinical trials
- IND goes into effect – it is not “approved”
- FDA has up to 30 days to review and issue an initial clinical hold
- Partial or full clinical hold can be placed at any time
- Delegation of regulatory responsibility to CRO/vendors through the Transfer of Regulatory Obligations (TORO)

# IND Application

- The IND application must contain information in three broad areas:
  - Animal Pharmacology and Toxicology Studies:
    - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans
    - Any previous experience with the drug in humans (often foreign use)
  - Manufacturing Information
    - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product
    - FDA must ensure that sponsor has the capability to adequately produce and supply consistent batches of the drug
  - Clinical Protocols and Investigator Information
    - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks
    - Information on the qualifications of clinical investigators to assess whether they are qualified to fulfill their clinical trial duties
    - Commitments to obtain informed consent from the research subjects, to obtain review of the study by IRB, and to adhere to the IND regulations

# Investigational New Drug Exemption (IND)

- Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials
- During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk
- IND becomes a living document, and records and reports:
  - Protocol amendments
  - Safety reports
  - Annual reports

# IND Transfer

- IND can be transferred
- Simple notification to FDA from both the transferring out and transferring in party
- No waiting period, immediate effect
- Rights of reference

# Participants in Clinical Trials

- Sponsor
  - Entity that is responsible for and initiates, but does not conduct, a clinical investigation
- Investigator
  - Individual who conducts clinical investigation; responsible leader of a team performing research activities
- Institutional Review Board (IRB)
  - Committee formally designated by an institution to review, approve the initiation of, and to conduct periodic review of biomedical research involving humans

# Participants in Clinical Trials

- Contract research organization (CRO)
  - Entity that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor
- Monitor
  - Individual designated by Sponsor to oversee progress of investigation
- Subject
  - Human who participates in an investigation

# FDA Clinical Trial Regulations

- 21 CFR 312: Investigational New Drug Applications (INDs)
- Other applicable regulations:
  - 21 CFR 50: Protection of Human Subjects/ Informed Consent
  - 21 CFR 54: Financial Disclosure
  - 21 CFR 56: Institutional Review Boards
  - 21 CFR 11: Electronic Records and Signatures

# Adequate and Well-Controlled Studies

- 21 C.F.R. § 314.126
- Clear statement of study's objectives
- Summary of proposed or actual methods of analysis in protocol and study report
- Design that permits valid comparison with a control
- Method of selecting subjects that ensures they have disease or condition
- Method of assigning patients to treatment/control groups that minimizes bias
- Adequate measures to minimize bias of subjects, observers, and analysts

# Good Clinical Practices Under ICH-E6

- International Conference on Harmonization (ICH) E6 Guidance: Good Clinical Practices
  - A uniform standard among the EU, Japan and the US to facilitate acceptance of clinical data by regulatory authorities
  - FDA adopted the International Conference on Harmonization (ICH) GCP Guidance in April 1996 as an FDA guidance document
  - FDA updated to the latest version of the ICH GCP Guidance, E6(R2) in March 2018

# Clinical Studies

- Four general phases of clinical investigation:
- Phase I, II, and III investigations
  - Provides data on new products or new intended uses
  - While phases are defined in regulations, the distinctions are generally meaningless to the FDA regulatory process
- Phase IV investigations
  - Provides data on approved products and uses
  - Conducting a phase IV study may be a condition of approval
  - Typically evaluate drug risks, benefits, and optimal use

# Phase I Study

- Initial administration to human beings
  - Administration generally limited to healthy subjects, but patients may also be included
- Small number of subjects (range of 20-80)
- Assess toxicity, absorption, distribution, metabolism, elimination
- Focus on:
  - Safe dosage range
  - Appropriate route of administration

# Phase II Studies

- Expanded investigations
- Limited number of patients with targeted condition (usually no more than several hundred)
- Focus on:
  - Effectiveness
  - Side effects and risks
  - Dosing
- Successful phase II studies may be sufficient for NDA approval in exceptional circumstances (oncology)

