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2nd Semi-Annual Meeting

Regulatory Practicum
Preclinical Development to Enable Clinical Studies: What Does FDA Require?

Kay Fuller, RAC
President - MDRS, LLC

January 31, 2019
Ann Arbor, Michigan

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AGENDA

- MPWRM FUNDED ITP PROJECTS OVERVIEW
- FDA'S CENTERS FOR REGENERATIVE MEDICINE PRODUCT OVERSIGHT
- HOW DOES FDA REGULATE YOUR PROPOSED PRODUCT?
- PRECLINICAL DEVELOPMENT TIPS FOR SUCCESS:
  - DEVICES
  - DRUGS/THERAPEUTICS
  - BIOLOGICS
  - CELLULAR/TISSUE
  - COMBINATION PRODUCTS
- ENABLNG FDA APPROVED IND AND IDE CLINICAL STUDIES

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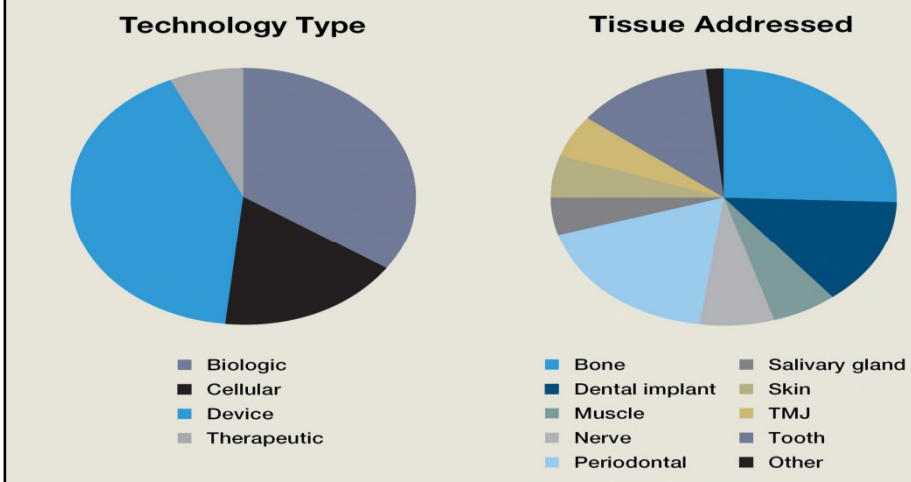
FUNDED PROJECTS OVERVIEW

16 Total ITP Funded Projects:



HOW WILL FDA REGULATE YOUR PROPOSED PRODUCT?

Let's Take a Quick Poll:

- How Many of You Know Your Product's Regulation Category?
- How Many of You Know Your Product's Intended Use Goal?
- How Many of You "Kind of Know"?
- How Many of You Would Like to Know…for Certain?
  - What is Your Product's Target Patient Population?
  - Do You Have a Preliminary Regulatory Assessment?
  - **What's a Preliminary Regulatory Assessment?**

HOW THE FDA REGULATES YOUR PRODUCT?…IT DEPENDS:

- **Is it a DEVICE?**
  - 21 CFR §820 – QSR/cGMP
  - 21 CFR §812 – IDE Investigational Device Exemption
  - 21 CFR §807.81 Premarket Notification PMN / 510(k)
  - 21 CFR §814 – PMA/ Premarket Approval
- **Is it a DRUG?**
  - 21 CFR §210 & §211 – Drug / Pharmaceutical GMP
  - 21 CFR §312 – IND Investigational Drugs
  - 21 CFR §314 – NDA/ New Drug Application
- **Is it a BIOLOGIC?**
  - 21 CFR §600-680 – Biologics / BLA
  - 21 CFR §312 – BB-IND
- **Is it HUMAN CELLULAR / TISSUE?**
  - 21 CFR §1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P)
  - 21 CFR §312 – IND Investigational Drugs
- **Is it a COMBINATION Product?**
  - 21 CFR § 4 – Regulation of Combination Products
  - 21 CFR §812 – IDE Investigational Device Exemption (PMOA-DEVICE)
  - 21 CFR §312 – IND Investigational Drugs (PMOA– BIOLOGIC/TISSUE/CELLULAR)

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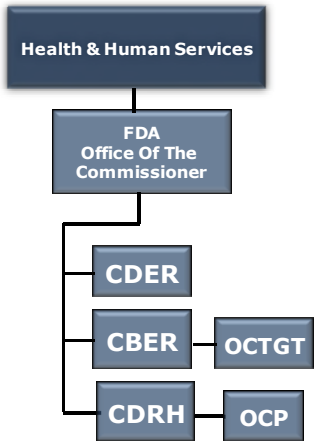
16 Total ITP FDA REGULATED Projects!

9 DEVICE	Device	TMJ
	Device	Tooth
	Device	Bone, Dental Implant
	Device	Tooth
	Device	Nerve
	Device	Bone
	Device	Bone, Dental Implant
	Device	Tooth
	Device	Bone
1 CELLULAR	Cellular	Muscle, Nerve, Skin
2 BIOLOGIC	Biologic	Periodontal
	Biologic	Dental Implant, Periodontal
4 COMBINATION	Cellular, Device	Bone, Skin
	Biologic, Device	Tooth
	Biologic, Device	Salivary gland
	Biologic, Cellular	Tooth

