Gene Therapy for Blood Disorders

March 3-5, 2020 | Boston, MA

Strategic Gene Therapy Product Platforms and Partnerships:

From Co-development to Companion Products

March 3, 2020

Angela N. Johnson, MSE, PMP, RAC

Angela@angelanjohnson.com

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Angela@angelanjohnson.com

Meet the Presenter

- 15+ years strategic leadership of clinical trials projects in cell and gene therapy, medical devices, and combination products
- Prior Sr Manager of Clinical Operations for GE Healthcare, and Director of Strategic Development of Quintiles/IQVIA
- ASGCT Government Relations Board Member
- ARM EU and US Regulatory Committee Member
- Author of 2017 GCP, and 2019 Gene & Cell Therapy chapters in Best-selling RAPS regulatory strategy textbooks

Agencies Wrote the Regulations.
We Wrote the Book.

Fundamentals of US Regulatory Affairs, 10th Edition

Agenda

3:00 - 3:45 pm

US and EU IVD, Diagnostics, and Companion Products: Regulatory Fundamentals

BREAK

4:00 - 4:45 pm

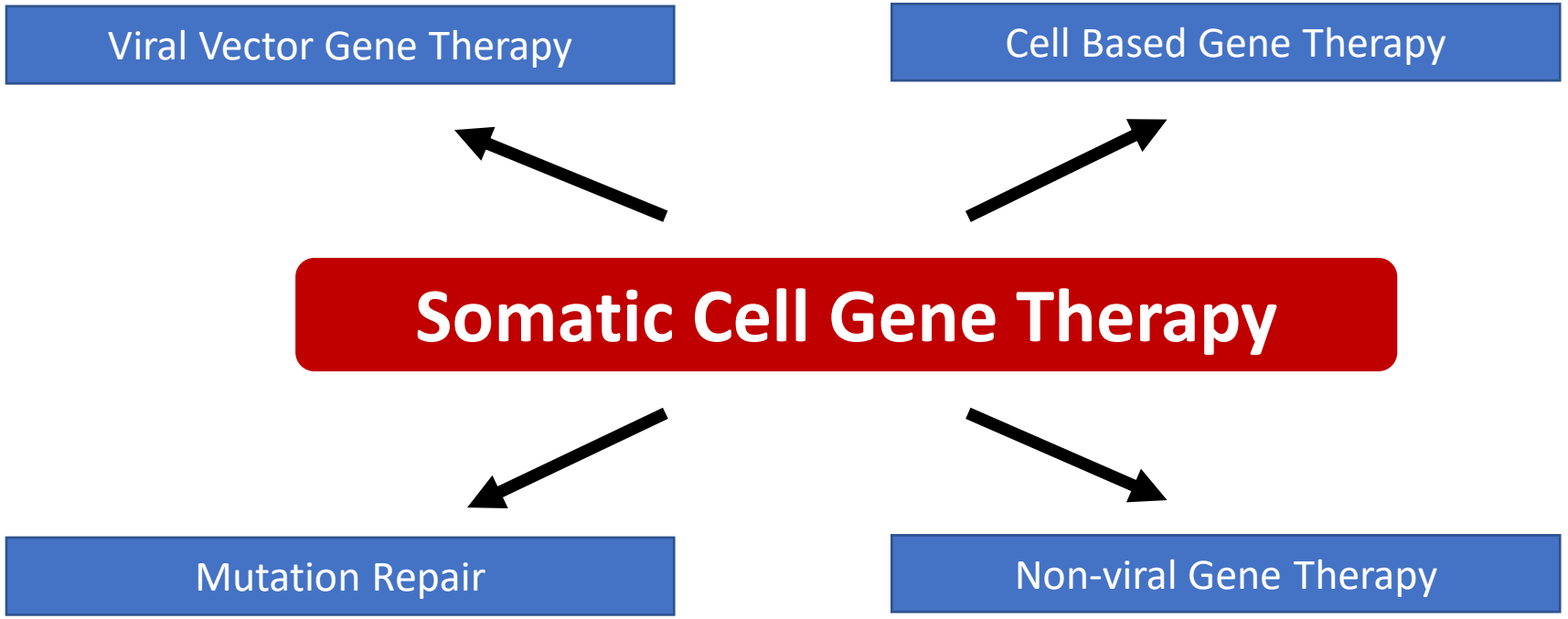
Clinical Strategies for Co-Development of Gene Therapy Products

BREAK

5:00 - 5:30 pm

Strategy Recap and Q&A

Types of Gene Therapy



Targets for Gene Therapy

Hemophilia
Von Willebrand Disease
Cystic Fibrosis
Muscular Dystrophy
Sickle Cell Disease
Thalassemia
Gaucher's Disease
β-Thalassemia
Pompe Disease

Monogenic Diseases

Pathology primarily due only to a single gene defect, providing good targets for gene therapy

Leukemia
Non-Hodgkins' Lymphoma

Oncologic Diseases

Several therapies are being developed to target cancers

e.g. Kymriah, Novartis

KYMRIAH® (tisagenlecleucel)

Types of Companion Products

A **companion diagnostic device** can be and

- **in vitro diagnostic (IVD) device**
- **nucleic acid-based companion diagnostic tests (human or microbial genetic tests)**
- **imaging tool (quantitative & qualitative)**

that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

Interactive – Background

Take the next 5 minutes to discuss in your tables the devices, diagnostic imaging, and/or in vitro diagnostic (IVD) (e.g. tests/assays) that you encounter in your therapeutic area.

What are you hoping to get out of this session?

Example IVD Products in Bleeding Disease

Hemophilia

ZYMUTEST™ Anti FVIII IgG Mono Strip	Hemophilia A | Auto and Allo-antibodies Anti-Factor VIII
BIOPHEN™ FIX	Hemophilia B | FIX Assay
BIOPHEN™ FVIII:C	Hemophilia A | FVIII Assay
Factor VIII:C Deficient Plasma	Hemophilia A | Immunodepleted Plasma for Clotting Assays
Factor IX Deficient Plasma	Hemophilia B | Immunodepleted Plasma for Clotting Assays
ZYMUTEST™ Factor IX	Hemophilia B | FIX Assay

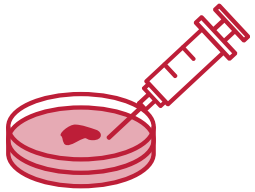
Von Willebrand's Disease

LIAPHEN™ vWF:Ag	Immunoturbidimetric assay for vWF:Ag
ZYMUTEST™ vWF	ELISA for vWF
ZYMUTEST™ vWF:CBA	ELISA for collagen binding activity of vWF
Lyophilized platelets	vWD | Platelet aggregation reagent
Ristocetin	vWD | Platelet aggregation reagents

Sickle Cell & other hemoglobinopathies

Sickle SCAN®	rapid, qualitative lateral flow immunoassay kit for the identification of sickle cell disorder of hemoglobins A, S, and C
PreciseType™ HEA	human erythrocyte antigen

Growing Market Opportunity



Cell Therapy (allogeneic/autologous)

$2.7 Billion → $8.2 Billion

Gene & Gene Modified Cell Therapy

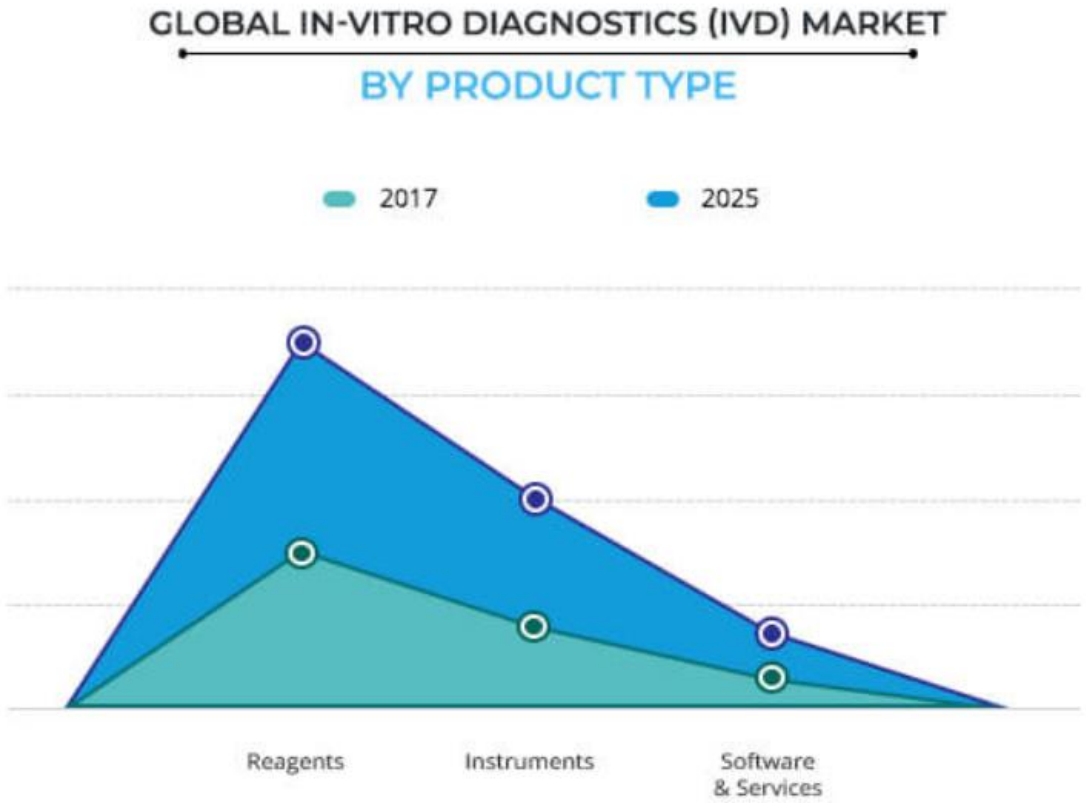
$3.8 Billion → $13.0 Billion

In Vitro Diagnostics (IVD)

