FDA Regulatory Considerations in U.S. Government Collaborations

A Venable Webinar

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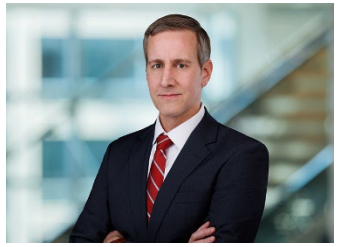
Drugs, Biologics, and Medical Devices Team

Jeremiah J. Kelly
Partner
Bio



Justin A. Coen
Partner
Bio

Together, we have more than 35 years of experience shepherding drugs, biologics, and medical devices through the regulatory process.

Prior to joining Venable, Jeremiah and Justin served in the U.S. Army Medical Research and Development Command (USAMRDC), Office of the Staff Judge Advocate (OSJA). Jeremiah was the chief of the FDA Regulatory Law Division, and Justin was the primary legal advisor on regulated medical products to the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRND). They both led the DoD's legal team during the COVID-19 pandemic response, contributing to more than $83B of contract awards for vaccines, therapeutics, and diagnostics.

Additionally, Jeremiah's previous government experience includes over seven years in the FDA Commissioner's Office in the Office of the Chief Counsel (OCC) and the Office of Legislation (OL), and Justin's previous government experience includes three years at the Senate Finance Committee.

Both Jeremiah and Justin have also worked for private sector law firms, with a background in food and drug law, healthcare, and life sciences litigation.

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Venable FDA Areas of Focus

Strategic Advice

- Regulatory pathways for drugs, biologics, and devices
- Exclusivity claims
- Priority Review Vouchers and other marketing incentives
- Citizen Petitions
- Bayh-Dole compliance
- Public Law 115-92
- APA challenges to rulemaking
- Legislative changes

Medical Product Development

- Regulatory submission of INDs, IDEs, NDAs, BLAs, 510(k)s, PMAs, and others
- FDA meeting preparation
- Animal Rule development
- Manufacturing and quality (cGMP, QSR)
- Expedited approval mechanisms
- Expanded access INDs, IDEs, GLP, and GCPs
- Emergency Use Authorizations
- Labeling

Post-Marketing & Compliance

- Response to FDA inspection and compliance actions
- Negative 483s, EIRs, Warning Letters
- Risk evaluation and mitigation strategies (REMS)
- Product recalls
- GxP compliance
- Advertising and promotion
- Government reviews and investigations
- Imports & exports

Transactions

- Regulatory due diligence
- Preparation for exit or funding event
- Government contracts (OTA, FAR contract, CRADA, grant, cooperative agreement)
- Joint venture / joint development agreements
- Clinical trial agreements
- CDMO / CRO agreements
- Quality agreements

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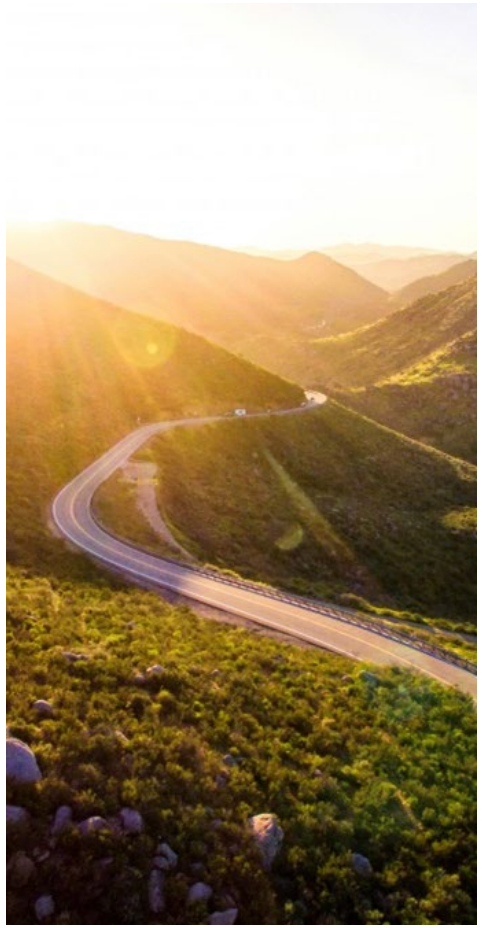
Roadmap



1. Keys for Successful Medical R&D Collaborations with the U.S. Government
2. Basics of FDA Medical Product Regulation
   - Drugs
   - Biologics
   - Devices
3. Expedited Approval Mechanisms and Regulatory Incentives
4. FDA Regulatory Considerations in U.S. Government Contracts

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Keys for Successful Medical R&D Collaborations with the U.S. Government

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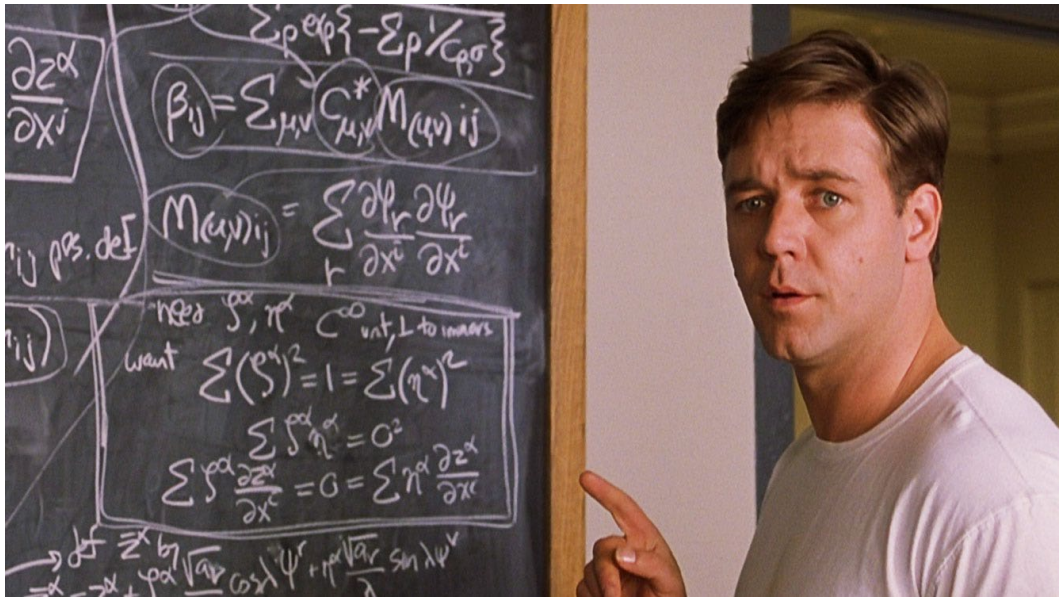
The Challenge



FDA-Regulated product development is hard!
(well, for most of us …)