FDA'S CENTERS FOR MEDICAL PRODUCTS OVERSIGHT

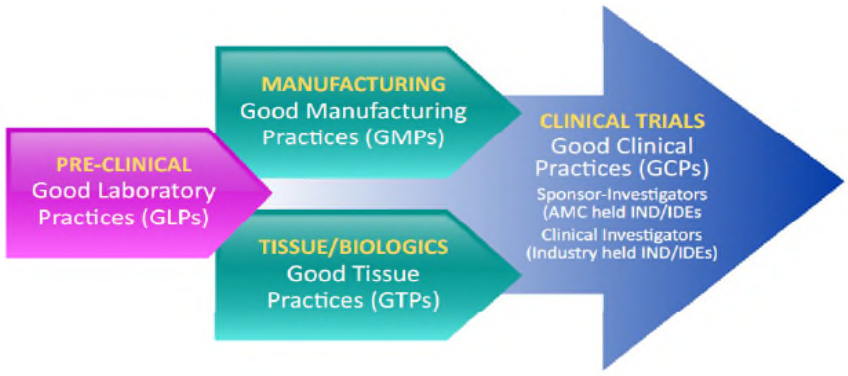
FDA is one of 20 agencies under DHHS
- Over 14,000 employees
- 3 FDA Centers for Medical Products Oversight

The FDA's mission:
To promote and protect the public health
by helping safe and effective products reach the market
& monitor products for continued safety



- ➢Center for Drug Evaluation & Research
- ➢Center for Biologics Evaluation & Research
  - ✓Office of Cellular, Tissue & Gene Therapies
- ➢Center for Devices and Radiological Health
  - ✓Office of Combination Products

GxP Categories of FDA-Regulated Translational Research: "Bench-to-Bedside"



From Kaigler D, Fuller K, Giannobile W. Regulatory process for the evaluation of dental drugs, devices, and biologics. In *Clinical Research in Oral Health* (2010), Giannobile W, Burt B, Genco R, Editors. Wiley-Blackwell Publishers, New York.

U.S. Statutory Regulations

FDA REGULATED

21 Code of Federal Regulations (CFR)

21 CFR § 4 – Regulation of Combination Products
21 CFR §11 – Electronic Records
21 CFR §50 – Protection of Human Subjects
21 CFR §54 – Financial Disclosures by Clinical Investigators
21 CFR §56 – Institutional Review Board
21 CFR §58 – Good Laboratory Practices
21 CFR §210 & §211 – Drug / Pharmaceutical GMP
21 CFR §807.81 Premarket Notification PMN / 510(k)
21 CFR §820 – Device/cGMP/QSR
21 CFR §312 – IND Investigational Drugs / BB-IND
21 CFR §314 – NDA / New Drug Application
21 CFR §600-680 – Biologics / BLA
21 CFR §812 – IDE Investigational Device Exemption
21 CFR §814 – PMA / Premarket Approval
21 CFR §1271 – Human Cells, Tissues, and Cellular and Tissue-Based Products (GTP)

E6 (R2) ICH-GCP – Good Clinical Practice Guidelines

FEDERALLY FUNDED

45 Code of Federal Regulations (CFR)

45 CFR Part 46 Human Subjects Protection

Institutional Assurance (OHRP)

HOW WILL FDA REGULATE YOUR PROPOSED PRODUCT?

- How is your product Characterized?
  - What is its *Intended Use*?
  - What is its Primary Mode of Action?
  - What is its Route of Administration / Delivery to Patient?
  - Is it Implanted? (> 29 Days) or (< 29 Days) ?
- What kind of tissue will your product contact?
  - Mucosa / Tissue
  - Bone
  - Blood / Other
- How Will it be Packaged – Is it Sterile?
- Have You Validated Sterility – EtO / Gamma / Other?

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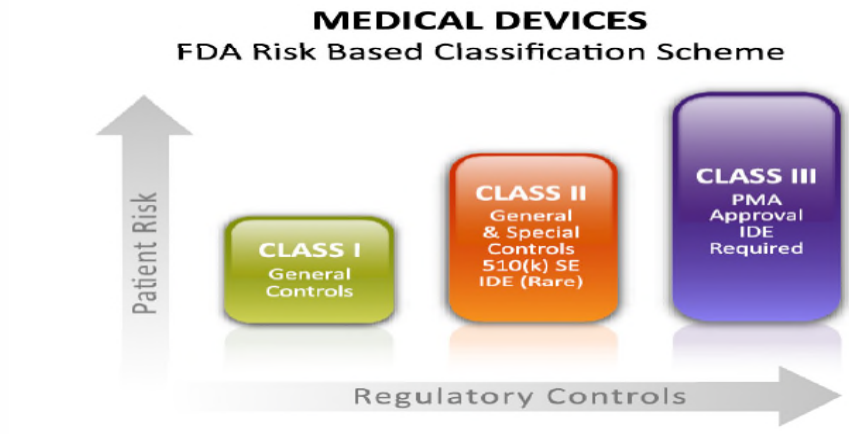
Is it a DEVICE?

Per Section 201(h) of the FD&C Act [21 USC 321(h)]

- **A Device is** "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- 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
- **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 any of its primary intended purposes."

FDA DEVICE CLASSIFICATION



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What's a Preliminary Regulatory Assessment?