$61.2 Billion → $87.1 Billion

Increase from 2018 to 2026

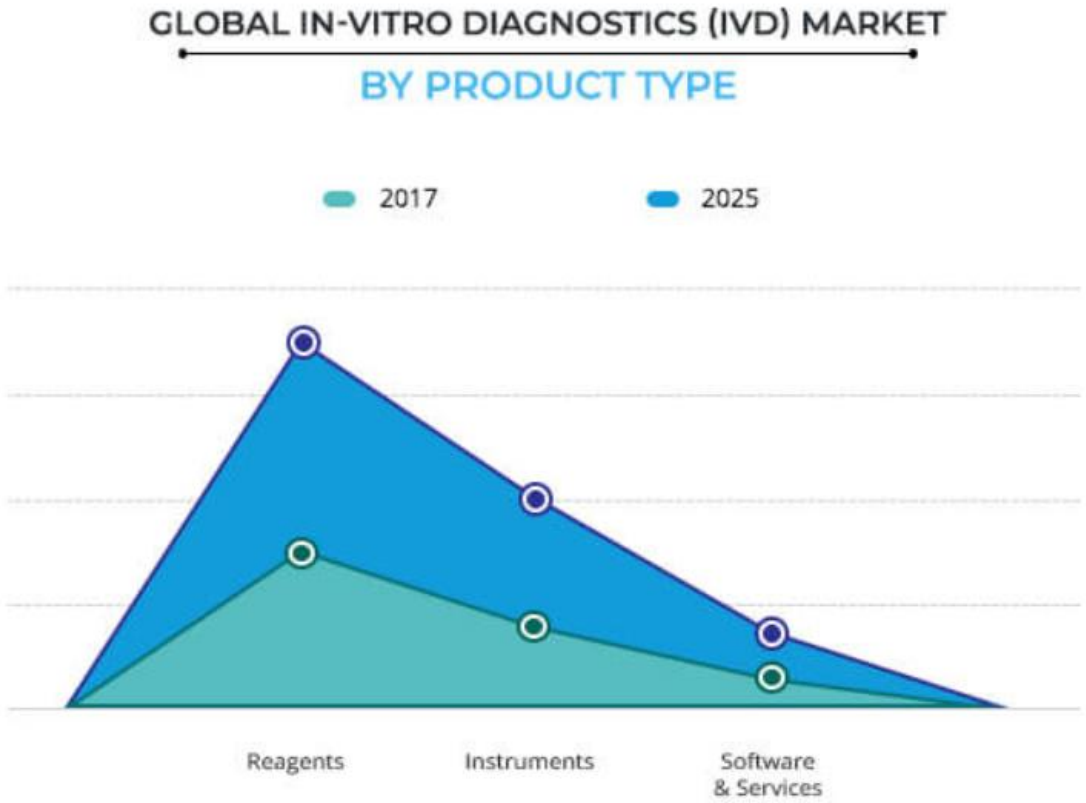
Growing IVD & Companion Product Market



Source: Allied Market Research 2018

- **Reagent**: chemical, biological or immunological components, solutions or preparations
- **Instrument:** equipment or apparatus intended by the manufacturer to be used as IVD medical device
- **Software/Service**: standalone software intended for data analysis or monitoring therapeutic measurements

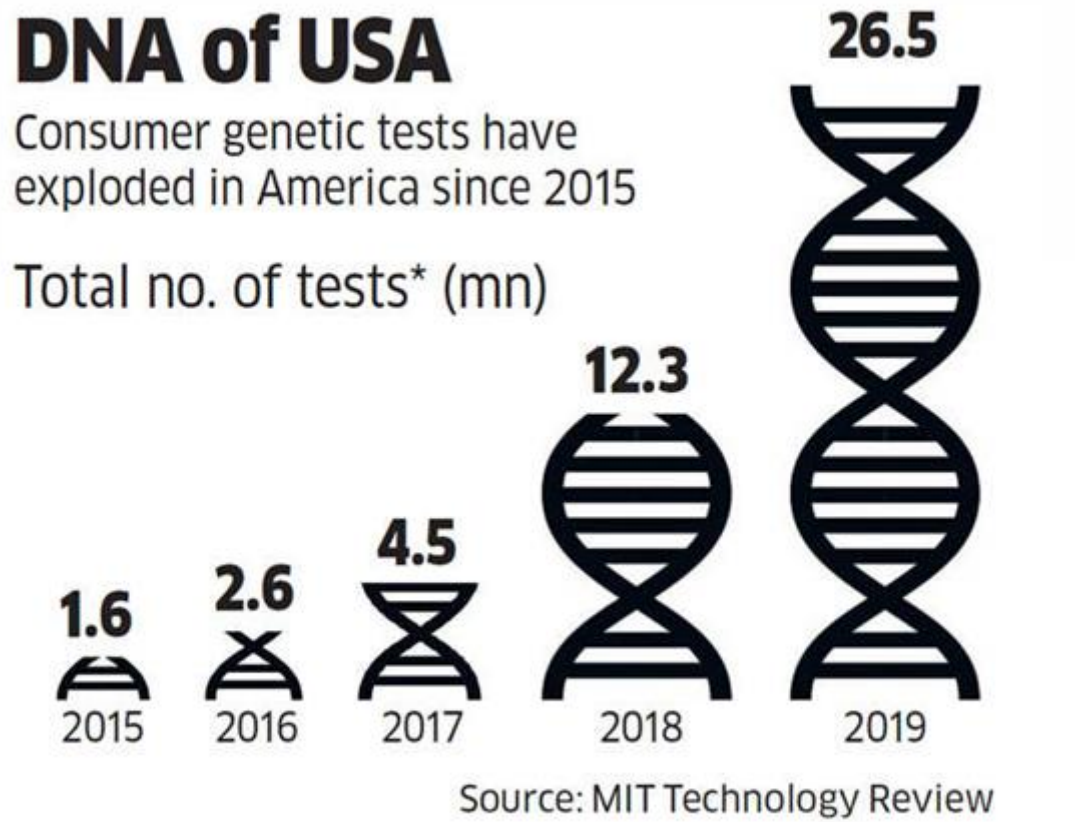
Growing IVD & Companion Product Market



Source: Allied Market Research 2018

Reagents are one of the largest groups of products reviewed as medical devices by FDA **Center for Biologics Evaluation and Research (CBER)**

Growing consumer genetic testing



What is an In Vitro Diagnostic (IVD)

A medical device is an **in vitro diagnostic medical device (IVD)** if it is a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with other diagnostic goods for in vitro use.

Why companion diagnostic (CDx)?

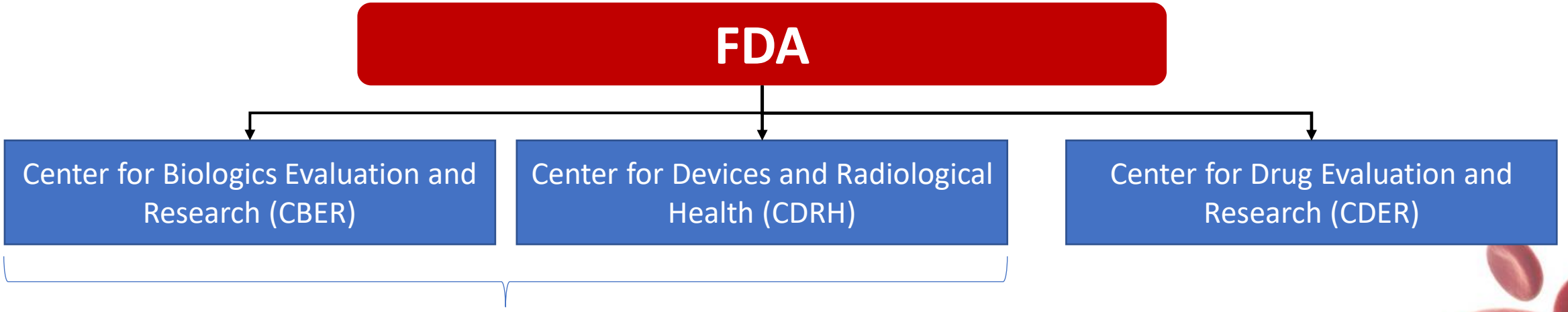
A **companion diagnostic (CDx)** is a medical device, often an in vitro diagnostics (IVD), which provides information that is **essential for the safe and effective use** of a corresponding drug or biological product.

Companion diagnostics can:

- **identify patients** most likely to benefit from a particular therapeutic product
- identify **risk for serious side effects** as a result of treatment
- **monitor response to treatment** to achieve improved safety or effectiveness.
- **select optimal dose** of a particular therapeutic

FDA Review of IVD/CDx Products

IVD/CDx products are reviewed by either FDA Center for Devices and Radiological Health (CDRH) or Center for Biologics Evaluation and Research (CBER), which as reviewed products since the 1940s (e.g. products containing antibodies).