# Phase III Studies

- Pivotal Trials:
  - Definitive assessment of the investigational product's effectiveness and safety, as compared to placebo or the current standard treatment
- Large numbers of patients (several hundred to several thousand)
- Initiating a phase III study generally requires reasonable assurance of safety and effectiveness from phase I and II studies:
  - End-of-Phase-II Meeting
- Focus:
  - Primarily efficacy
  - Safety
  - Optimal dosing

# Adaptive Clinical Trial Design

***Adaptive Designs for Clinical Trials for Drugs and Biologics* (FDA Draft Guidance September 2018)**

- FDA defines an adaptive design as “a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial”
- Describes principles for designing, conducting and reporting the results from an adaptive clinical trial
    - Advises sponsors on the types of information FDA needs to evaluate the results from trials with adaptive designs
    - Explains how adaptive trial designs can allow a trial to adjust to information that was not available when the trial began
    - Recommends a variety of approaches

# Adaptive Clinical Trial Design

- **FDA's announcement of guidance –**

  "Adaptive clinical trials can give sponsors the flexibility to react to clinical evidence as it's being collected, and modify the design and enrollment in trials by including more patients with characteristics that help predict that they're more likely to derive a benefit. Or exclude patients with characteristics that suggest that they're more likely to suffer a side effect. By enriching the enrollment in the trial for patients with characteristics that are likely to predict clinical success, it has the potential to make the development process more efficient. This approach also allows us to potentially learn much more about the characteristics that can inform safer prescribing. All of these efforts are part of our broader program to modernize the FDA's science-based framework for making clinical trials more efficient and lower cost while strengthening the agency's gold standard for safety and efficacy."

# Diversity in Clinical Trial Enrollment

- "FDA expectations are that sponsors enroll participants who reflect the demographics for clinically relevant populations with regard to age, gender, race, and ethnicity . A plan to address inclusion of clinically relevant subpopulations should be submitted for discussion to the Agency at the earliest phase of development and, for drugs and biologics, no later than the end of the phase 2 meeting. Inadequate participation and/or data analyses from clinically relevant subpopulations can lead to insufficient information pertaining to medical product safety and effectiveness for product labeling."

- *Guidance: Collection of Race and Ethnicity Data in Clinical Trials*

# Human Subject Protection in Clinical Trials

- 21 CFR Part 50
- 21 CFR Part 56 (IRBs)
- HHS Common Rule (45 CFR Part 46) and HIPAA
  - Privacy Rule (45 CFR 160, 164)

# Key Issue in Clinical Trials: Informed Consent

"In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent."

*The Declaration of Helsinki, Principle 9*

- **Informed consent is a process, not just a document**

# Informed Consent

- Each subject must provide legally effective informed consent prior to participation in the study, UNLESS
  - Consent is waived by IRB
  - Emergency research
- Basic and additional elements of informed consent detailed in the regulation (21 CFR 50.25)
- Consent may not include exculpatory language by which subject appears to waive legal rights

# Informed Consent

- Process is as important as the document
  - Must not be coercive
  - Must be provided in language understandable to the subject
  - Subject must be given an opportunity to discuss study with others before consenting
  - Subject must be given an opportunity to have any questions answered prior to consenting
  - Subject must be provided a copy of signed/dated consent form
- Consent must notify that medical information collected during study may be disclosed to sponsor, IRB, FDA , others
  - Although research is exempt under HIPAA, consent may include a HIPAA authorization permitting disclosure of PHI for use in study

# Pediatric and OUS Trials

- Required Pediatric Trials (Pediatric Research Equity Act (PREA))
  - “Stick”

- Pediatric Studies Performed Under Written Request (Best Pharmaceuticals for Children Act (BPCA))
  - “Carrot”

- Clinical Trials Conducted Outside of the United States
  - OIG reports over half of all clinical trials sites are OUS
  - OUS study conducted under IND must comply with all US regulations
  - OUS study not under IND may be accepted if
    - GCP compliant
    - FDA can validate data by 0n-site inspection

# Question/Discussion

Given the importance of informed consent for a study subject to participate in a clinical trial,


How would you expect human subject protection to apply to minors?