MDRS,LLC Doc. Number FM1-SOP-001	Rev. A	DCO 14-001	Eff. Date 01/08/2014	Page 3 of 9 Proprietary & Confidential MDRSllc RELEASED QS DOCUMENT
FORM TITLE: PRELIMINARY REGULATORY STRATEGY RECORD FORM				

PRELIMINARY REGULATORY STRATEGY CONCLUSIONS SUMMARY	
FDA Device Classification:	Class I (Class II) Class III Other:_____ (Circle Correct Classification)
FDA Premarket Notification / 510(k) Required?:	(Yes) No [510(k) Exempt]
FDA Combination Product?:	Yes (No) (Drug Supplied Separately)
PRIMARY Medical Specialty / FDA Panel:	80 - General Hospital
FDA Seven-Digit Regulation Number/Code:	21 CFR Part 880.6920 - Syringe Needle Introducer - KZH
SECONDARY Medical Specialty / FDA Panel:	80 - General Hospital
FDA Seven-Digit Regulation Number/Code	21 CFR Part 880.5860 - Piston Syringe - PQX & NSC

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Sterilization	
ANSI/AAMI/ISO 17665-1: 2006	Sterilization of Health Care Products – Moist Heat – Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices
ANSI/AAMI/ISO 11135-1:2007	Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical device
ISO 10993-7:2008	Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals
USP 27:2004	Sterility, Biocompatibility, Biological Tests and Assays, Bacterial Endotoxin Test (LAL), Pyrogen Test (USP Rabbit Test), or other applicable tests related to the drug/biological product and delivery of the drug/biological product
AAMI/ANSI/ISO 11737-1:2006	Sterilization of medical devices-microbiological methods-Part 1: Determination of the population of microorganisms on product
Biocompatibility	
ISO 10993-1: Ed. 5 2018	Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process
Packaging and Distribution	
ANSI/AAMI/ISO 11607:2006	Packaging for terminally sterilized medical devices
ASTM D4169: 2016	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM F1980: 2016	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
***NOTE: Standard's Edition May Change - Confirm Current Edition Prior to Use; Additional Standards May Be Applicable**	
Risk Management & Usability Engineering	
BS EN ISO 14971:2012	Medical Devices - Application of risk management to medical devices
ANSI/AAMI HE 75:2013	Human factors engineering – design of medical devices
AAMI/IEC 62366-1:2015	Medical Devices – Application of usability engineering to medical devices
Labeling	
FDA 89-4203	Labeling Regulatory Requirements for Medical Devices
FDA # G91-1	Device Labeling Guidance #G91-1 (blue book memo)
ISO 15223:2016	Medical devices - Symbols to be used w/medical device labels, labeling & information to be supplied.

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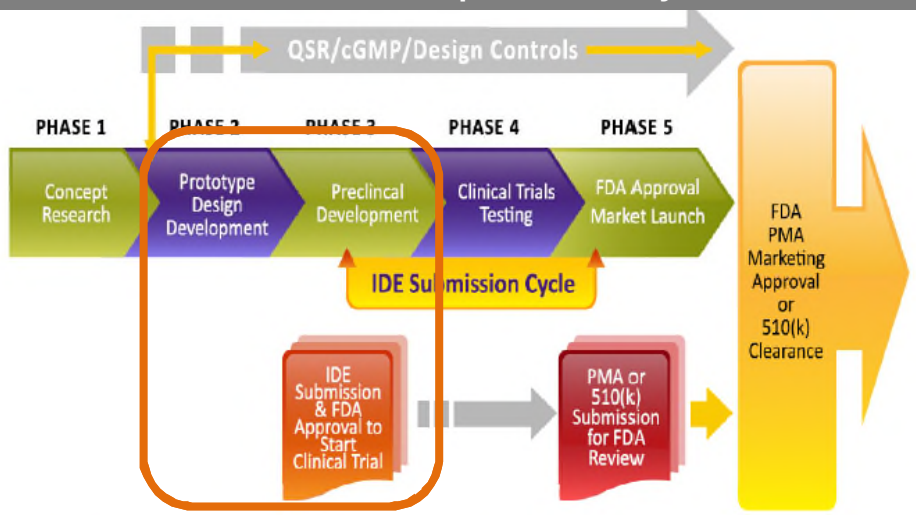
Key FDA Guidance Documents (Partial List)
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2015) https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf
Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074957.pdf
Guidance for Industry: S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceutical https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf
Guidance for Industry: M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals https://www.fda.gov/downloads/drugs/guidances/ucm073246.pdf
Guidance for Industry and Staff: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585403.pdf
Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design (2016) https://www.fda.gov/downloads/medicaldevices/.../ucm259760.pdf
FDA Design Control Guidance for Medical Device Manufacturers (1997) https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm070642.pdf
FDA Guidance Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry (2016) https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf
Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf
Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

U. S. Medical Device Development Life Cycle Overview



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Qualify Your GLP Vendor!

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GOOD LABORATORY PRACTICES
GLP Self - Assessment / Audit Questionnaire

The purpose of this questionnaire is to help qualify potential GLP services related vendors

Vendor / GLP Facility Information

Vendor Name:	
Vendor Address:	
Vendor Contact Info:	
Project Name:	
Project Manager:	
Project Sponsor:	
Project Customer:	
Self Assessment Facilitator:	
Review Date:	

Item #	21 CFR Part 58	Item / Issue for GLP Assessment	Yes/No/NA	Comments
	Subpart A - General Provisions			
1.	§ 58.10	Has the sponsor, in utilizing the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, notified them that the service is part of a nonclinical laboratory study and must be conducted in compliance with the provisions of this part?	☐ Yes ☐ No ☐ NA	
2.	§ 58.15	Does the testing facility permit the FDA, at reasonable times and in a reasonable manner, to inspect the facility and all records and specimens required to be maintained?	☐ Yes ☐ No ☐ NA	
	Subpart B – Organization and Personnel			
3.	§ 58.29(a)	Does each individual engaged in the conduct of or supervision of the study have the education, training, and experience to perform the assignments?	☐ Yes ☐ No ☐ NA	
4.	§ 58.29(b)	Does the facility maintain a current summary of training, experience, and job descriptions for each person engaged in or supervising the study?	☐ Yes ☐ No ☐ NA	
5.	§ 58.29(c)	Are there sufficient personnel for the timely and proper conduct of the study according to the protocol?	☐ Yes ☐ No ☐ NA	
6.	§ 58.29(d)	Do personnel take sanitation and health precautions to avoid contamination of test and control articles and test systems?	☐ Yes ☐ No ☐ NA	