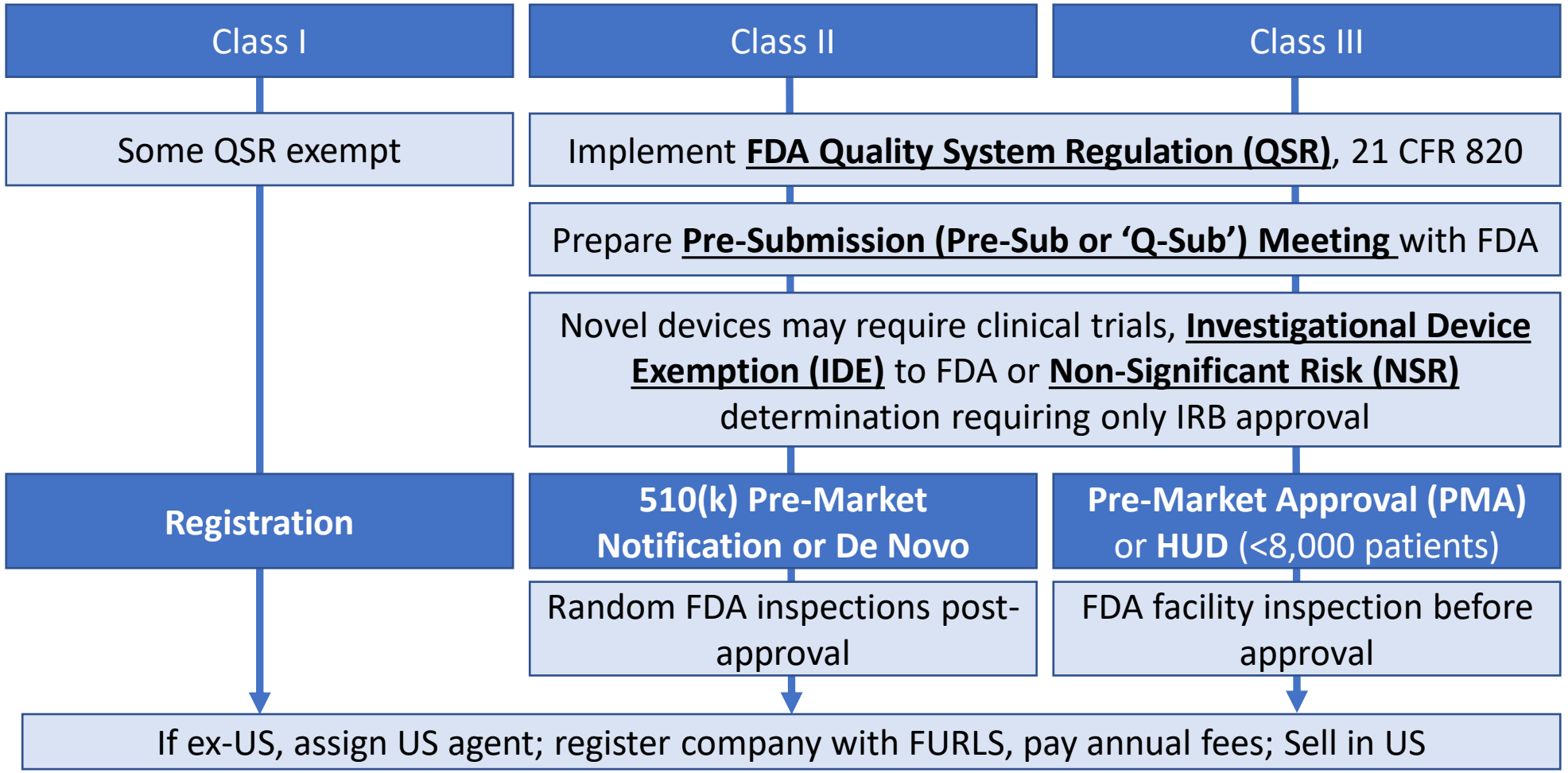


US FDA Classification of IVD/CDx Products

Risk level of IVD/CDx is based on consequence of false result, in three levels:

- **Class I** common, low risk devices (~50% of all IVDs)
  e.g. lactic acid, erythrocyte sedimentation rate tests, differential culture media
- **Class II** more complex, moderate risk (~42% of all IVDs)
  e.g. factor deficiency tests, antimicrobial susceptibility tests, thyroid stimulating hormone tests
- **Class III** most complex, high risk, or novel intended use (~8% of IVDs)
  e.g. hepatitis C virus test

US FDA IVD / CDx Pathways



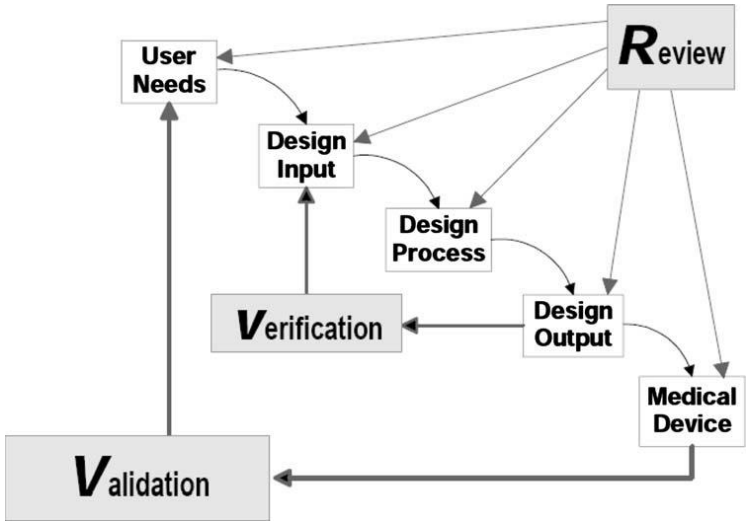
US FDA: Class I IVD/CDx products

Class I are common, low risk devices

- Subject to general controls
- Registration and listing, manufacturers must register their facilitates
- Subject to **21 CFR 820 Quality System Regulation (QSR)**, which described good manufacturing practices for medical devices and diagnostics
- Reporting of Adverse Events and Recalls
- Device labelling provisions
- Subject to records and provision of reports to FDA

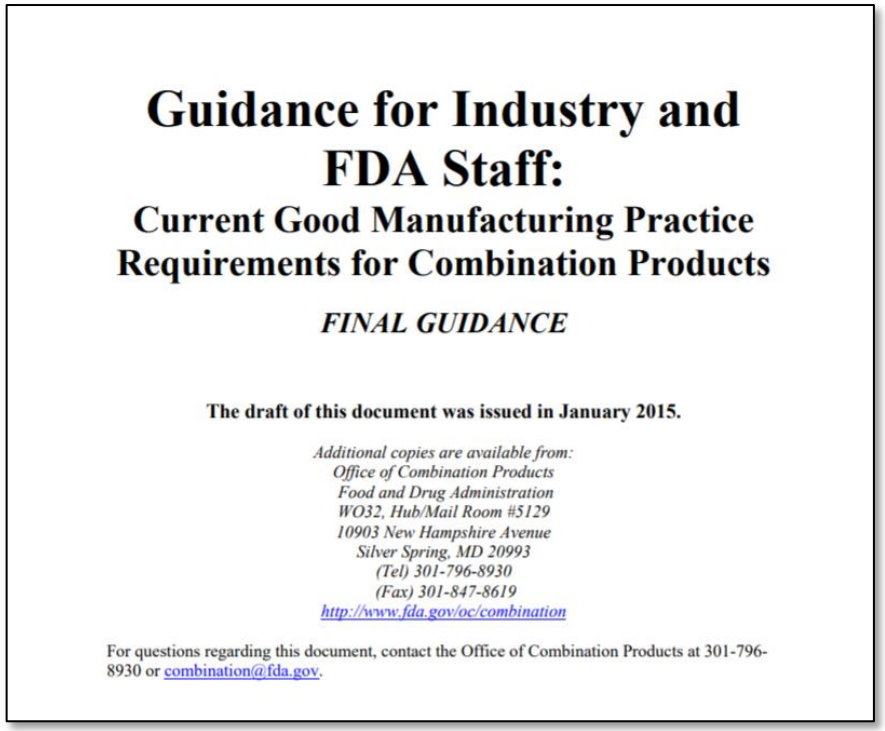
Understanding cGMP and QSR

For many drug and biologics manufacturers, **Current Good Manufacturing Practice (cGMP)** requirements are already in place, but medical device **Quality Systems Regulation (QSR)** can require new investment, training, and procedures. QSR adds requirements for manufacturing and validation of medical device systems, e.g. 21 CFR 820.30 - Design controls.



“Streamlined” cGMP & QSR

For combination products, in 2015 FDA establishes a streamlined QSR/cGMP process



Guidance for Industry and FDA Staff:

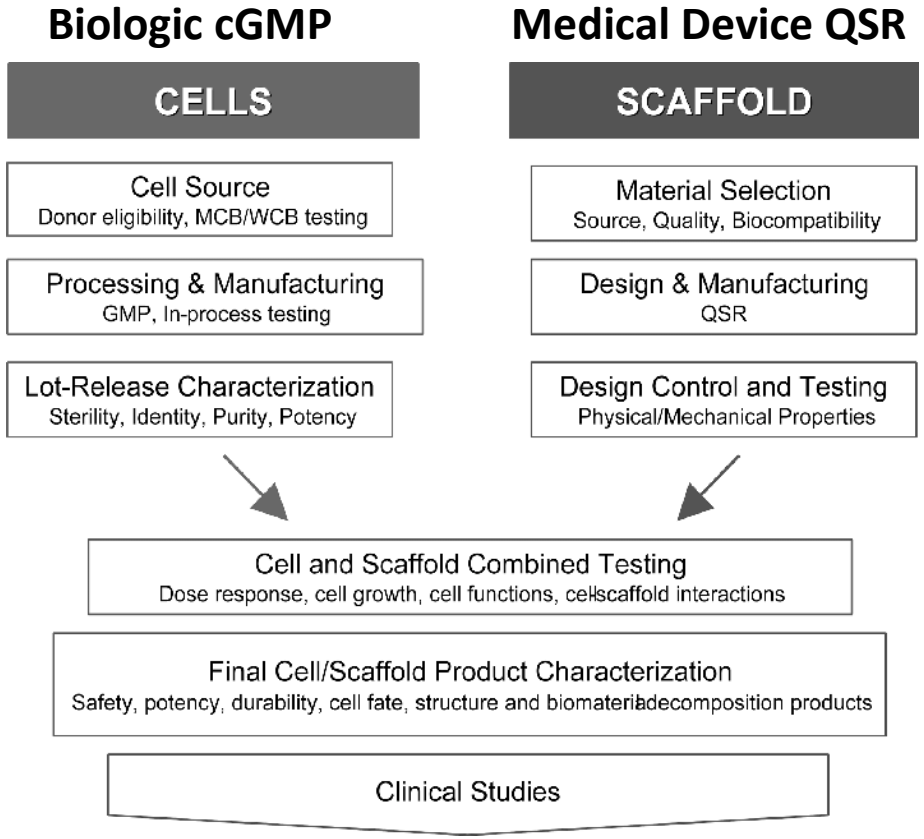
Current Good Manufacturing Practice Requirements for Combination Products

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.