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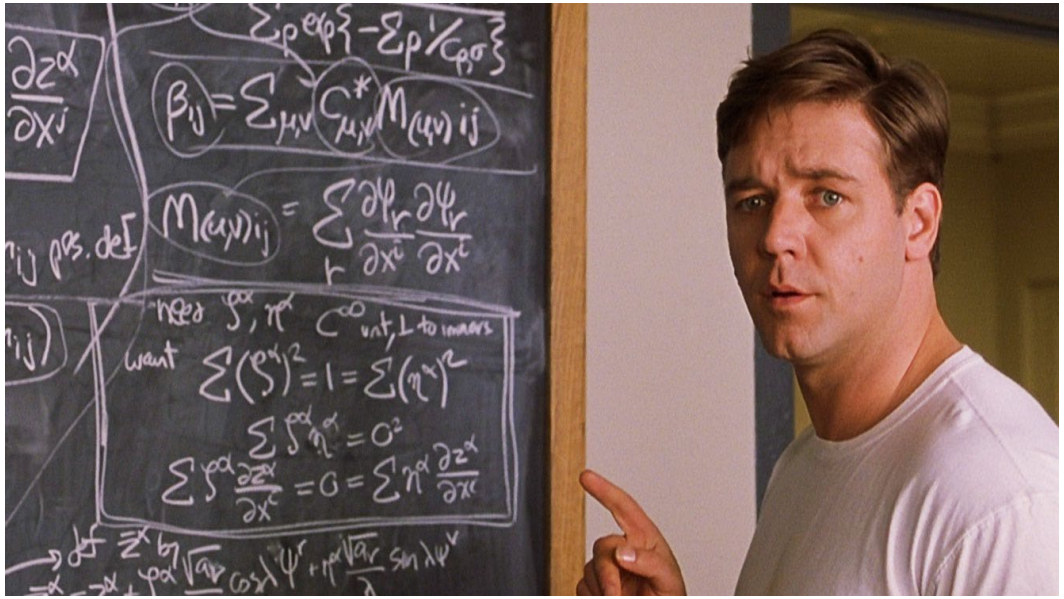
The Challenge



Federal funding adds new opportunities, but also new complexity

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The Reward

USG Partnerships can be a springboard –
incredible things are possible

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USG Non-dilutive Funding

- Biomedical Advanced Research & Development Authority (BARDA)
- National Institutes of Health (NIH)
- Advanced Research Projects for Health (ARPA-H)
- Defense Health Agency (DHA)
  - U.S. Army Medical Research & Development Command (USAMRDC)
  - Congressionally Directed Medical Research Program (CDMRP)
- Joint Program Executive Office for Chemical, Biological, Nuclear and Radiological Defense (JPEO-CBRND)
- Defense Threat Reduction Agency (DTRA), Joint Science & Technology Office (JSTO)
- Defense Advanced Research Projects Agency (DARPA)
- Uniformed Services University (USU)
- U.S. Air Force Research Laboratory (59th Performance Wing)
- U.S. Navy Medical Research Command (NMRC)

R&D Legal Vehicles

- Solicitations (SAM.gov)
- Program Announcements (grants and cooperative agreements)
- Broad Agency Announcements (BAAs)
- Cooperative Research and Development Agreements (CRADAs)
- Bilateral OTAs
- OTA Consortiums
  - Medical Technology Enterprise Consortium (MTEC)
  - Medical CBRND Defense Consortium (MCDC)
  - Rapid Response Partnering Vehicle (BARDA)
  - BioMap (BARDA)
- Commercial Solutions Offerings
- Experimental Supply Contracts
- DoD-Specific Research Foundations
  - Henry M. Jackson Foundation
  - Geneva Foundation
  - Metis Foundation

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Keys to a Successful USG Collaboration

Proposal Stage:

- Mark submissions to ensure USG protects commercial confidential information and trade secrets
- Describe your government collaborations, as the government likes to show it's "right" by investing in things they've already put money toward
- Target a "capability gap" – you can't offer a Swiss Army knife unless that is the requirement, as it may get ignored
- Align company and USG objectives
  - Hard to "walk and chew gum" where FDA and R&D with the USG meet – overlapping or distinct indications can be a challenge and it's often best to focus on priority targets
- Understand the competitive process (Broad Agency Announcement, Solicitation/RFP, Commercial Solution Opening, etc.)
- Know which contracting vehicle the government is using (and advocate for flexible vehicles when available)

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Keys to a Successful USG Collaboration (cont.)

Contract Scoping and Negotiation:

- Incremental development vs. development through licensure and delivery
- Fiscal law considerations:
  - It is good to know fiscal nature of funds and time frame (e.g., 2-year RDT&E funds vs. no-year money, DoD. 6.1-6.7 funds and other restrictions on certain stages of development)
  - Fully funded SOW vs. optional CLINs
- Who pays for NDA/BLA/PMA/510(k) submission and any postmarketing studies?
- Contracting for a platform technology has unique considerations
  - Scoping IP – "in" vs. "out"
  - Precise data rights
- Set a system to mark deliverables (can be challenging for repurposing efforts)

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FDA Medical Product “Basics”

FDA Medical Product "Basics"

Drugs	Biologics	Devices
"The term 'drug' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." 21 U.S.C. § 321(g)(1).	"The term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, 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." 42 U.S.C. § 262(i)(1).	"The term 'device' (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is- (A) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term 'device' does not include software functions excluded pursuant to section 360j(o) of this title." 21 USC § 321(h)(1).

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FDA Medical Product "Basics"

Product Type	Drugs	Biologics	Devices
Investigational Phase	Investigational New Drug Application (IND)	Investigational New Drug Application (IND)	Investigational Device Exemption (IDE)
Premarket Approval Applications (Full)	§505(b)(1) New Drug Application (NDA)	§351(a) Biologics License Application (BLA)	§515 Premarket Approval Application (PMA)
Premarket Approval Applications (Abbreviated)	§505(b)(2) NDA §505(j) ANDA Over-the-counter (OTC) non-Rx drugs monograph	§351(k)(2)(A) biosimilar §351(k)(2)(B) interchangeable biosimilar	§510(k) Premarket Notice
Expedited Approval Mechanisms	Fast Track, Accelerated Approval, Breakthrough Therapy Designation, Orphan Drug Designation, RMAT Designation, DoD Priority under PL 115-92		Breakthrough Device Designation, DoD Priority under PL 115-92
Alternative Pathways	Accelerated Approval, Animal Rule		De Novo Review
Incentives	Marketing Exclusivity, Priority Review Vouchers (PRVs), Patent Term Restoration		None

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FDA Medical Product "Basics"

Product Type	Drugs	Biologics	Devices
Manufacturing Registration	Yes, 21 CFR 207.21(a)		Yes, 21 CFR 807
Product Listing	Yes, 21 CFR 207.21(b)		Yes, 21 CFR 807
Manufacturing Requirements	cGMP under 21 CFR 210, 211		Quality System Regulation under 21 CFR 820
Labeling	Must not be false or misleading in any (21 CFR 201 for drugs and biologics, 21 CFR 801 for devices)		
Post-Approval/Clearance Adverse Event Reporting	Serious and unexpected adverse events: within 15 calendar days of receipt of information All other adverse events: quarterly for 3 years after approval, annually thereafter 21 CFR 314.80		Death, serious injury, malfunction: 30 calendar days Incident requiring remedial action to prevent risk of substantial harm to public health: 5 working days 21 CFR 803
Post-Market Changes	CBE, CBE-30, PAS		Under 21 CFR 807, new 510(k)/PMA required for significant change Special 510(k) PMA supplement, 180-, 30-, and 0-day notices under 21 CFR 814

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The Drug & Biologics Regulatory Frameworks

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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; and
  - manufacturing, processing, and packing are adequate to ensure identity, 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.