Item #	21 CFR Part 58	Item / Issue for GLP Assessment	Yes/No/NA	Comments
	Subpart C - Facilities			
41.	§ 58.41	Is the testing facility of suitable size and construction to facilitate the proper conduct of the study?	☐ Yes ☐ No	
	Subpart D - Equipment			
63.	§ 58.61	Is equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control of appropriate design and adequate capacity to function according to the protocol?	☐ Yes ☐ No ☐ NA	
	Subpart E – Testing Facilities Operation			
74.	§ 58.81(a)	Are the SOPs in writing setting forth study methods adequate to insure the quality and integrity of the data generated in the course of a study?	☐ Yes ☐ No ☐ NA	
	Subpart F – Test and Control Articles			
115.	§ 58.105(a)	Are the identity, strength, purity, and composition or other characteristics that will appropriately define the test or control article (TCA) determined and documented for each batch?	☐ Yes ☐ No ☐ NA	
	Subpart G - Protocol for and Conduct of a Nonclinical Laboratory Study			
131.	§ 58.120(a)	Does each study have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study?	☐ Yes ☐ No	
	Subpart J – Records and Reports			
157.	§ 58.185(a)	Has a final report been prepared for each nonclinical laboratory study?	☐ Yes ☐ No ☐ NA	

BIOCOMPATIBILITY TESTING MATRIX
Nelson Laboratories Tests for Consideration
[Based on ISO 10993-1 and FDA G95-1 Guidelines]

Contact Duration
A- Limited [≤ 24 hrs]
B- Prolonged [>24 hrs to ≤30 days]
C- Permanent [>30 days]

Body Contact			Initial Biological Effect								Other*	
			Cytotoxicity	Sensitization	Irritation	Systemic Toxicity	Subacute (Subchronic Toxicity)	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity
Surface Devices	Skin	A	●	●	●							
		B	●	●	●							
		C	●	●	●							
	Mucosal Membranes	A	●	●	●							
		B	●	●	●	○	○		○			
		C	●	●	●	○	●	●	○		○	
	Breached or Compromised Surfaces	A	●	●	●	○						
		B	●	●	●	○	○		○			
		C	●	●	●	○	●	●	○		○	
External Communicating Devices	Blood Path, Indirect[3]	A	●	●	●	●				●		
		B	●	●	●	●	○			●		
		C	●	●	○	●	●	●	○	●	●	●
	Tissue[1]/Bone/Dentin Communicating	A	●	●	●	○						
		B	●	●	●	●	●	●	●			
		C	●	●	●	●	●	●	●		●	●
	Circulating Blood[3]	A	●	●	●	●		○[2]		●		
		B	●	●	●	●	●	●	●	●		
		C	●	●	●	●	●	●	●	●	●	●
Implant Devices	Tissue/Bone	A	●	●	●	○						
		B	●	●	●	●	●	●	●			
		C	●	●	●	●	●	●	●		●	●
	Blood[3]	A	●	●	●	●			●	●		
		B	●	●	●	●	●	●	●	●		
		C	●	●	●	●	●	●	●	●	●	●

Nelson Laboratories

KEY STEPS FOR PRE-CLINICAL TESTING OF MEDICAL DEVICES

1

» DESIGN & DEVELOP DEVICE:
In Compliance w/ FDA Engineering Design Control Regulations
[US FDA QSR: 21 CFR 820.30 (a)–(j)]

» FREEZE PROTOTYPE DESIGN:
For Design Verification
Design Inputs = Design Output Requirements
[US FDA QSR: 21 CFR 820.30(f)]

» APPROVE DEVICE DESIGN:
Build Devices For Bench Testing

2

» PASS BENCH TESTING

» QUALIFY GLP VENDOR
[US QSR & 21 CFR 58]

» PREP ANIMAL PROTOCOL
[Primary Endpoints Prove Safety/Some Efficacy, if Possible]