US FDA Classification of IVD Products

Class II are more complex, moderate risk devices

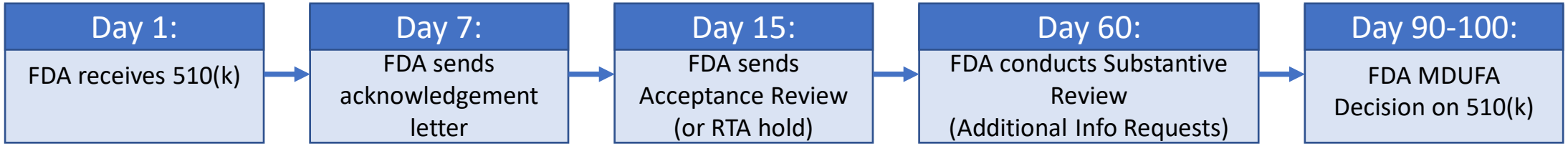
- 510(k) Pre-market Notification Required for Most Devices
- FDA clearance based on “substantial equivalence” to a predicate device (similar intended use, similar performance characteristics)
- Summary of review posted to FDA’s website

A “Predicate Device” may be based on a different technology, with similar intended use and performance characteristics

US FDA Classification of IVD Products

Class II are more complex, moderate risk devices; clinical trials may or may not be required.

Summary of 510(k) Pre-Market Notification Process

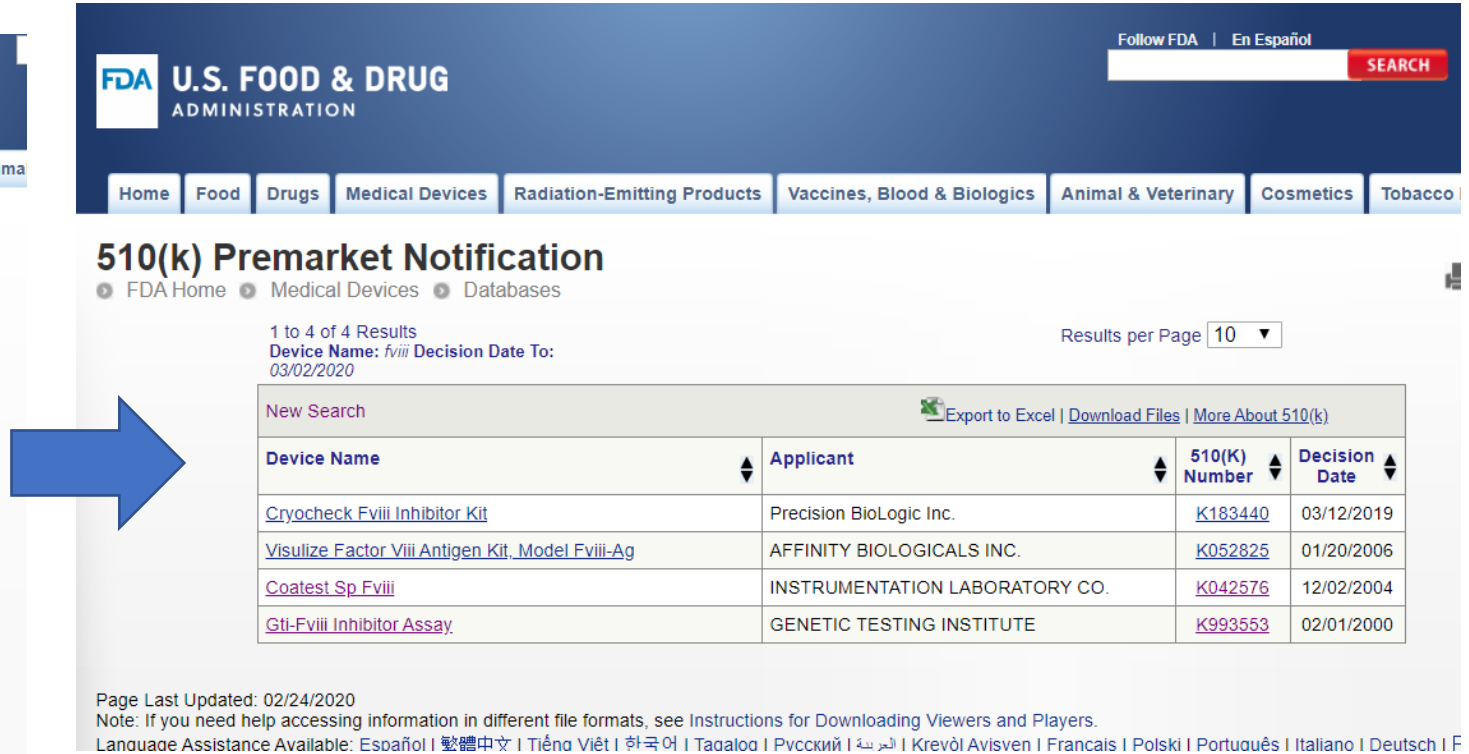


FDA 510(k) Database – Strategic Information

The FDA 510(k) data base allows searching of all 510(k)-cleared products wit their 7-digit “K” number, along with a public summary of the FDA assessment, and can be used to:

- See how similar devices are classified
- Identify predicate(s) products
- Explore data submitted to support clearance of similar products
- Plan strategically for clinical development requirements

FDA 510(k) Database – Strategic Information



FDA 510(k) Database – Strategic Information

510(k) Premarket Notification

FDA Home ◉ Medical Devices ◉ Databases

CDRH SuperSearch

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

New Search | Back To Search Results

Device Classification Name	Test, Qualitative And Quantitative Factor Deficiency
510(K) Number	K183440
Device Name	CRYOcheck FVIII Inhibitor Kit
Applicant	Precision BioLogic Inc. 140 Eileen Stubbs Avenue Dartmouth, CA B3b 0a9
Applicant Contact	Karen M. Black
Correspondent	Precision BioLogic Inc. 140 Eileen Stubbs Avenue Dartmouth, CA B3b 0a9
Correspondent Contact	Karen M. Black
Regulation Number	864.7290
Classification Product Code	GGP
Subsequent Product Code	GGN
Date Received	12/12/2018
Decision Date	03/12/2019
Decision	Substantially Equivalent (SESE)
Regulation Medical Specialty	Hematology
510k Review Panel	Hematology
Summary	Summary
FDA Review	Decision Summary
Type	Traditional
Reviewed By Third Party	No
Combination Product	No

FDA U.S. FOOD & DRUG ADMINISTRATION

March 12, 2019

Precision BioLogic Inc.
Karen Black
VP of Compliance & Product Development
140 Eileen Stubbs Avenue
Dartmouth, Nova Scotia B3B 0A9
Canada

Re: K183440
Trade/Device Name: CRYOcheck FVIII Inhibitor Kit
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor deficiency test
Regulatory Class: Class II
Product Code: GGP
Dated: December 10, 2018
Received: December 12, 2018

Dear Karen Black:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, t enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordanc with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a

Activity – FDA's 510(k)/PMA Database

Take the next 15 minutes to pull the summary of one the products your identified. What sticks out to you?

Navigate to FDA's 510(k)/PMA database and search for the product, locate:

- Class, Product Code
- Predicate
- Clinical tests performed (Y/N)

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm or type "FDA 510(k) database" into your search engine

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm or type "FDA PMA database" into your search engine

US FDA Classification of IVD Products

Class III are the most complex, high risk, or novel intended use

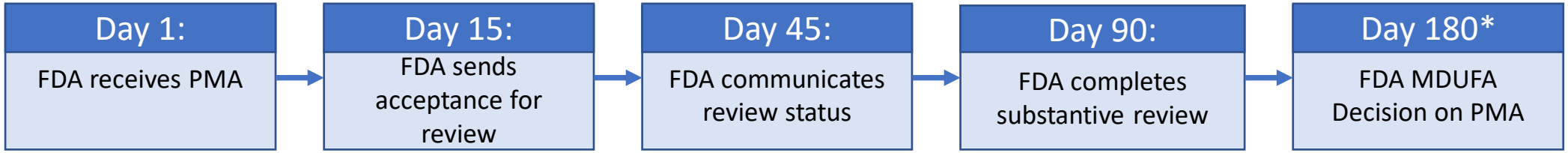
- Does not use predicates
- Submissions often include clinical data
- Pre-approval inspective is performed by FDA
- FDA may seek advisory input before approval
- Summary of safety and effectiveness (SSED) data published on the web, see FDA PMA Database (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm)

A PMA requires demonstration of “effectiveness” and safety, not just performance

US FDA Classification of IVD Products

Class III are the most complex, high risk, or novel intended use

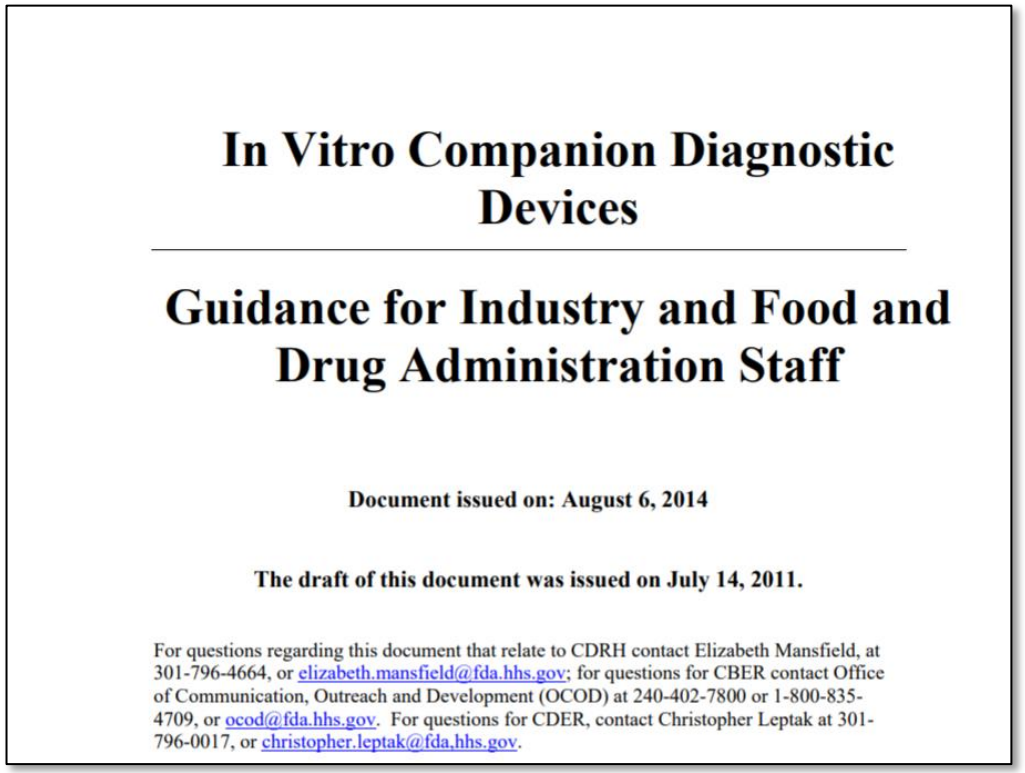
Summary of FDA Pre-Market Approval (PMA) Process