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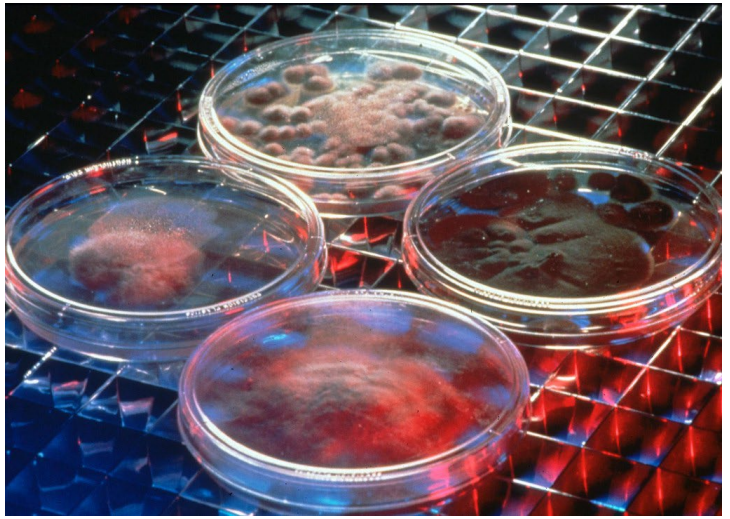
Preclinical Testing/Investigation

Goals of nonclinical testing:

- Characterize toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility;
- Estimate an initial safe starting dose and dose range for the human trials;
- Characterize potential adverse effects; and
- Identify parameters for clinical monitoring for potential adverse effects.



In vitro

In vivo

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:

1. Investigator (typical model for new drug approval);
2. Emergency Use IND (investigational product); and
3. Treatment IND (initial studies show benefit for serious or life-threatening condition).

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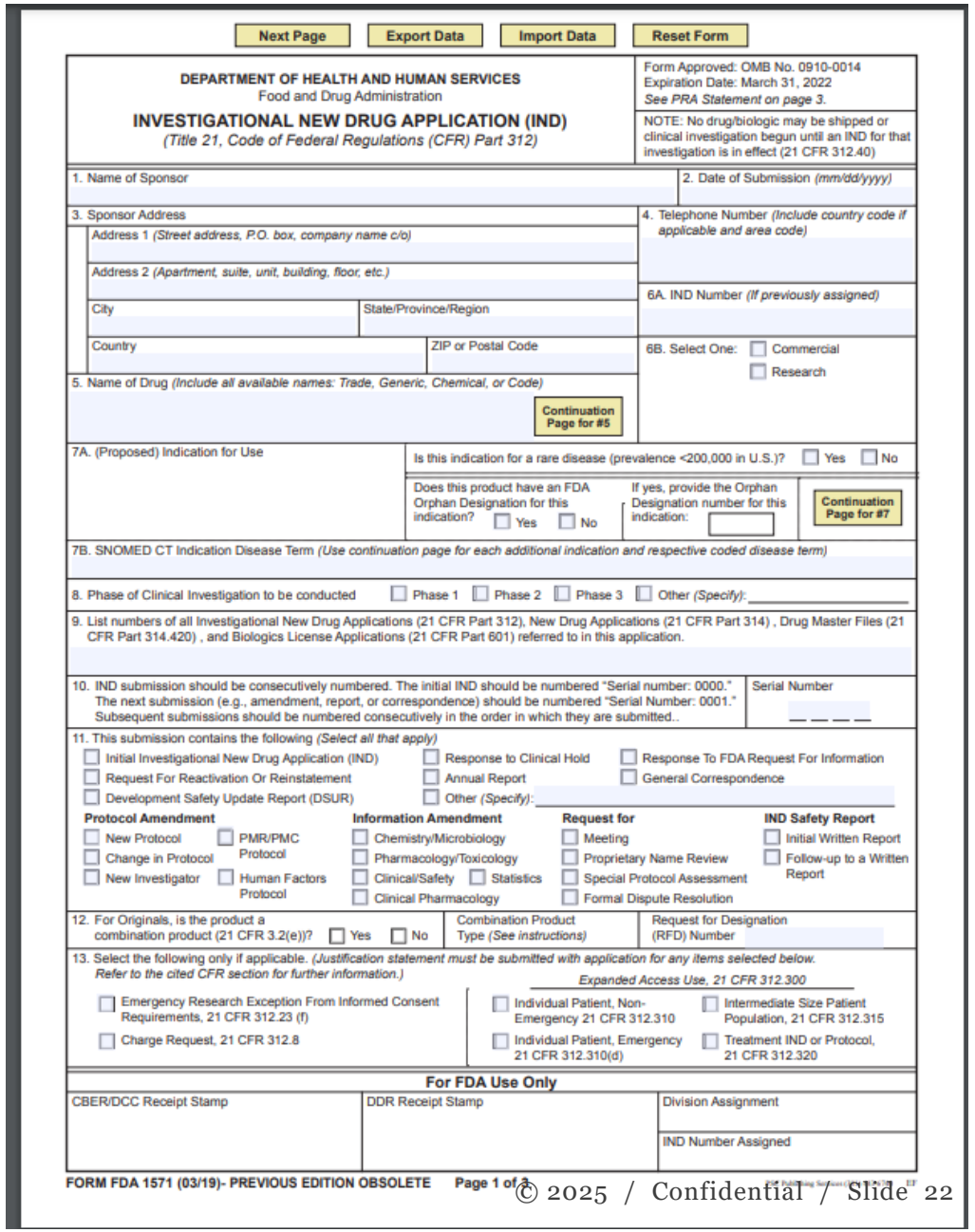
IND Content and Format

- Cover Sheet (Form FDA 1571);
- Table of Contents;
- Introductory Statement;
- General Investigational Plan;
- Investigator's Brochure;
- Protocol;
- Chemistry, Manufacturing and Control (CMC) Information;
- Pharmacology and Toxicology Information; and
- Previous Human Experience with the Investigational Drug.



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission *(mm/dd/yyyy)*
3. Sponsor Address
Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number *(Include country code if applicable and area code)*
6A. IND Number *(If previously assigned)*
6B. Select One: Commercial Research
5. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
Continuation Page for #5
7A. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
7B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*
8. Phase of Clinical Investigation to be conducted Phase 1 Phase 2 Phase 3 Other *(Specify)*:
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..
Serial Number
11. This submission contains the following *(Select all that apply)*
Initial Investigational New Drug Application (IND)
Response to Clinical Hold
Response To FDA Request For Information
Request For Reactivation Or Reinstatement
Annual Report
General Correspondence
Development Safety Update Report (DSUR)
Other *(Specify)*:

Protocol Amendment	Information Amendment	Request for	IND Safety Report
New Protocol	Chemistry/Microbiology	Meeting	Initial Written Report
Change in Protocol	Pharmacology/Toxicology	Proprietary Name Review	Follow-up to a Written Report
New Investigator	Clinical/Safety	Special Protocol Assessment	
PMR/PMC Protocol	Statistics	Formal Dispute Resolution	
Human Factors Protocol	Clinical Pharmacology		

12. For Originals, is the product a combination product (21 CFR 3.2(e))? Yes No
Combination Product Type *(See instructions)*
Request for Designation (RFD) Number
13. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Expanded Access Use, 21 CFR 312.300
Individual Patient, Non-Emergency 21 CFR 312.310
Intermediate Size Patient Population, 21 CFR 312.315
Individual Patient, Emergency 21 CFR 312.310(d)
Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only

CBER/DCC Receipt Stamp	DDR Receipt Stamp	Division Assignment
		IND Number Assigned