» GAIN ANIMAL STUDY APPROVALS TO BEGIN

3

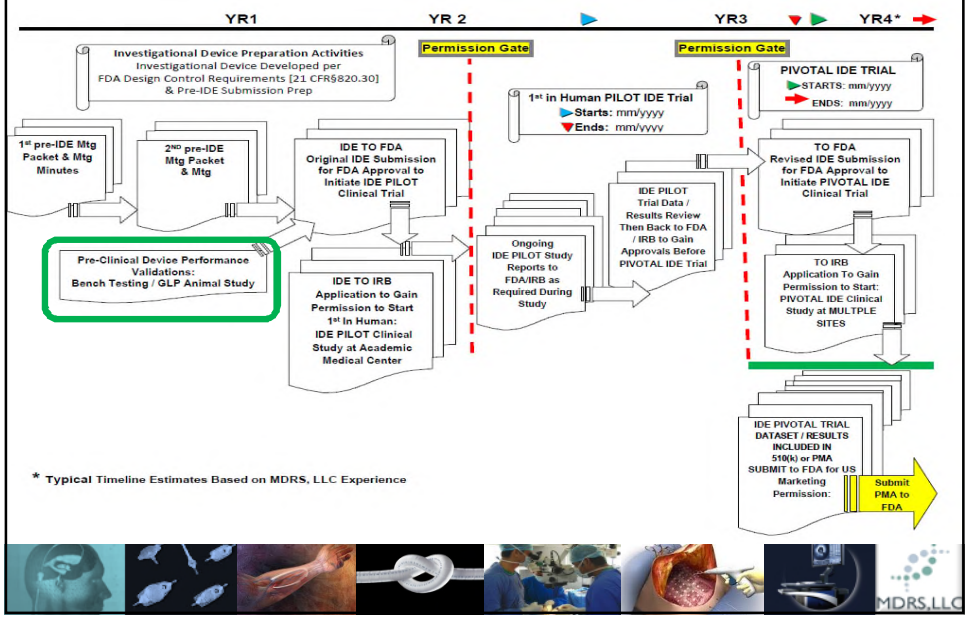
» CONDUCT GLP ANIMAL STUDY

» SUMMARIZE ANIMAL STUDY RESULTS / DATA

» ADD TO IDE SUBMISSION FOR FDA APPROVAL TO START HUMAN TRIALS
[US FDA 21 CFR 812]

TO FDA

TYPICAL FDA IDE PREP & SUBMISSION ACTIVITIES FOR CLASS III PMA DEVICE



FDA Submissions…Just a Little Paperwork!

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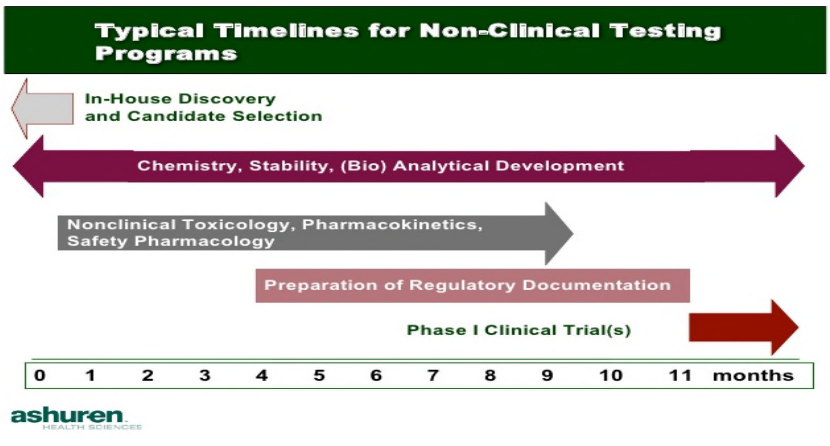
PRECLINICAL TRANSLATIONAL DEVELOPMENT



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PRECLINICAL TRANSLATIONAL DEVELOPMENT DON'T FORGET TO:

- ❑ Have Clear Intended Use Statement
- ❑ Preliminary Regulatory Assessment
- ❑ Get Early Preclinical Planning Support
- ❑ Delivery Route / Implantation Duration
- ❑ GLP Species / Model to Enable IDE / IND
- ❑ Plan Biocompatibility / Toxicology Testing
- ❑ Plan Sterility/Packaging/Stability Shelf-Life

- ✓ It Defines Regulatory Pathway Requirements
- ✓ Qualify GLP Vendor EARLY
- ✓ Preclinical Testing to Support GCP Trial
- ✓ GLP Study Design = GCP Protocol / Study Design
- ✓ GLP Compliant –
- ✓ or GLP GAP Rationale
- ✓ To Test Investigational Product in GLP / GCP

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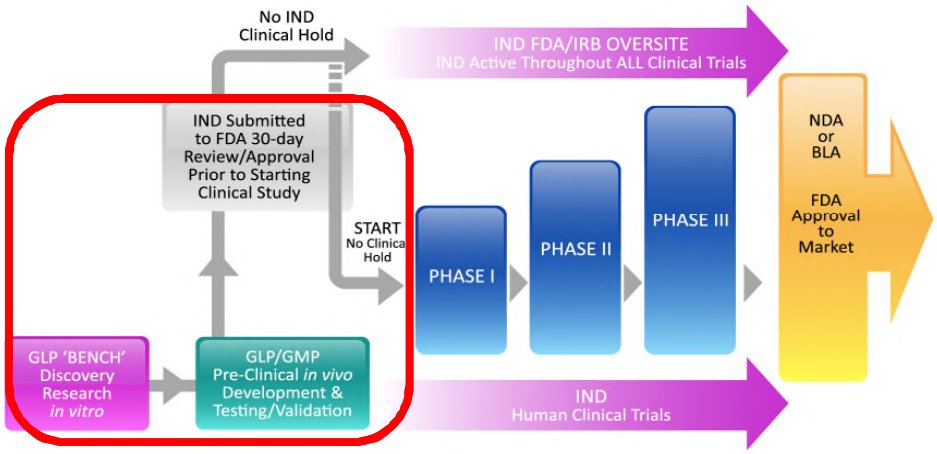
Is it a DRUG?



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Is it a BIOLOGIC?

21 CFR§ 600.3 Definitions

(h) ***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:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

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Is it a BIOLOGIC?

Guidance for Industry

S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

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Is it a BIOLOGIC?

4.2.2 Nonclinical Studies for Biologics

Similar to other drugs, biologics must undergo laboratory and animal testing to define their pharmacologic and toxicologic effects before they can be studied in humans.[32] The legal framework for preclinical testing of biologics is essentially similar to that for drugs; for example, the FDA's good laboratory practice (GLP) regulations typically apply.[33] Nevertheless, biologics present special issues, necessitating a "flexible, case-by-case, science-based approach" to preclinical testing.[34]

For biotechnology-derived pharmaceuticals, the FDA has adopted the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) S6 guidance, which describes the unique

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Is it a BIOLOGIC?