**Day 320 if Advisory Board is needed*

FDA Regulation of Codeveloped Products

2014



In Vitro Companion Diagnostic Devices

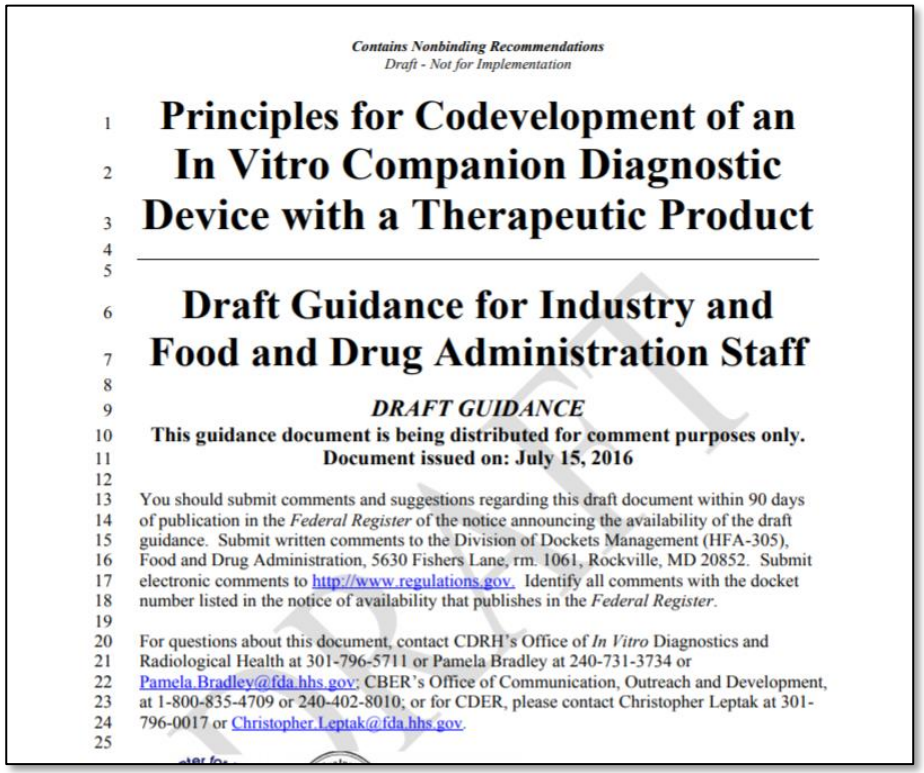
Guidance for Industry and Food and Drug Administration Staff

Document issued on: August 6, 2014

The draft of this document was issued on July 14, 2011.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 240-402-7800 or 1-800-835-4709, or ocod@fda.hhs.gov. For questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

2016



Contains Nonbinding Recommendations
Draft - Not for Implementation

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: July 15, 2016

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact CDRH's Office of *In Vitro* Diagnostics and Radiological Health at 301-796-5711 or Pamela Bradley at 240-731-3734 or Pamela.Bradley@fda.hhs.gov; CBER's Office of Communication, Outreach and Development, at 1-800-835-4709 or 240-402-8010; or for CDER, please contact Christopher Leptak at 301-796-0017 or Christopher.Leptak@fda.hhs.gov.

EU IVD Directive to Regulation

The European Union has established the **Medical Device Regulation (MDR)** and **In Vitro Diagnostic Regulation (IVDR)** replacing the directive in place for over 25 years, which will go into effect on May 26, 2020 and May 26th, 2022, respectively

- IVDR expanded Classes (Class A-D)
- Under IVDD up to 90% of IVDs could self-certify, now 90% will require Notified Body (NB) Review
- Software devices and services are now in scope
- MDR and IVDR require Notified Bodies to certify to the new regulation

EU IVD Directive to Regulation: IVDR

IVDR (2017/746)

Article 2(2) - For the purposes of this Regulation, the following definitions apply:

'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, **software** or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

(a) concerning a physiological or pathological **process** or state;
(b) concerning congenital **physical or mental impairments**;
(c) concerning the predisposition to a medical condition or a disease;
(d) to determine the safety and compatibility with potential recipients;
(e) to predict treatment response or reactions;
(f) to **define** or monitor therapeutic measures

IVDD (98/79/EC)

Article 1, 2(b) - For the purposes of this Directive, the following definitions shall apply:

'in vitro diagnostic medical device` means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or

- to determine the safety and compatibility with potential recipients, or

- to monitor therapeutic measures

	Words	Pages	Articles	Annexes
IVDD (98/79/EC)	19,127	43	24	10
IVDR (2017/746)	85,639	157	113	15

EU In Vitro Diagnostics Regulation (IVDR) 2017/746

New IVDR & existing IVDD Certificates Valid
May 26, 2017 – publication of new IVDR 2017/746
Start of 5-year transition period to May 25th 2022

New IVDR & existing IVDD Certificates Issued before May 2020
May 26, 2020 to May 25, 2024

IVDR Certificates only
May 25, 2024

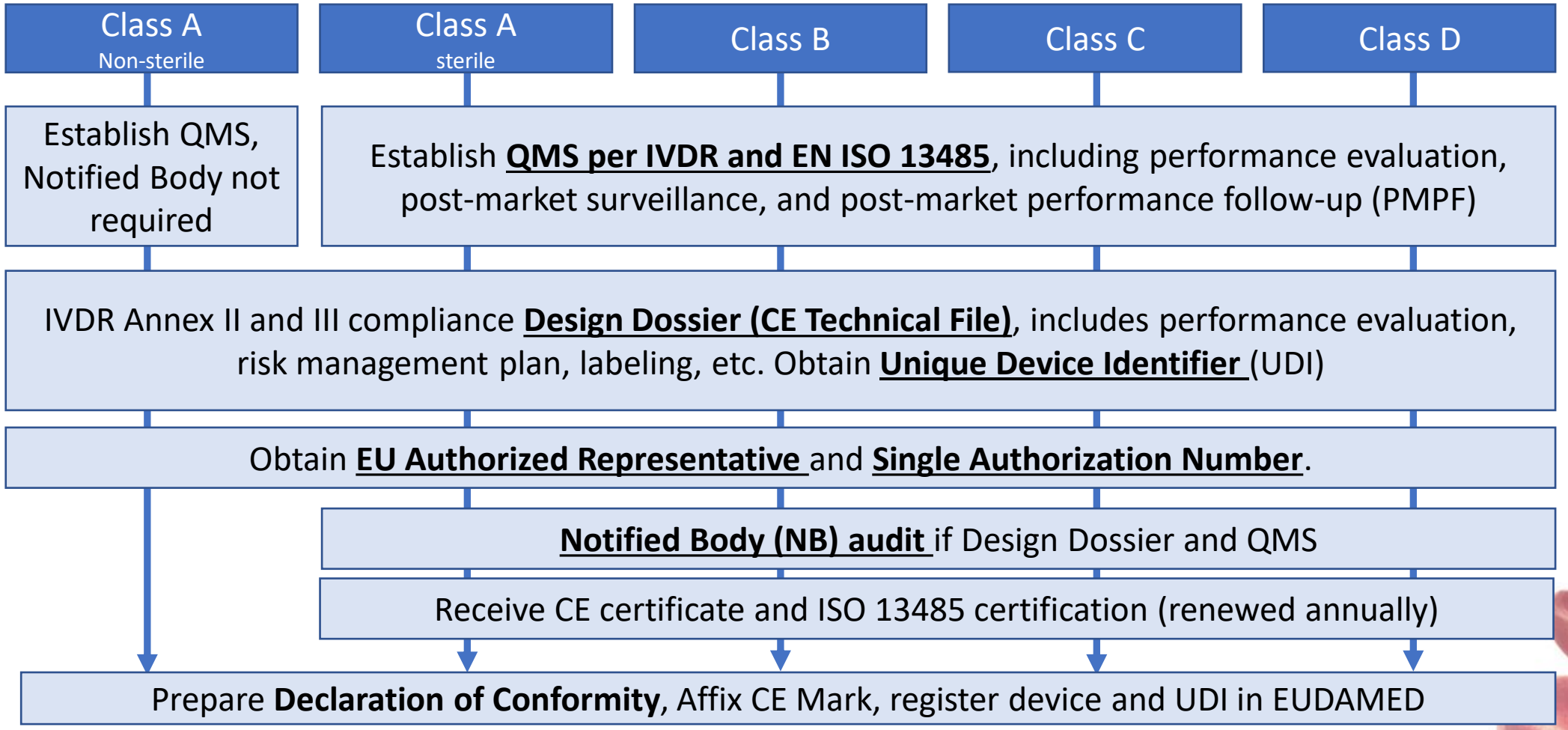
New MDR & existing MDD Certificates Valid
May 26, 2017 – publication of new MDR 2017/745
Start of 3-year transition period to May 25th 2022

New IVDR & existing IVDD Certificates Issued before May 2020
May 26, 2020 to May 25, 2024