FORM FDA 1571 (03/19)- PREVIOUS EDITION OBSOLETE Page 1 of 3

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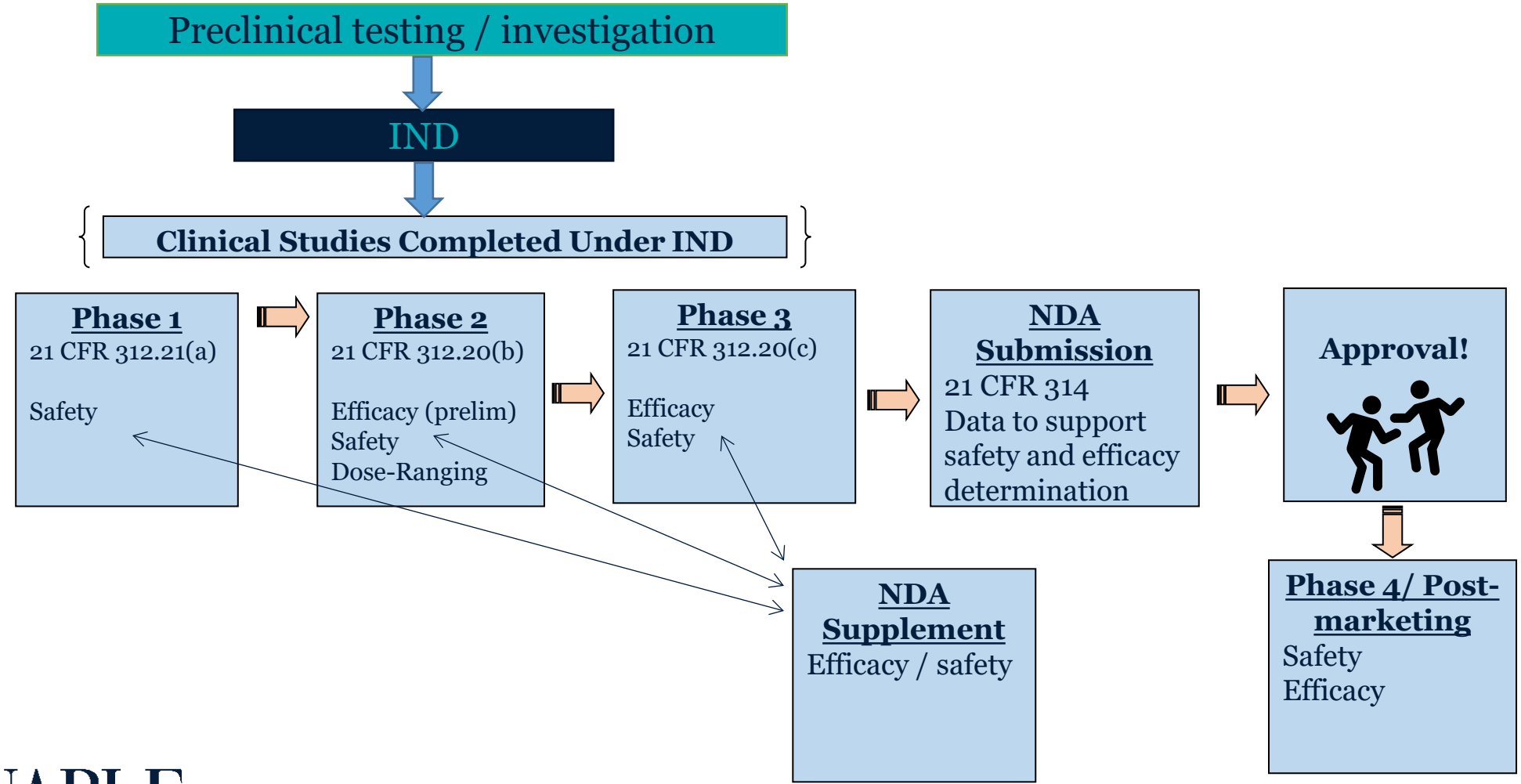
Overview of Drug and Biologics Regulatory Process



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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).

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BPCI Act of 2009

Biologics Price Competition and Innovation Act of 2009

- Signed into law on 3/23/10;
- Intent of the statute similar to Hatch-Waxman Amendments to FD&C Act;
- Aligns with the FDA's long-standing policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing;
- Balances additional incentives to innovate and price competition; and
- Created abbreviated approval pathway for biologics.

§351(k)(2)(A) Biosimilar BLA

"Biosimilar"

- "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency" (351(i) of the PHSA);
- Not "generics" like 505(b)(1) because the active ingredients are not the same, but merely similar; and
- FDA approved first biosimilar product on 3/6/15 (Sandoz Inc's Zarixo is biosimilar to Amgen Inc.'s Neupogen as treatment for patients receiving forms of chemotherapy).

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§351(k)(2)(B) Interchangeable BLA

Interchangeable

- Meets the standards in subsection 351(k)(4) and "biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product" (351(i)(3));
- 351(k)(4) requirements;
  - "Biosimilarity,"
  - "can be expected to produce the same clinical results as the reference product in any given patient," and
  - No additional risk of switching between reference and interchangeable product;
- Most heated dispute on this issue; and
- Semglee (insulin glargine-yfgn) – first interchangeable biosimilar.

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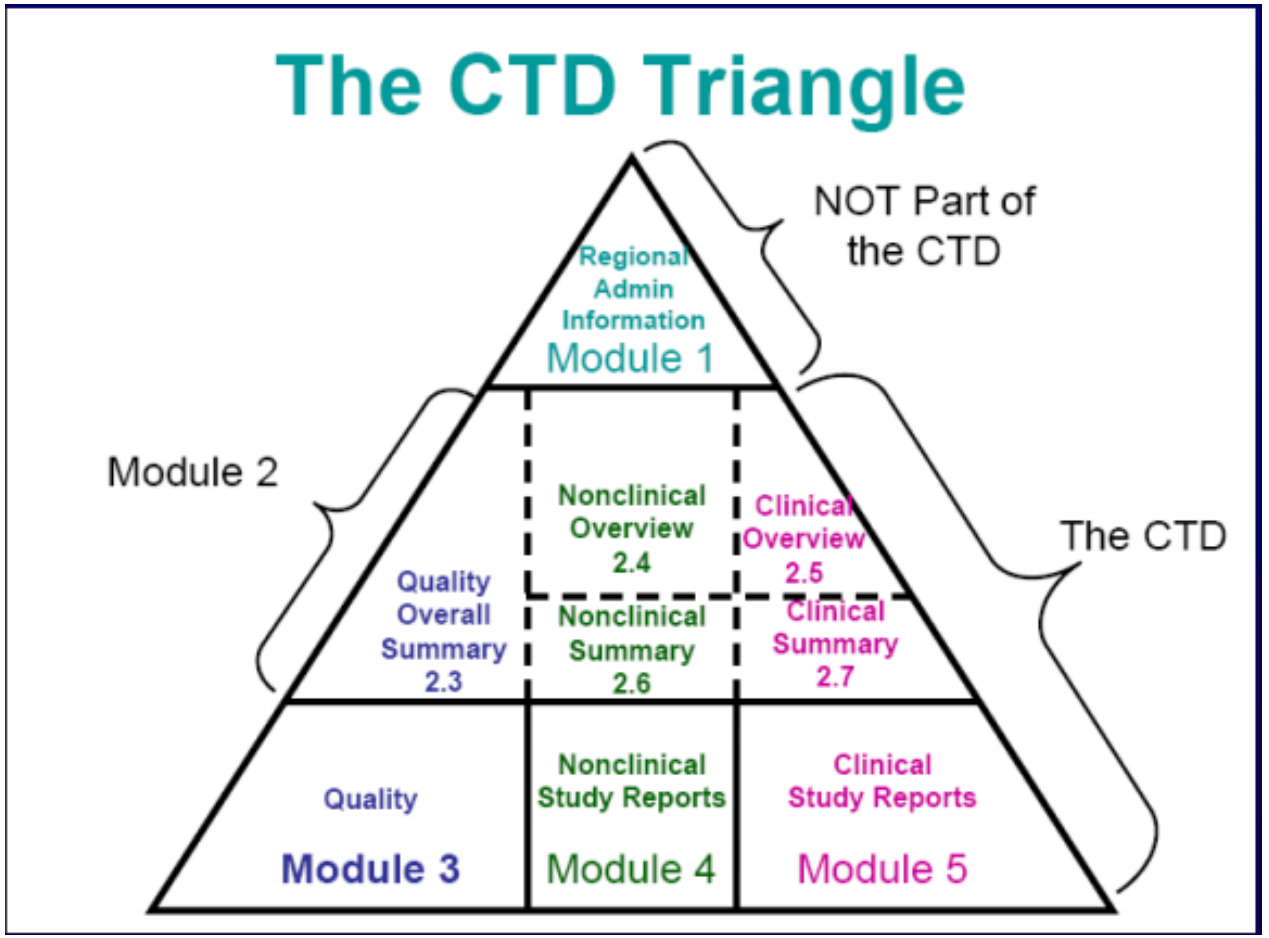
Electronic Common Technical Document (eCTD) for NDAs and BLAs