4.2.2.3 Typical Preclinical Testing Sponsors usually must conduct PD studies, such as *in vitro* binding assays and *in vivo* studies that assess the product's pharmacologic activity and define its mechanism of action.[48] Biologics typically undergo single- and repeat-dose toxicity studies using relevant species, as noted earlier.[49] Safety pharmacology studies, which evaluate the product's functional effects on major body systems and specific organs, and local tolerance testing can be done separately or subsumed in toxicity testing.[50]

Sponsors also usually conduct single- and multiple-dose PK and/or toxicokinetic studies to assess absorption, disposition, exposure, and clearance (in particular, antibody-mediated clearance) and explore dose–response relationships.[51] This information is used to predict margins of safety for human studies. Immunogenicity testing might include screening and mechanistic studies, but animal models are not highly predictive of human immunogenicity.[52]

Typical carcinogenicity bioassays are "generally inappropriate" for biologics, although the S6 guidance calls for assessment of carcinogenicity when warranted based on the "duration of clinical dosing, patient population, and/or biological activity."[53] If concern exists regarding carcinogenic potential, the sponsor can consider several approaches to assess risk, including testing in a variety of malignant and normal human cells and further testing in relevant species.[54] According to ICH S6, reproductive and developmental toxicity studies may or may not be recommended, depending on "the product, clinical indication, and intended patient population."[55] Such studies using primate species pose challenges because of these animals' heterogeneous drug responses, high background abortion rate, and low number of offspring.[56]

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Is it a BIOLOGIC?

Developing a Biologic is Different From a Drug

Differences between small molecules and biologics
– a generalization

Small Molecule Drug	Biologic
Low molecular weight	High molecular weight
Familiar antecedents	Potentially unique
Known impurities	Unfamiliar impurities
Often orally dosed	Often parenteral, IV dosing
Maximal tolerated dose	Optimal biologic dose
Meaningful chronic tox	Uncertain chronic tox
Species-independent	Species-specific
Biotransformed	Degraded
Not immunogenic	Immunogenicity issues

ashuren HEALTH SCIENCES

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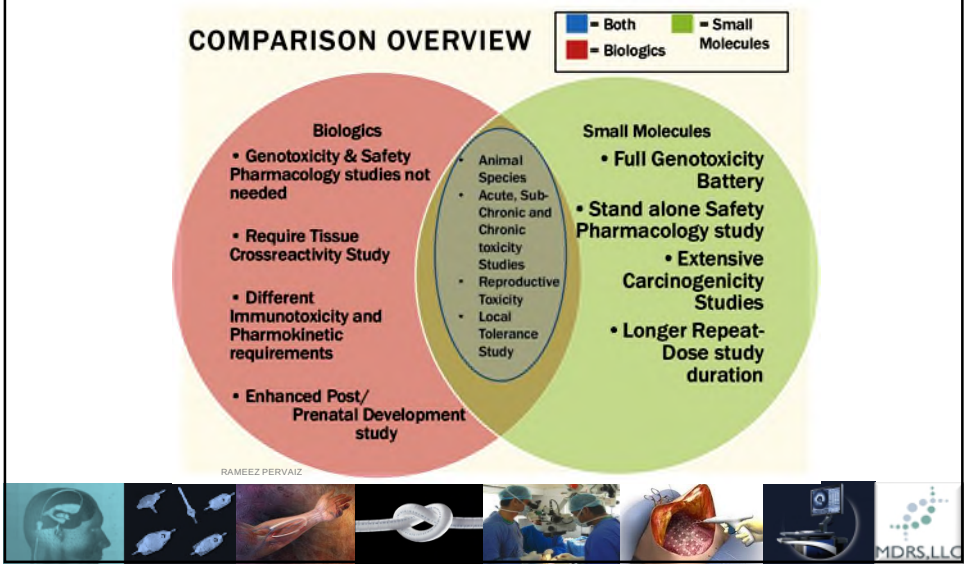
Is it a BIOLOGIC?



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Is it a BIOLOGIC?

- **CMC/cGMP**
  - Cell Line Development
  - Protein Characterization & Testing
  - Bioprocess Development
  - Cell Banking Testing & Viral Clearance / Sterilization
- **GLP**
  - GLP Non-clinical Studies
- **GCP**
  - Submit BB-IND for FDA Approval to Begin Clinical Trial

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Is it a BIOLOGIC?

Two study species required:

Rodent: Mice/Rats	Nonrodent: Rabbits, Nonhuman Primates (NHP), Dogs

Biologics: Require relevant species

Biologically active	contains epitope/target	Can use one species → must justify

RAMEEZ PERVAIZ

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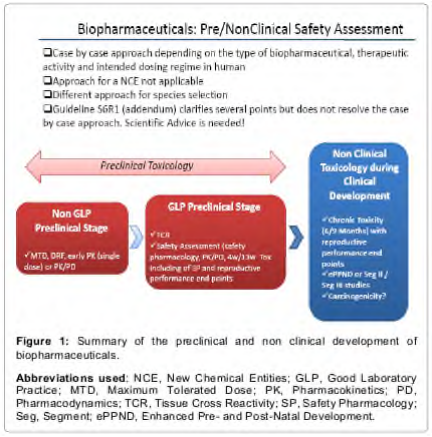
Is it a BIOLOGIC?



Maraschiello C (2014) The Relevance of Immunogenicity in Preclinical Development. J Bioanal Biomed 6: 001-004

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Is it HUMAN CELLULAR / TISSUE (HCT/P)?