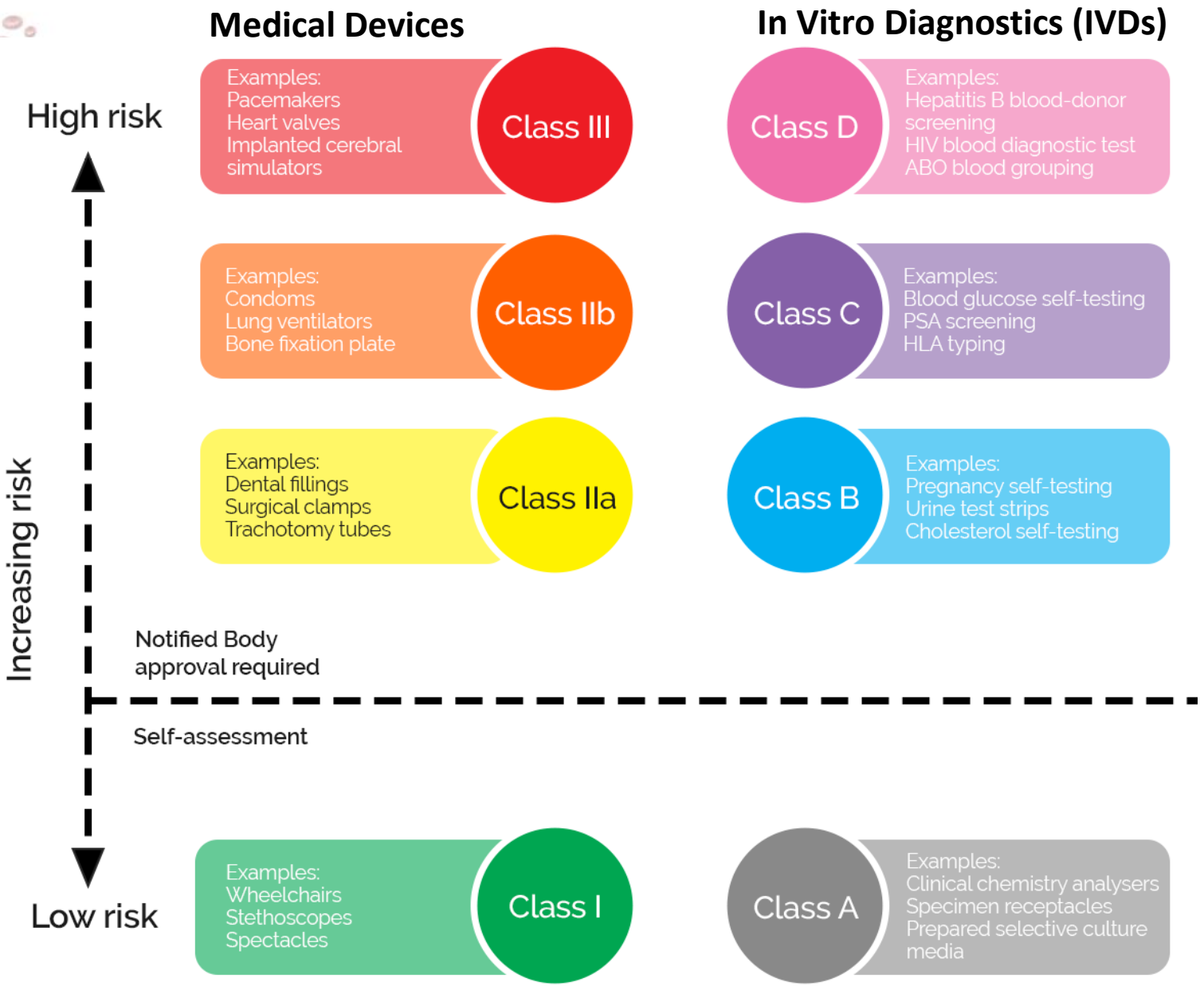
MDR Certificates only
May 25, 2024

EU Medical Device Regulation (MDR) 2017/745

EU Notified Body IVD / CDx Pathway (CE)



EU In Vitro Diagnostics Regulation (IVDR) 2017/746


Medical Devices
In Vitro Diagnostics (IVDs)
High risk
Increasing risk
Low risk
Examples:
Pacemakers
Heart valves
Implanted cerebral simulators
Class III
Class D
Examples:
Hepatitis B blood-donor screening
HIV blood diagnostic test
ABO blood grouping
Examples:
Condoms
Lung ventilators
Bone fixation plate
Class IIb
Class C
Examples:
Blood glucose self-testing
PSA screening
HLA typing
Examples:
Dental fillings
Surgical clamps
Trachotomy tubes
Class IIa
Class B
Examples:
Pregnancy self-testing
Urine test strips
Cholesterol self-testing
Notified Body approval required
Self-assessment
Examples:
Wheelchairs
Stethoscopes
Spectacles
Class I
Class A
Examples:
Clinical chemistry analysers
Specimen receptacles
Prepared selective culture media

EMA and Companion Products

The role of the European Medicines Agency (EMA), specifically identified as responsible party for CDx and combination products, is evolving

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2010
EMA/CHMP/641298/2008
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development

Draft

Draft Agreed by Pharmacogenomics Working Party	June 2010
Adoption by CHMP for release for consultation	24 June 2010
End of consultation (deadline for comments)	30 November 2010

- Developing guidance for CDx (Joint CIE and IVD TG on performance studies)
- Aligning requirements for clinical trials (medicine) and clinical performance studies (CDx)
- Timetables for CDx CE marking and medicine MAA
- Engage with NBs to agree on data requirements for the consultation
- PGWP Expert meeting on co-dev June 2018

Challenges for CDx in EU

Data requirements for CDx (detail, overlap): **analytical / clinical**
(Cross-) Labelling considerations for CDx and medicinal product


Article · Full-text available

Pharmacogenomic information in drug labels: European Medicines Agency perspective

February 2015 · The Pharmacogenomics Journal 15(3)
DOI · 10.1038/tpj.2014.86
Source · PubMed

Future interactions between EMA/NCA and NBs (as in IVDR)

Post-authorisation and pharmacovigilance requirements for CDx

Data requirements and review process / regulatory oversight for "follow-on" assays (CDx)

Clinical trials including medicines and CDx

New In IVDR

IVDR Article 48(3) NEW

- For companion diagnostics the notified body shall consult **the concerned competent authority** designated in accordance with Directive 2001/83/EC or the European Medicines Agency (EMA)

ANNEX IX, Chapter II - 5.2. Assessment of the technical documentation of companion diagnostics NEW

- The notified body shall, before issuing an EU technical documentation assessment certificate for the companion diagnostic and on the basis of the draft summary of safety and performance […] consult one of the competent authorities […] regarding the suitability of the device in relation to the medicinal product concerned.

General Regulatory Advice for CDx

- Engage with Regulatory Authorities early in development and discuss companion diagnostic development strategy, e.g. Pre-IND/EOP meetings, Pre-Sub/Q-Sub, Scientific Advice
- Identify where prototype development fits in the gene therapy development program
- Classify the device and identify if clinical data is needed; if so, can data be extracted from existing development studies for the biologic/drug or are separate studies needed

Interactive – Overcoming Barriers

What are the barriers to early discussions of companion device / CDx development in your experience?

Other questions?

Break 3:45 – 4:00 PM

4:00 - 4:45 pm

Clinical Strategies for Co-Development of Gene Therapy Products

Precision Medicine in Practice

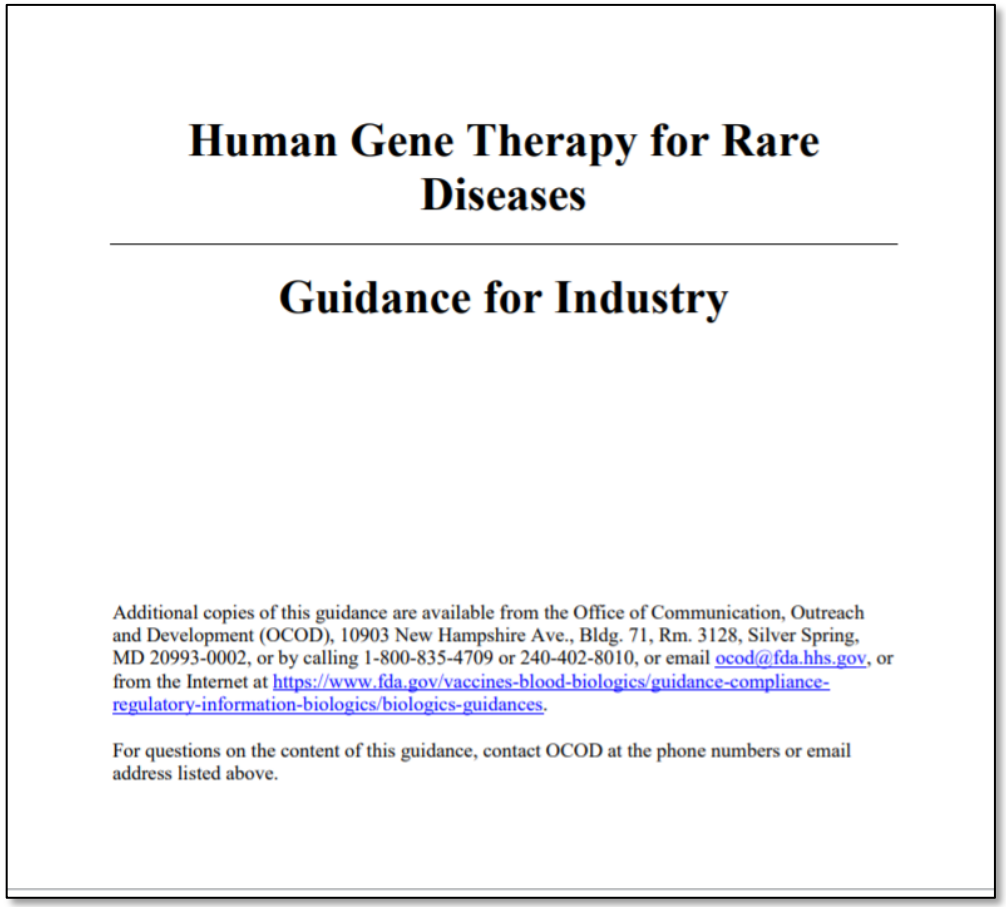
- More than 1 of 3 drugs approved over the past two years is a personalized medicine
- In oncology, multiple drugs are already approved based on a biomarker (not tumor type; e.g. Vitrakvi/larotrectinib)
- Marketing authorizations granted for first pharmacogenetic and cancer risk-related genetic tests for consumers (e.g. 23&me)
- First gene therapy submitted with companion PMA (Biomarin)