# Question/Discussion

As it turns out,


- Minor subjects require:
  - Parental permission
  - Child assent (as developmentally appropriate)

# Sponsor Responsibilities

- File and maintain IND
- Select qualified investigators
- Keep appropriate records
- Provide sufficient information to investigators to conduct the trial
- Oversee the trial and enforce compliance
- Monitor trial progress
- Review and evaluate safety and effectiveness
- Submit records/reports to FDA (and DEA, if applicable)

# Sponsor Responsibilities: Monitoring and Oversight

- Ensure studies are conducted according to the protocol and regulations
- If an investigator is not complying with the protocol or regulations, sponsor must:
  - Promptly secure compliance **OR**
  - Cease shipment of investigational drug to the investigator
  - Discontinue investigator's participation
  - Require destruction or return of all study drug in the investigator's possession **AND**
  - **Inform FDA of action**

# Sponsor Responsibilities: Safety Reporting

Sponsor: FDA and Investigators

- Within 7 calendar days of receipt of information of any
  - Unexpected fatal or life threatening experience associated with the use of study drug
- Within 15 calendar days of receipt of information of any
  - Serious and unexpected adverse experience associated with the use of the study drug
  - Findings from other studies or from animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug
  - Any clinically important increase in rate of serious suspected adverse reactions that are listed in protocol or IB

# Investigator Responsibilities

- Conduct study according to protocol and regulations
- Maintain and retain appropriate records
- Control of drugs under investigation
  - Administer only to enrolled subjects under investigator's supervision
  - Maintain records of investigational drug disposition
- Protect rights, safety and welfare of subjects
  - Obtain informed consent of each subject
  - Ensure study is overseen by an IRB that complies with regulations at Part 56
- Submit records/reports to Sponsor

# Investigator Responsibilities: Safety Reporting

- Investigators: Sponsor
  - Must immediately report any serious adverse event
    - Whether or not considered drug related
    - Must include assessment of whether there is a reasonable possibility that the study drug caused the event
- Investigators: IRB
  - Must promptly report all
    - Changes in research activity and
    - Unanticipated problems involving risks to human subjects or others

# IRB Oversight

- Clinical trials must be reviewed and approved by an IRB complying with FDA regulations
    - Protocol
    - Investigator
    - Informed consent document and process
    - Advertising materials
- IRBs ensure risks are minimized and reasonable in light of anticipated benefits
- Conduct continuing review at least annually

# IRB Oversight

- Any change in the research requires IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects
- IRBs must:
  - Be registered with HHS
  - Be comprised of membership consistent with regulations
  - Maintain and document compliance with policies consistent with regulations

# Clinical Trials Outsourcing

Most sponsors outsource a significant portion of their clinical research activities

- CROs
- SMOs
- Clinical Labs
- Data Management
- Research Sites
- Clinical Investigators
- Bioanalytical Labs
- Electronic Data Capture
- Clinical Trial Management Systems
- Central IRBs
- Subject Recruitment
- Biostatistics
- Medical Writing
- Study Drug Packaging/Distribution
- Data Safety Monitoring Committee
- Other Consultants

# Clinical Trials Outsourcing

- **CRO – a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor**

- Regulations permit sponsors to transfer responsibility to a CRO
  - Transferred responsibilities must be described in writing (“TORO”)
  - CRO assumes regulatory obligations of a sponsor for each transferred obligation and is subject to regulatory action for noncompliance

# Clinical Trials Outsourcing

- Vendor Selection
  - Determine Scope of Services to be Outsourced
    - Services required
    - Geographic scope
    - Limited Source Equipment/Services
    - Budget
  - Full Service CRO/Multiple Vendors
  - RFP Process
  - Preferred Vendor Arrangements

# Clinical Trials Outsourcing

- Negotiate and Execute Contracts
  - CDA
    - Prior to providing information for RFP process
  - Definitive Agreement
    - Master Services Agreement/Work Orders
    - Individual Project Agreement

**Key vendor agreements may take months to negotiate.**
**Plan accordingly.**

# Clinical Trials Outsourcing Key Terms

- Detailed description of services
  - Include applicable standards, deliverables, key personnel
- Fees and expenses
  - Milestone v. hourly
  - advance payments for pass-through expenses
- Confidentiality
  - May be unilateral or mutual, depending on the services being provided
- Ownership of intellectual property
  - Sponsors need to protect interests in their products and any new uses developed during the study
- Publication
- Indemnification
- Subject Injury