21 CFR §1271.3 HCT/Ps Definition
(d) ***Human cells, tissues, or cellular or tissue-based products (HCT/Ps)*** means articles **containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient**. Examples of HCT/Ps include, but are not limited to, **bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive** tissue.

The following articles are not considered HCT/Ps:

(1) Vascularized human organs for transplantation;
(2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;
(3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P;
(4) Minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);
(5) Ancillary products used in the manufacture of HCT/P;
(6) Cells, tissues, and organs derived from animals other than humans; and
(7) In vitro diagnostic products as defined in 809.3(a) of this chapter.
(8) Blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

Guidance for Industry and Food and Drug Administration Staff

For questions on the content of this guidance, contact Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD) at 240-402-8010 or 800-835-4709. For questions about this document concerning products regulated by Center for Devices and Radiological Health (CDRH), contact the Office of the Center Director at 301-796-5900. If you need additional assistance with regulation of combination products, contact the Office of Combination Products (OCP) at 301-796-8930.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Office of Combination Products
November 2017
Corrected December 2017

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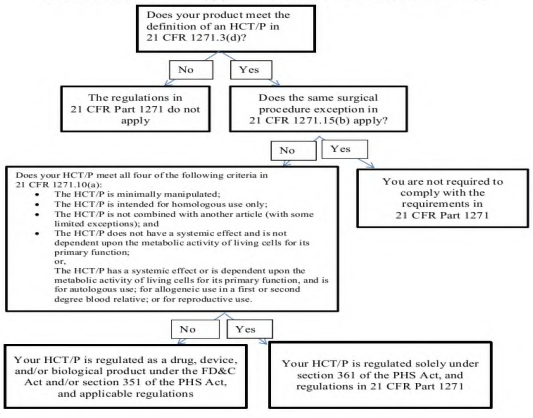
HCT/Ps may fail to meet more than one of the four criteria in 21 CFR 1271.10(a). The following flowchart illustrates how manufacturers and healthcare providers should apply the criteria outlined in 21 CFR 1271.15(b)[9] and 1271.10(a) for HCT/Ps:

Flowchart to illustrate how to apply the criteria in 21 CFR 1271.15(b) and 1271.10(a)



[9] For additional information about applying the exception in 21 CFR 1271.15(b), see the "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry" dated November 2017.

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Is it HUMAN CELLULAR / TISSUE (HCT/P)?

III. PRECLINICAL STUDY CONSIDERATIONS

A. Preclinical Program Objectives

The preclinical studies that are conducted are an important element of the overall development pathway for an investigational product. The overall objectives for a sufficient preclinical program for a CGT product include, as applicable:

1. Establishment of biological plausibility.
2. Identification of biologically active dose levels.
3. Selection of potential starting dose level, dose-escalation schedule, and dosing regimen for clinical trials.
4. Establishment of feasibility and reasonable safety of the investigational product's proposed clinical route of administration (ROA).
5. Support of patient eligibility criteria.
6. Identification of physiologic parameters that can guide clinical monitoring.
7. Identification of potential public health risks (e.g., to the general public, caregivers, family members, close contacts (for example co-workers), and intimate contacts).

The resulting data from preclinical studies should address these objectives in order to guide the design of early-phase clinical trials, as well as establish a platform for the conduct of future preclinical studies, such as reproductive/developmental toxicity studies, that may be needed to support later phases of product development.

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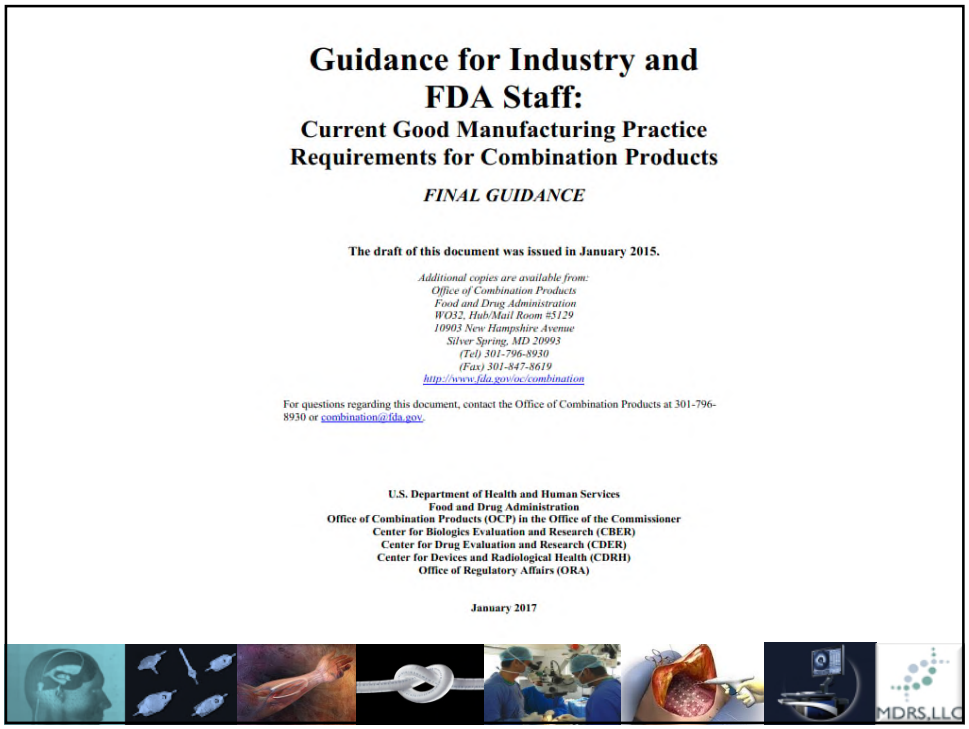
Is it a Combination Product?