FDA Finalizes Gene Therapy Framework

On **January 28th, 2020**, FDA announced finalization of several guidance documents in it's gene therapy framework (**total of 27 FDA guidance documents now for gene therapy**):

- Draft Guidance: Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations
- Final Guidance: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- Final Guidance: Long Term Follow-Up After Administration of Human Gene Therapy Products
- Final Guidance: Human Gene Therapy for Hemophilia
- Final Guidance: Human Gene Therapy for Rare Diseases

FDA Encourages CDx in Gene Therapy for Rare Disease



Human Gene Therapy for Rare Diseases

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

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

A. Study Population

Selection of the study population should consider existing preclinical or clinical data to determine the potential risks and benefits for the study subjects. In addition, sponsors should consider whether the proposed study population is likely to provide informative safety and/or efficacy data (Ref. 11). The following points should be considered with respect to trials of GT products for rare diseases:

- If the disease is caused by a genetic defect, the sponsor should perform genetic test(s) for the specific defect(s) of interest in all clinical trial subjects. This information is important to ensure correct diagnosis of the disorder of interest. In addition, since many of these disorders can involve either deletions or functional mutations at any of several loci within a specific gene, safety and effectiveness may be linked to genotype in unpredictable ways. Given this, early understanding of such associations may help in planning future clinical trials. Therefore, if there are no readily available, reliable means of obtaining the needed genetic diagnosis, a companion diagnostic may be needed and therefore should be considered early in development (Ref. 12).

- Sponsors may choose to exclude patients with pre-existing antibodies to the GT product. In such cases, the sponsor should strongly consider contemporaneous development of a companion diagnostic to detect antibodies to the GT product. If an *in vitro* companion diagnostic is needed to appropriately select patients for study (and later, once the GT product is approved, for treatment), then submission of the marketing application for the companion diagnostic and submission of the biologics license application for the GT product should be coordinated to support contemporaneous marketing authorizations.

FDA Maintained Lists for CDx

FDA maintained a list of all companion diagnostic products (imaging and IVD) and, separately, a listing of all nucleic acid based tests:

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

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A *companion diagnostic device* can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

The use of an IVD companion diagnostic device with a specific therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

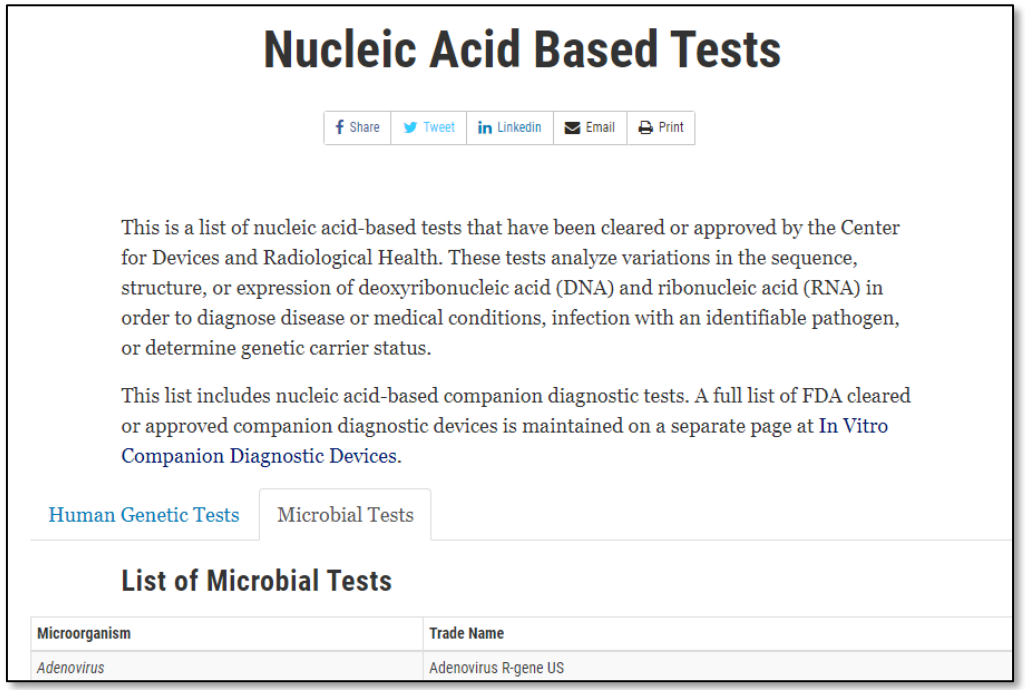
For FDA cleared or approved nucleic acid based tests, see Nucleic Acid Based Tests.

This table lists devices in the order of approval, with most recently approved device at the top.

Download a Printable Version of this Table

Diagnostic Name	PMA / 510(k) / HDE	Diagnostic Manufacturer	Trade Name (Generic) - NDA/BLA

https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools



Nucleic Acid Based Tests

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This is a list of nucleic acid-based tests that have been cleared or approved by the Center for Devices and Radiological Health. These tests analyze variations in the sequence, structure, or expression of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in order to diagnose disease or medical conditions, infection with an identifiable pathogen, or determine genetic carrier status.

This list includes nucleic acid-based companion diagnostic tests. A full list of FDA cleared or approved companion diagnostic devices is maintained on a separate page at In Vitro Companion Diagnostic Devices.

Human Genetic Tests | Microbial Tests

List of Microbial Tests

Microorganism	Trade Name
Adenovirus	Adenovirus R-gene US

https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests

Interactive – Exploring CDx

Take a look at FDA Lists of Companion Diagnostics:

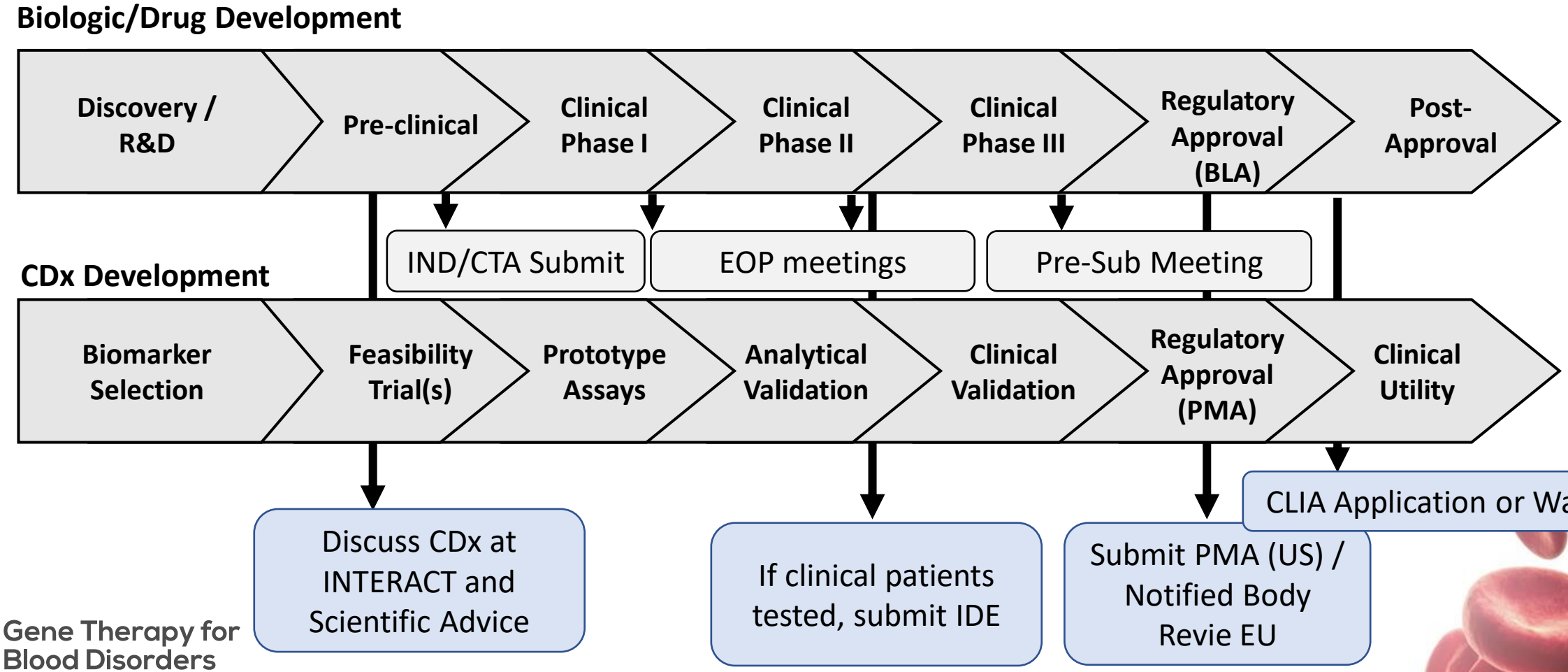
- What diagnostics are used in products you work with?
- Are new biomarkers being developed?
- What new ‘custom’ tests could benefit patients?

https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests

Parallel Development for CDx

In many cases, parallel development is possible for companion diagnostics



INTERACT Meetings (early engagement)

INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings allows sponsors to obtain preliminary informal consultation with the Agency at an early stage of development prior to a pre-IND meeting, and can be used for initial discussion of patient selection and CDx development.