As of May 5, 2017, all NDAs and BLAs required in eCTD format

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
Guidance for Industry



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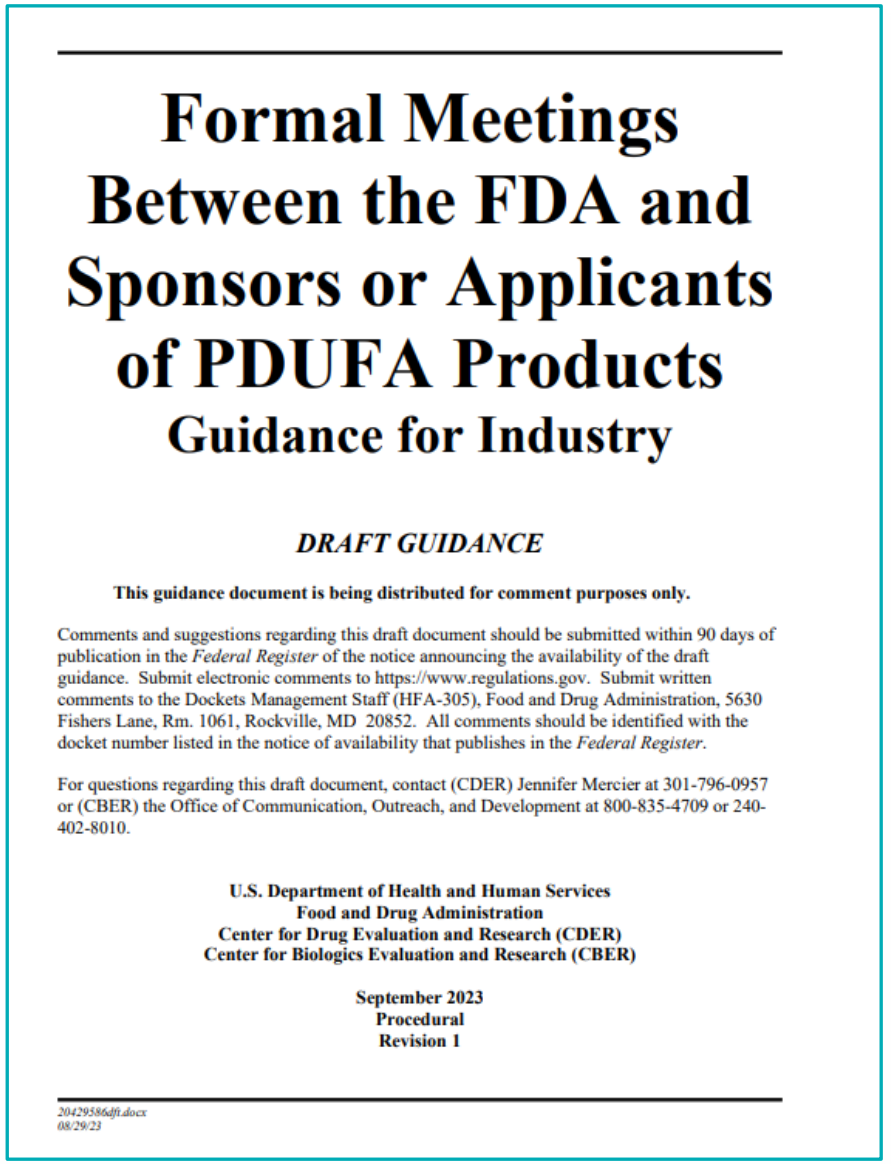
Meetings with FDA

- 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); and
  - End Phase 2/Begin Phase 3, Pre-NDA/BLA (21 CFR 312.47).
- Type C:
  - Other.



Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Jennifer Mercier at 301-796-0957 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2023
Procedural
Revision 1

20429586dfi.docx
08/29/23

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Meetings with FDA (cont.)

- Type D:
  - Narrow set of issues (no more than two) re: follow-up questions that raise a new issue after a formal meeting, general question about an innovative development approach that does not require extensive, detailed advice.
- INTERACT:
  - Early sponsor engagement to answer “novel, challenging” questions where FDA Guidance is not available; and
  - Goals: reduce hurdles in the IND-enabling phase to facilitate first-in-human (FIH) clinical phase of drug and biologics development.

The Medical Device Regulatory Framework

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Pop Quiz: Which of These Is a Medical Device?

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Medical Device Classification

General Controls (apply to all classes):

- **Register** the establishments that manufacture or prepare devices (21 CFR Part 807)
- **List** the medical devices distributed in the U.S. (21 CFR Part 807)
- **Reporting adverse events and device malfunctions** (MDR reporting, 21 CFR Part 803)
- **Device tracking and unique identifier marking** (21 CFR Parts 821 and 830)
- **Post-market surveillance** (21 CFR Part 822)
- Manufacturing must comply with the **Quality System Regulations** (QSRs, 21 CFR Part 820).

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Medical Device Classification (cont.)

Medical device classification is based on the level of control necessary to ensure the safety and efficacy of the device (risk-based paradigm).

Class I:

- Common, low-risk devices;
- General controls (§513(a)(1) of FD&C Act);
- Exempt: no premarket 510(k) submission; and
- Non-exempt: premarket 510(k) required.

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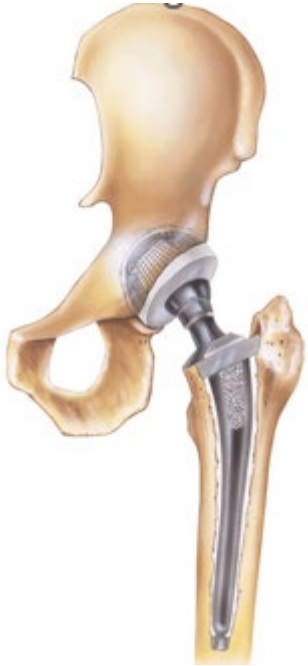
Medical Device Classification (cont.)

Class II:

- More complex, higher risk, defined class effect;
- General controls and special controls (§513(a)(1)(B) of the FD&C Act);
- Exempt: no premarket 510(k) submission; and
- Non-exempt: premarket 510(k) required.

21 C.F.R 860.3: *Special controls* means the controls necessary to provide reasonable assurance of safety and effectiveness for a generic type of device that is class II. Special controls include performance standards, performance testing, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the Federal Food, Drug, and Cosmetic Act), recommendations, and other appropriate actions, as the Commissioner deems necessary to provide such assurance.