# Clinical Trial Agreements

- Agreements with investigators/ research sites conducting research
- Parties
  - Sponsor – Institution (PI is Institution Employee)
  - Sponsor – Institution – PI
  - CRO – Institution (PI is Institution Employee)
  - CRO – Institution – PI
- If CRO executes agreements on behalf of the sponsor, an indemnification may be required between the Sponsor & Institution/Investigator

# Interactions with FDA on Biological Product Development Programs

- CBER Advance Technology Team (CATT) Meetings
  - Interactive mechanism for early agency interaction to discuss advanced technologies
- **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s (INTERACT)
  - Informal non-binding consultation with CBER for innovative investigational products at an early stage of development
- PDUFA milestone meetings (Types A, B, C): pre-IND, EOP2, pre-BLA and as needed
- FDA information requests (IRs)
- Less formal correspondence (email, phone conferences)
- Collectively serves as administrative record, which is critical as the asset and personnel on both sides change over time

# Expedited Programs and Designations

**Orphan Drug Exclusivity**

- Applicable to indication for rare disease/condition
  - <200,000 patients needing treatment on annual base
  - >200 000 patients annually with no reasonable expectation that R&D costs will be recovered through sales
- Advantages = Seven (7) years of marketing exclusivity
  - Plus tax incentives, study design assistance, exemption from filing fees, possible grants for clinical trials
- Approximately 7,000 orphan indications (majority genetic)
  - Drug market value expected $110M (2016) → $220 billion (2022)

# Pediatric Drug Exclusivity

Best Pharmaceuticals for Children Act (BPCE) (2002)

- Intended to provide incentive for drug companies to conduct pediatric studies
- Allows FDA to issue “written requests” to sponsors for pediatric development for products
    - Sponsor must conduct pediatric studies in accordance with “written request” from FDA
- Grants six additional months of exclusivity extending after all other forms of exclusivity have expired
    - Pediatric exclusivity applies only for products that already have another form of marketing exclusivity
    - Pediatric exclusivity designation cannot stand on its own

# Accelerated Timelines

- Fast Track
  - Serious or life-threatening condition and fill unmet medical need
  - Early and frequent communication with FDA
  - Rolling review and accelerated approval
- Breakthrough Therapy
  - Serious condition and preliminary clinical evidence indicates the drug may demonstrate substantial improvement over available therapy on clinically significant endpoints
  - Benefits if FT plus FDA guidance and commitment
- Accelerated Approval
  - Serious condition and fill unmet need
  - Shortens study time by using surrogate endpoints
  - Confirmatory studies required
- Priority Review
  - Drugs that offer major advance in current treatment
  - Drugs that treat non-life-threatening illness are eligible
  - Priority Review Voucher Program

# Regenerative Medicine Advance Therapy (RMAT)

- RMAT designation established by 21st Century Cures Act
- Advantages of RMAT
  - Benefits of Fast Track and Breakthrough
  - Potential surrogate or intermediate endpoints to support accelerated approval

| Breakthrough Therapy | RMAT |
|---|---|
| FDA Safety and Innovations Act(2012) | 21st Century Cures Act (2016) |
| Drugs and biologics | "Regenerative medicines" = cell, tissue, gene therapies, combination with biological PMOA |
| "Preliminary clinical evidence" of "substantial improvement" over existing therapies | No substantial improvement requirement |
| Serious condition | |
| Submit request with IND or after, ideally not later than EOP2 meeting | |
| FDA will respond to request within 60 days | |

# Compliance and Enforcement Risks and Considerations

- Agency Compliance Considerations During Development
  - Clinical holds
  - Promotion
  - Charging for investigational drugs
  - SEC oversight
  - Compliance programs
- Registration of Trials
- Fraud and Abuse Risks
  - Risks arising from financial relationships with HCPs
- Clinical Trials Reimbursement
- Transparency Requirements
  - Physician Payment Sunshine & State Disclosure Requirements

# Agency Compliance Considerations During Development

- Clinical holds
  - Initial IND 30 day review, plus any time after
- Promotion of investigational drugs
  - Careful use of regulatory terms
  - “safe” “effective” “pure” “potent”
- Charging for investigational drugs
  - Cost recovery
- SEC considerations and interactions
  - Careful review of press releases, clinical trial data reporting
- Compliance programs
  - Policies and procedures for clinical operations

# Question/Discussion

Given the importance of establishing safety purity, and potency to be granted marketing approval for a biologics,


What limitations would you expect to see on promotion of investigational biologics?