A. Definition of a combination product

As set forth in part 3 (21 CFR part 3), a combination product is a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another).[5] The drugs, devices, and biological products included in combination products are referred to as "constituent parts" of the combination product.

Under 21 CFR 3.2(e), a combination product includes:

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity *(a "single entity" combination product, such as a prefilled syringe or drug-eluting stent)*;
- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products *(a "co-packaged" combination product, such as a surgical or first-aid kit)*;
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved, individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength,



Guidance for Industry and FDA Staff:

Current Good Manufacturing Practice Requirements for Combination Products

FINAL GUIDANCE

The draft of this document was issued in January 2015.

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
WO32, Hub/Mail Room #5129
10903 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-847-8619
http://www.fda.gov/oc/combination

For questions regarding this document, contact the Office of Combination Products at 301-796-8930 or combination@fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in the Office of the Commissioner
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Office of Regulatory Affairs (ORA)

January 2017

THE CHALLENGE OF COMBINATION PRODUCTS…

Product	Pre-Market Clinical Trial Submission	FDA Market Approval Submission	FDA Reviewing Center	Quality System	Safety Reporting
Device	IDE	PMA, 510(k)	CDRH	QSR	MDR
Drug	IND	NDA	CDER	GMP	AERS
Biologic	BB-IND	BLA	CBER / CDER	GMP	AERS

ENABLNG FDA APPROVED IDE AND IND CLINICAL STUDIES

MDRS,LLC
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MDRS TEMPLATE
Investigational Device Exemption Submission
Table of Contents

Page

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Page

ENABLNG FDA APPROVED IDE AND IND CLINICAL STUDIES

2. REPORT OF PRIOR INVESTIGATIONS
2.1. Review of [Device Name] Published Literature
2.2. Pre-Clinical Research Summary
2.2.1. *In Vitro* Testing
2.2.1.1. Performance Testing
2.2.1.2. Biocompatibility Testing
2.2.1.3. Sterility Assurance
2.2.1.4. Design Analysis and Validation Testing Summary
2.2.2. *In Vivo* Testing
2.2.2.1. GLP Compliance Statement
2.2.2.2. Acute Animal Study
2.2.2.2.1. Animal Model Rationale
2.2.2.2.2. Study Design
2.2.2.2.3. Endpoints
2.2.2.2.4. Study Size & Follow-Up Duration
2.2.2.2.5. Study Summary
2.2.2.3. Chronic Animal Study
2.2.2.3.1. Animal Model Rationale
2.2.2.3.2. Study Design
2.2.2.3.3. Endpoints
2.2.2.3.4. Study Size & Follow-Up Duration
2.2.2.3.5. Study Summary
2.3. Prior Clinical Research Summary
2.3.1. ROW Clinical Experience Statement

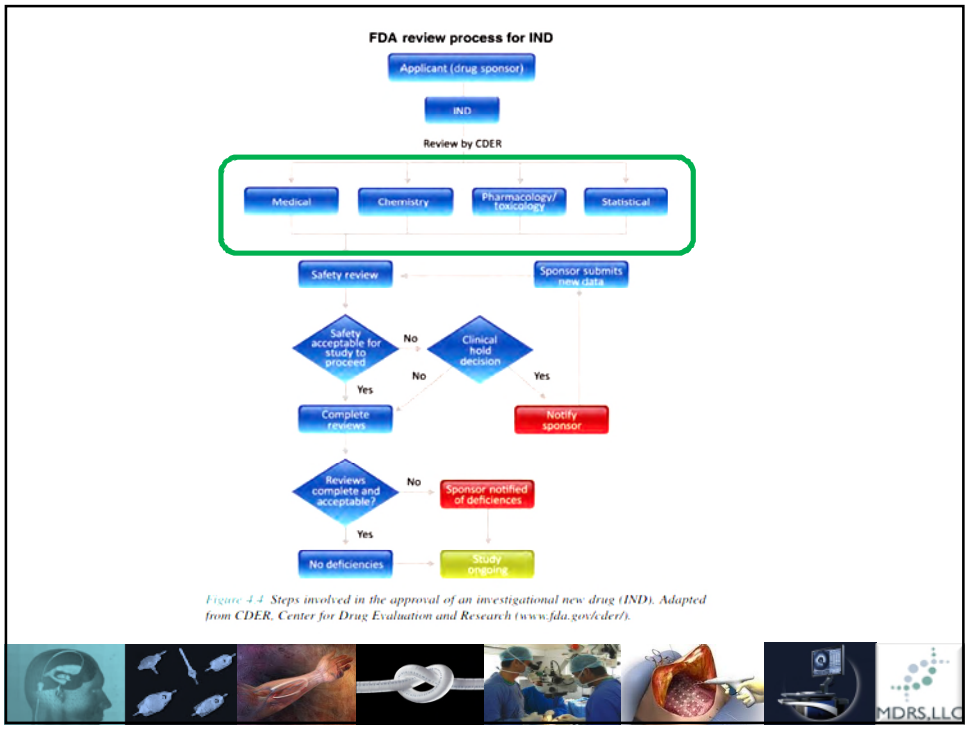

Figure 4.4 Steps involved in the approval of an investigational new drug (IND). Adapted from CDER, Center for Drug Evaluation and Research (www.fda.gov/cder/).

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2nd Semi-Annual Meeting

Thank You!

Kay Fuller, RAC
President - MDRS, LLC

January 31, 2019
Ann Arbor, Michigan