Medical Device Classification (cont.)

Class III:

- Most complex, highest risk, no class effect:
  - Supports or sustains human life;
  - Use is substantially important in preventing impairment of human health; and
  - Presents unreasonable risk of illness or injury;
- General controls; and
- Pre-market approval (PMA) application (515 FD&C Act) required.

Prosthetic Heart Valve

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Investigational Device Exemption (IDE)

Types of IDEs:

- IDE for Significant Risk Device Study:
  - Presents a potential for serious risk to the health, safety, or welfare of a subject; and
  - Requires IRB approval and FDA IDE filing.
- Abbreviated IDE for Non-significant Risk Device Study:
  - Does not pose a significant risk to the human subjects;
  - Requires IRB approval (21 CFR 50/56) only; no IDE submission to FDA required; and
  - Required to comply with abbreviated IDE requirements.

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§515 Pre-market Approval (PMA) Application

§515 of the FD&C Act requires PMA for Class III devices:

- Required where:
  - Device supports or sustains human life;
  - Substantial importance in preventing impairment of life; and
  - Unreasonable risk of illness or injury;
- General and specific controls are insufficient to provide adequate directions to ensure safe and effective use of the medical device;
- Most stringent device marketing application required by FDA;
- Analogous to the §505(b)(1) of drugs and the §351(a) BLA for biologics; and
- Clinical data almost always required.

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§510(k) Premarket Notification

510(k) is premarket submission to FDA to demonstrate that the device to be marketed is substantially equivalent to a predicate device (21 CFR 807.92(a)(3)).

510(k) required for Class I-III devices where:

- PMA is not required;
- No exemption applies; and
- Device exceeds a limit at exemptions listed at 21 CFR 862.9 and 864.9.

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§510(k) Premarket Notification (cont.)

"Predicate" device:

- Legally marketed device against which the investigational device is compared; and
- Can be a recent 510(k) cleared device.

"Substantial Equivalence":

- New device is "at least as safe and effective" as the predicate device; and
- Compared with predicate, has same intended use and technological characteristics (or changes raise no question of safety and effectiveness).

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§510(k) Premarket Notification (cont.)

Device may not be marketed without letter from FDA declaring substantial equivalence.

If "substantial equivalence" is not found ("NSE"), sponsor may:

- Resubmit 510(k) with additional data;
- Request Class I or II designation via de novo review:
  - ***new de novo process under FDASIA of 2012; no NSE needed before requesting de novo review;
- File reclassification; and
- Submit a PMA.

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De Novo Review

- § 513(f)(2) of the FD&C Act for "Evaluation of Automatic Class III Designation" or "De Novo"
  - Pathway to a Class I or Class II classification for medical devices for which general and special controls provide reasonable assurance of safety and effectiveness, but for which there is *no legally marketed predicate device;*
  - Avoids "automatic" class III designation by operation of Section 513(f)(1) of the FD&C Act;
  - Avoids PMA requirement devices that – despite their novelty – were low to moderate risk (Class I or IIs); and
  - "novel devices anew" (De Novo Classification Guidance, Oct. 5, 2021).
- De Novo Pathways:
  - Post "NSE" De Novo – 510(k) application "NSE" decision for "reclassification" (added by FDAMA of 1997); and
  - Direct De Novo – submit De Novo request to FDA directly w/out 510(k) first (§513(f)(2)(i), added by FDASIA of 2012, amended by 21st Century Cures Act of 2016).

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De Novo Review (cont.)

- De Novo request must include description of the device and detailed information and rationale for recommended classification (§513(f)(2)(A)(iii) of the FD&C Act, 21 CFR §860.240);
- FDA determination within 120 days of receipt of the request;
- If granted, device will be classified as a Class I or Class II device:
  - Classification regulation issued for new device type;
  - Device may not serve as a predicate device;
  - Federal Register notice re: special controls; and
- If denied, the device remains Class III and may not be marketed unless there is a PMA approved, a predicate becomes available, a reclassification petition is filed, or a new De Novo request is granted.

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Combination Products

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The Lead Center for Combination Products

- 21 USC §353(g)(1) requires that FDA refer a product application to a single center.
- FDA must determine the primary mode of action (PMOA) and, on that basis, choose a lead center with primary jurisdiction.
  - **Example:** Drug PMOA will be given to CDER, but §353(g)(2) allows the agency to bring to bear any necessary resources and, accordingly, CDRH will be "consulted" on device-related aspects of the product.
  - Centers can "collaborate" or "consult."

Request for Designation (RFD)

- Submitted where center jurisdiction for combo product or single-entity product is in question for purposes of determining jurisdiction.
- Should be submitted prior to submission of a pre-approval application.
- 21 CFR §3.7(b) elements must be included:
  - Product description, intended use, sponsor's recommendation.
- OCP Guidance for Industry, How to Write a Request for Designation (RFD) (April 2011).

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Expedited Approval Mechanisms and Regulatory Incentives

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Expedited Approval Mechanisms & Alternative Approval Pathways

- Special Review Designations
  - Fast Track
  - Breakthrough Therapy
  - Breakthrough Device Programs
  - **Priority Review (including voucher programs)**
  - Orphan Drug
  - Regenerative Medicine Advanced Therapy (RMAT)
  - **Military Medical Priorities under PL 115-92**
- Special Approval Pathways
  - Accelerated Approval
  - Animal Rule
  - Emergency Use Authorization