# Question/Discussion

As it turns out,


- FDA has specific limitations on dissemination of information for investigational products:
  - Careful use of regulatory terms
  - “safe” “effective” “pure” “potent”

# Registration of Trials with *ClinicalTrials.gov*

- Registry of federally and privately funded clinical research trials conducted in the U.S. and throughout the world involving drugs, biologics and devices
- Registry accepts the registration of all clinical trials
  - Approved by a human subject review board, and
  - Compliant with regulations of the appropriate national health authorities
- Registration entries include
  - Summary of the clinical trial protocol
  - trial purpose
  - recruitment status
  - inclusion and exclusion criteria
  - locations and contact information
- A trial must be registered within 21 days after the first subject is enrolled

# Fraud and Abuse

Federal law prohibits paying or receiving anything of value to a person or entity to induce the purchase of a product

> *Whoever knowingly and willfully solicits or receives (or offers or pays) any remuneration (including any kickback, bribe, or rebate) directly or indirectly, overtly or covertly, in cash or in kind … in return for purchasing, leasing, ordering, or arranging for or recommending purchasing, leasing, or ordering any good, facility, service, or item for which payment may be made in whole or in part under a Federal health care program.*
>
> *Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b)*

# Fraud and Abuse

- Illegal remuneration may include:
  - Payments in excess of fair market value
  - Payments for research that is not legitimate or necessary
  - Payments to more investigators than necessary to perform the research
  - Payments for services not performed
  - Providing equipment for uses other than performance of the research
  - A payment for legitimate, necessary services where the intent is to influence use of the manufacturer’s products

# Investigator Selection/Payment

- Study must be bona fide research intended to yield valid data that the company needs and intends to use, and is not duplicative
- HCPs selected as investigators should be:
  - Appropriate in number/not more than reasonably necessary to perform the study
  - Selected based on qualifications and ability to perform the research
- Payments to HCPs should be FMV payment for services rendered

# Research Grants

- Some research is sponsored by the investigator, not the manufacturer
  - Investigator known as a “sponsor-investigator”
  - Investigator is responsible for complying with regulatory requirements
  - Sponsor support may include financial support, product, technical assistance
- Support should be provided pursuant to a written grant agreement
- Grant recipients should be selected be a formal process free from influence by sales and marketing functions

# Clinical Trials Reimbursement

- Medicare and Medicaid cover some costs of certain clinical trials, including those performed under an IND
- Government must not be billed for any products or services provided by the sponsor
- Inappropriate billing for items and services associated with a clinical trial could result in a false claim; sponsor may be liable under the Federal False Claims Act if it is found to have caused a false claim to be submitted for payment to a federal healthcare program
- Any payments made by sponsors of clinical trials for complications or injuries arising out of the trials, such payments must be reported to CMS if the payments were made to or on behalf of Medicare beneficiaries

# Clinical Trials Transparency

- Payments to HCPs and teaching hospitals for clinical research services are subject to tracking and disclosure requirements under the transparency provisions of the health reform law and similar state laws requiring disclosure of payments to HCP
- Payments must be disclosed to HHS, but public disclosure by HHS will be delayed for up to 4 years after study completion
- Sponsors should ensure that tracking mechanisms are in place to ensure collection and disclosure of the necessary information

# Expanded Access Programs (EAPs) ("Compassionate Use")

- Size-based availability of investigational therapies to patients not meeting protocol criteria
  - Compassionate use/named patient basis
  - Intermediate size groups
  - Larger groups (including transition to approval)

- 21st Century Cures
  - Established requirement for sponsors to have a statement of their policy on EAP

# Thank You !

**Christopher M. Mikson, M.D.**
*Partner*
DLA Piper LLP (US)

T +1 215 656 3380
M +1 215 530 0569

christopher.mikson@dlapiper.com
dlapiper.com