Image source: https://www.pinterest.com/pin/251779435402005691/

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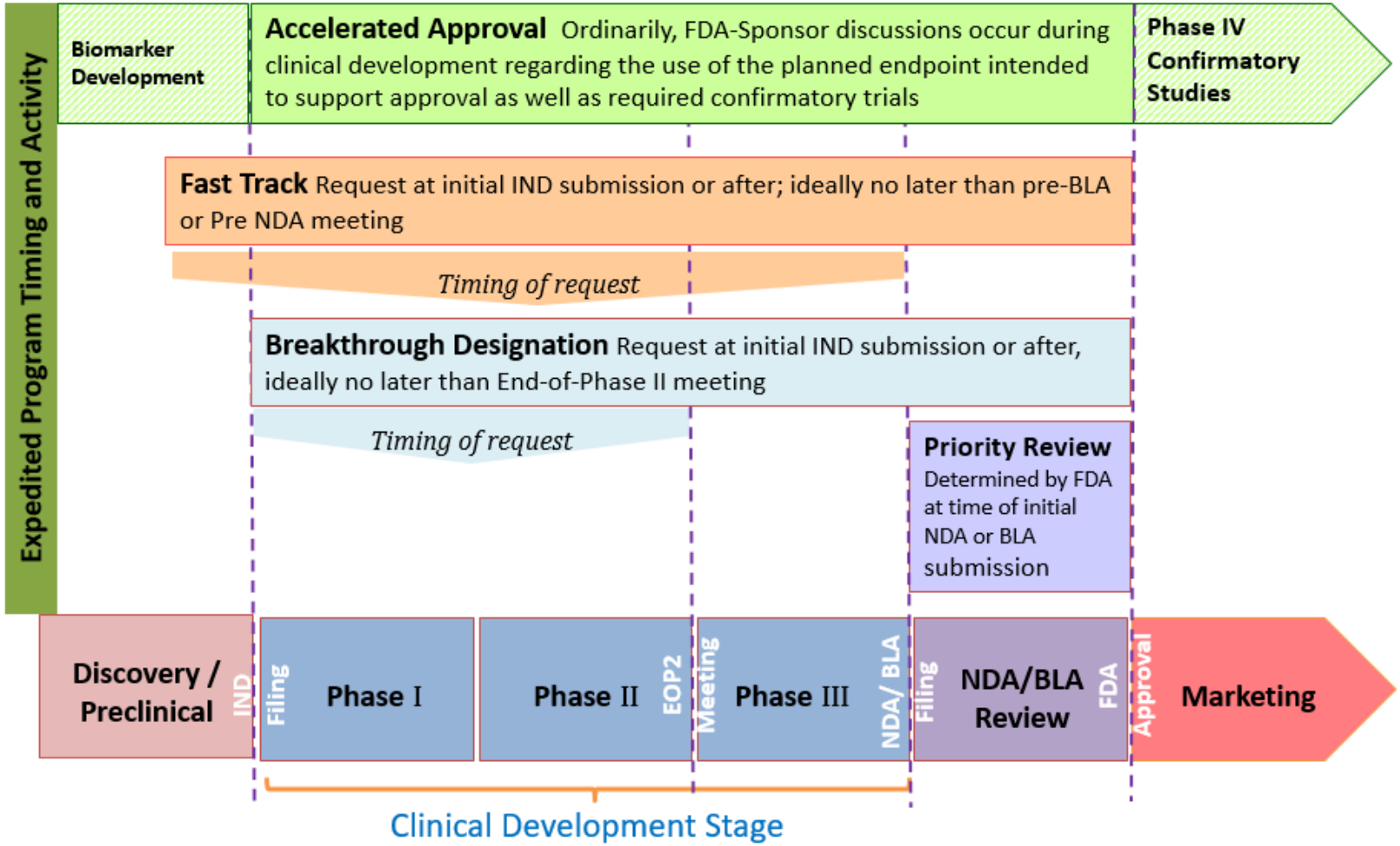
Expedited Approval Mechanisms & Alternative Approval Pathways (cont.)



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Public Law 115-92 (131 Stat. 2023-2025)

- **Expands FDA's emergency use authorization (EUA) authority** under §564 of the FD&C Act to allow FDA to issue EUAs for emergency use of unapproved medical products or unapproved uses of approved medical products to address additional types of threats (beyond chemical, biological, radiological, and nuclear (CBRN) agents) related to an attack with an "agent or agents that may cause, or are otherwise associated with, an imminently life-threatening and specific risk to the United States military forces" (*see* §1(a), P.L. 115-92)
- Allows the Secretary of Defense to request, and authorizes FDA to take, specific actions to **expedite the development of medical products**, and the review of investigational submissions, applications for approval/licensure, and submissions/notifications for clearance for such medical products reasonably likely to diagnose, prevent, treat, or mitigate a specific and life-threatening risk to the U.S. military (*see* §1(b), P.L. 115-92)
- **Requires semi-annual review between DOD and FDA of DOD's MPP portfolio** and requires quarterly DOD-CBER meetings for CBER-regulated MPPs (*see* §1(b)(3), P.L. 115-92)

Read more:

- Venable client alert
- US Army MRDC PL 115-92 Webpage
- FDA Webpage – Collaborations with DoD (includes examples of products shifted to the left)

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Three Statutory PRV Programs

1. Tropical Disease PRV
   - Applications for drugs for the treatment or prevention of certain tropical diseases under §524(a)(3) and (4) of the FD&C Act
   - Section 1102 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85) added Section 524 to the FD&C Act (21 U.S.C. 360n)
2. Rare Pediatric PRV
   - Applications for drugs to treat rare pediatric diseases as defined under 529(a)(3) of the FD&C Act
   - Section 908 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) (Pub. L. 112-144) added Section 529 to the FD&C Act (21 U.S.C. 360ff)
3. Material Threat Medical Countermeasure (MTMCM) PRV
   - "material threat medical countermeasure application," as defined under Section 319 of the Public Health Service Act
   - §3086 of the 21st Century Cures Act on 12/13/16 added section 565A to the FD&C Act (21 U.S.C. 360bbb-4a)

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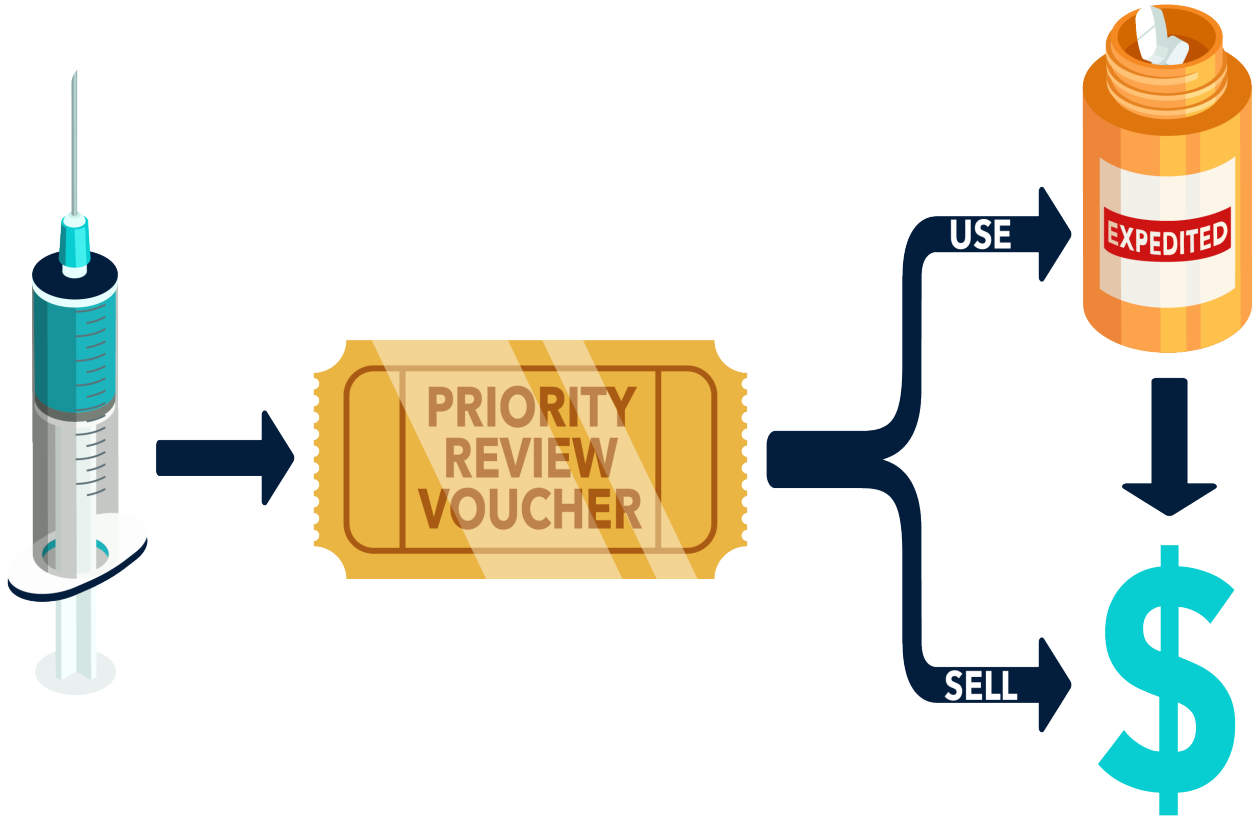
How Do PRVs Work?



FDA Regulatory Considerations in U.S. Government Contracts

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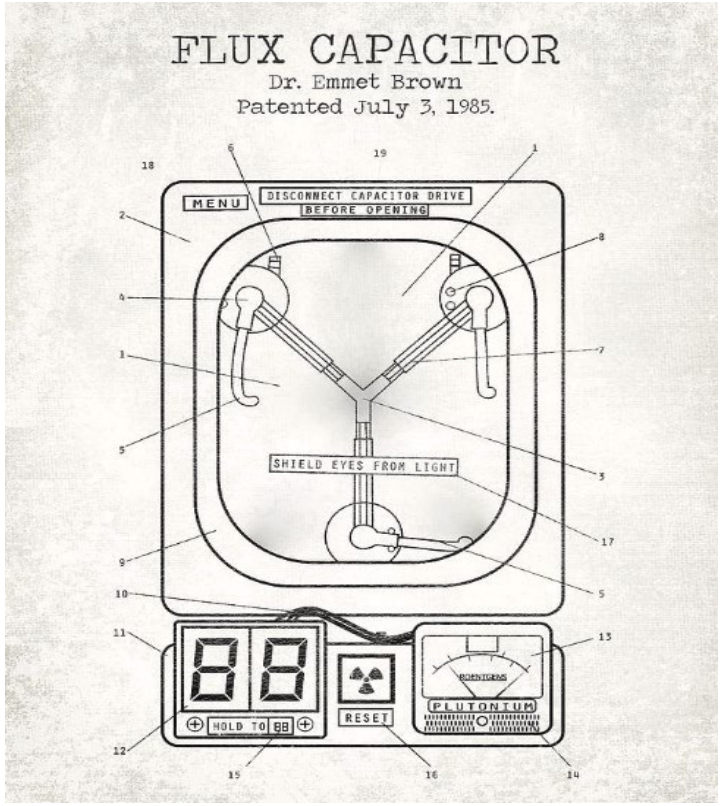
Strategic Considerations

Government R&D and Tech Transfer missions require strategic thinking regarding:

- Proper evaluation of the FDA-regulatory landscape (sponsor responsibilities, unique approval mechanisms, marketing exclusivity, PRVs)
- Correct selection of legal instrument (assistance agreement, contract, CRADA, OTA, or a combination)
- Including proper terms/clauses in legal agreements to ensure protection of intellectual property (patents, copyright, trademarks, etc.), technical data, and FDA regulatory rights

Failure in any one of these areas creates risk to the product development effort or the tech transfer mission.



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Senators Bayh and Dole

Senators Birch Bayh (L) and Bob Dole (R) at U.S. Capitol, Feb. 21, 1978 (Photo: AP Photo/John Duricka)

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Bayh-Dole Act—Key Definition

"Funding Agreement" (35 U.S.C. § 201(b)):

> "The term 'funding agreement' means any **contract, grant, or cooperative agreement** entered into between any Federal agency, other than the Tennessee Valley Authority, and any contractor **for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government**."

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The Bayh-Dole Act—Apportionment of Rights

The rights in federal **"funding agreements"** per 35 U.S.C. § 202:

- For **Subject Inventions made by the Contractor**, the Contractor has the right to own Subject Inventions (take title)
  - Government receives a Government-purpose license
  - If the Contractor declines to take title (or fails to take appropriate steps), the Government may take title
    - Contractor will normally receive a non-exclusive license, with the Government retaining a right to revoke or modify if necessary
- For **Joint Inventions,** the Government obtains joint ownership through its employee-inventor
  - Contractor needs to elect title, file, prosecute, and pay for patent to preserve Contractor's joint ownership interest

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The *Quid Pro Quo* under Bayh-Dole

Contractor must:

1. Execute all necessary instruments to protect IP
2. Require employees to disclose inventions
3. Notify Government of all Subject Inventions
4. Notify Government of decisions to elect title
5. Notify Government of decisions to abandon IP
6. Notify public of Government interest
   - Per 37 C.F.R. § 401.14(f)(4), patent must include this statement: "This invention was made with government support under (identify the contract) awarded by (identify the Federal agency). The government has certain rights in the invention."
7. Provide Government with a confirmatory instrument (license) so Government doesn't pay royalties or restrict Government use of the invention

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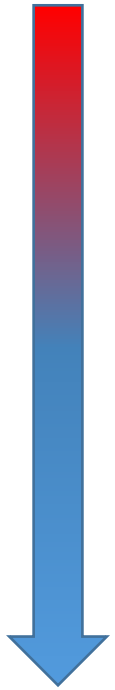
Levels of Government Rights

Greater Government rights



Lesser Government rights

Unlimited Rights

The right to use, modify, reproduce, display, release, or disclose technical data in whole or in part, in any manner, and **for any purpose whatsoever**, and to have or authorize others to do so.

Government Purpose Rights

The right to use, duplicate, or disclose technical data for Government purposes only, and to have or permit others to do so **for Government purposes only**. Government purposes include competitive procurement, but do not include the right to permit others to use the data for commercial purposes.

Limited Rights

The rights to use, modify, reproduce, release, perform, display, or disclose technical data **within the Government**. With few exceptions, the Government may not release or disclose the technical data outside the Government without the written permission of the party asserting limited rights.

Restricted Rights

Related to computer software only. Developed exclusively at private expense.

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What Are "Regulatory Rights"?

As used in USG OTA agreements, "regulatory rights" include:

1. Indication of who will be regulatory sponsor
   - Usually the contractor, but sometimes can be the Government (ASPR, OTSG)
   - Two key implications: (1) Sponsor will have responsibility for regulatory filings; and (2) Sponsor has exclusive right to communicate with FDA and FDA cannot disclose under § 301(j) of the FD&C Act
2. Communications with FDA
   - Notification of formal meetings, right to participate
3. Rights of reference (RoR) to technology
   - Government will seek broad RoR to all regulatory submissions to advance similar Government technology

What Are “Regulatory Rights”? (cont.)

4. Compliance requirements with GxPs:
   - Good Laboratory Practices, 21 CFR 58
   - Good Clinical Practice Guidelines, 21 CFR 50-56
   - Current Good Manufacturing Practices, 21 CFR 210-211
5. Potential Audit Obligations, applicable Manufacturing expectations, Clinical Investigations, etc.
   - “Man in the Plant”
   - Notice Obligations
   - Remedies of violations w/in X date

What Are "Regulatory Rights"? (cont.)

6. Potential "Clawback Clause" (OWS Example)
   - If certain specified "product development failures" occur, company will transfer ball of rights (IP, data, regulatory) to Government that are necessary for Government to continue development (internally or with third party)
   - Circumstances are largely within contractor's control:
   - Agreement is terminated for nonperformance
     - High bar – "tried and failed" is not reason enough for Government to invoke
   - Contractor voluntarily decides not to continue development
   - Contractor fails to obtain commercial approval and/or market product within time specified in agreement
     - Time is negotiable and should reflect outer limit of reasonable time to get FDA approval and commercialize

Final Thoughts

1. FDA-regulated medical product development is largely **a data-driven enterprise**; **so are R&D agreements** with the U.S. Government

2. Solidify your **FDA regulatory strategy** to get to market
   - Your strategy may not be aligned with the USG need; be careful – there is complexity in balancing your regulatory strategy in the USG R&D ecosystem

3. Focus on **big-ticket items** in the agreements:
   - Protect Intellectual Property
   - Protect Technical Data rights
     - Often, "data deliverables" will include FDA submissions and important "background" data that the government didn't pay for…
   - Protect your FDA Regulatory Rights and cede control only where necessary

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