- Response from CBER within 21 calendar days of receipt
- Meeting will be held within 90 calendar days of request
- Sponsor should provide a meeting package
- Informal and non-binding

Pre-IND vs Pre-Submission (Q-Sub)

Pre-IND meetings for biologics/drugs under PDUFA and Pre-Submission ("Q-Sub") meetings for devices under MDUFA are both formal meeting types. For co-development programs:

- Recommended to meet with lead product review center first
- State in meeting request and questions that you intend to discuss CDx as part of meeting, and relevant attendees should be invited
- Conduct a Pre-Sub on additional questions related to the device development, if needed

Challenges for Clinical Validation of CDx

- Identification of gold standard, particularly in rare disease
- Analytical design (cut-off values, sensitivity and specificity, reproducibility, cross validation)
- Recruitment of diagnostic negative patients into pivotal trial
- Concordance testing between development stages, e.g. clinical trial assay (CTA) and market ready assay (MRA)

Model Predictions	Actual Results: Positive	Actual Results: Negative
Positive	**True Positive** — The number of observations the model predicted were positive that were actually positive	**False Positive** — The number of observations the model predicted were positive that were actually negative
Negative	**False Negative** — The number of observations the model predicted were negative that were actually positive	**True Negative** — The number of observations the model predicted were negative that were actually negative

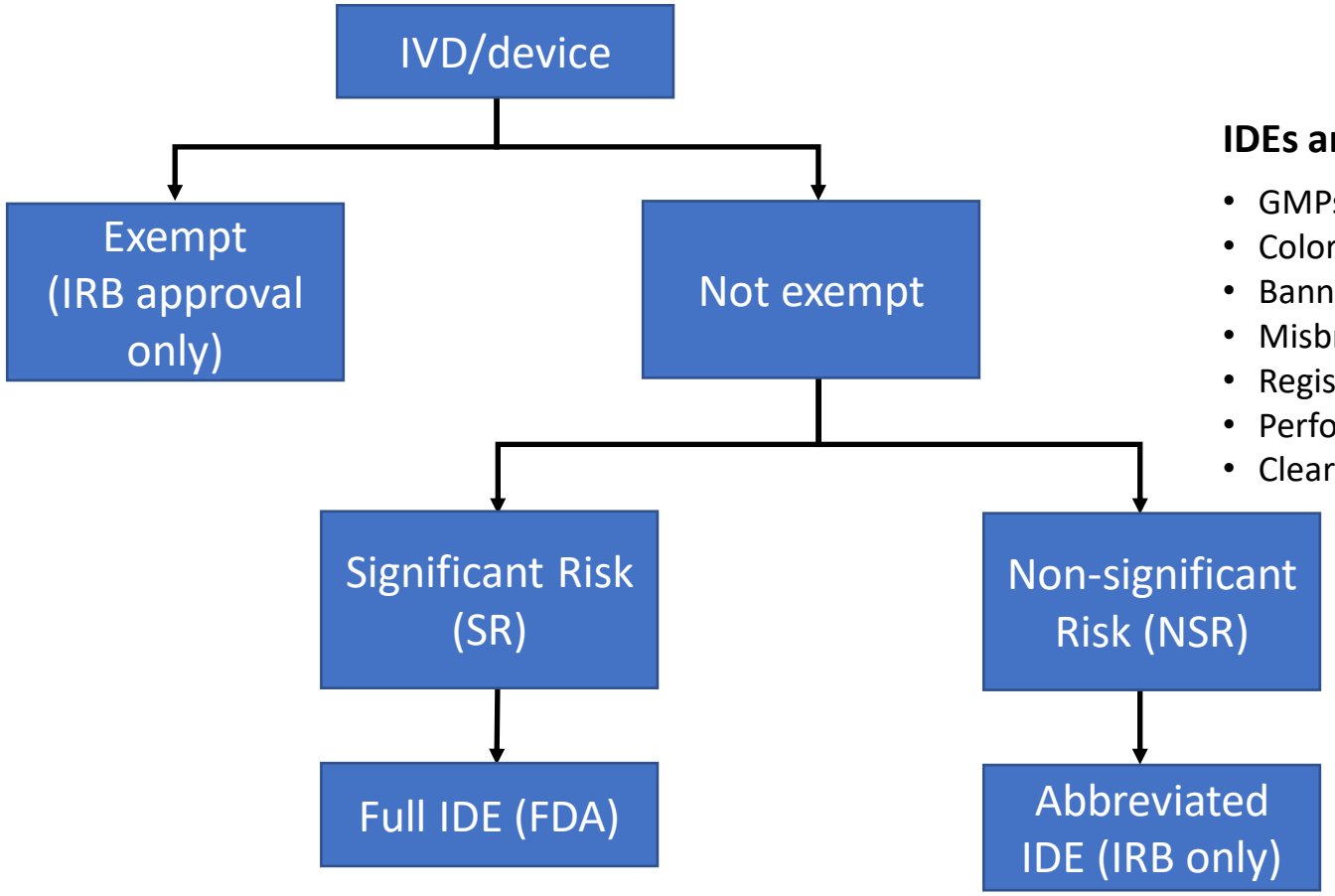
Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)
PPV = TP/(TP+FP)
NPV = TN/(FN+TN)

Study Risk Determination / IDE

For trials of IVD/device CDx products, determine Study Risk and if Investigational Device Exemption (IDE) is needed for clinical trials.

Exempt Studies do <u>not</u> require an IDE when using:

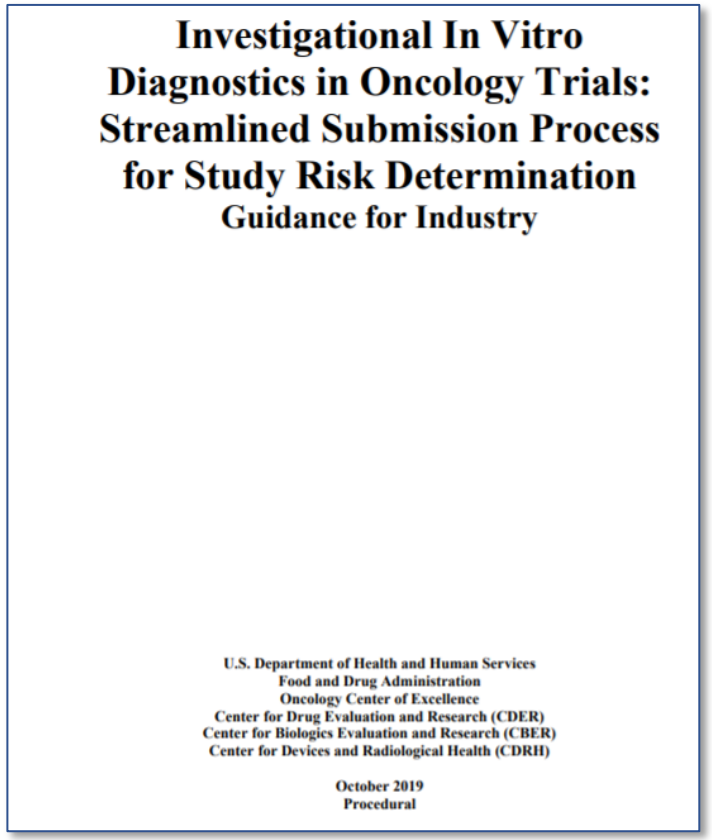
- Commercial devices used on label
- Many diagnostic devices
- Consumer preference, of a modification, or of a combination of devices, when not determining safety or effectiveness and not putting subjects at risk
- Veterinary devices or research on/with laboratory animals
- Custom devices



IDEs are exempt from:

- GMPs except Design Controls
- Color Additive testing
- Banned/Restricted Devices
- Misbranding
- Registration
- Performance Standards
- Clearance/approval

Streamlined Oncology IVD Co-development


Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination
Guidance for Industry

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

October 2019
Procedural

Streamlined process for study risk determination:

- Single lead sponsor for both products
- Include IVD test plan in IND
- Identify “streamlined IVD” process on 1571
- Within 30-day IND review, CBER will consult with CDRH and confirm NSR status

Partner Co-Development: Multiple Sponsors

Where multiple sponsors for a biologic/drug and IVD are engaged in co-development, clear communication is needed on:

- Shared regulatory meeting feedback
- Access to clinical protocols and IND, where sampling is done for IVD development
- Coordinated submission of IND and IDE, BLA and PMA contents

Interactive – Challenges in Co-development

What Challenges do you see for gene therapy organizations co-developing products?

First Gene Therapy Companion Product

On February 20th 2020, BioMarin's Biologics License Application (BLA) for *Valoctocogene Roxaparvovec was* Accepted for Priority Review by FDA with Review Action Date of August 21, 2020.

BIOMARIN®

ARUP® LABORATORIES

(nonprofit and academic reference laboratory)

The FDA has also accepted the premarket approval application for a companion diagnostic, which identify the patients it can treat. The companion diagnostic is an AAV5 total antibody assay, consisting of simple blood test to help identify patients most likely to respond to AAV5-based gene therapy, used in multiple clinical studies. BioMarin estimates that approximately 80% of people with hemophilia A in the US do not have preexisting immunity to AAV5 that would make them ineligible for AAV5-mediated gene therapy treatment.

The test is made by ARUP Laboratories, a nonprofit enterprise of the University of Utah and its department of pathology.

Future of Companion Product Development

- Companion diagnostics will become increasingly important for gene therapy, in particular for patient selection
- Challenges of IVD manufacturing can be mitigated by streamlined regulatory approach and partnering with contract diagnostic R&D and manufacturing centers
- Early regulatory strategy consultation will be essential to the most streamlined process
- Timing is important, with final companion product design aligning with late-phase trials and market authorization filings

Platforms & Pipelines

- Use of biologics DMFs in US; similar paradigm being discussed in EU; China NMPA opens DMFs to biologics
- Possible use of companion products and combo components across multiple products
- Validation of components can reduce clinical burden

Interactive – Q&A

Questions about platform and companion co-development?

Break 4:45 – 5:00 PM

5:00 - 5:30 pm

Strategy Recap and Q&A

Strategic Reasons for CDx Co-development

Select strategic reasons for CDx Development:

Rare disease – an appropriate genetic test is not commercially available

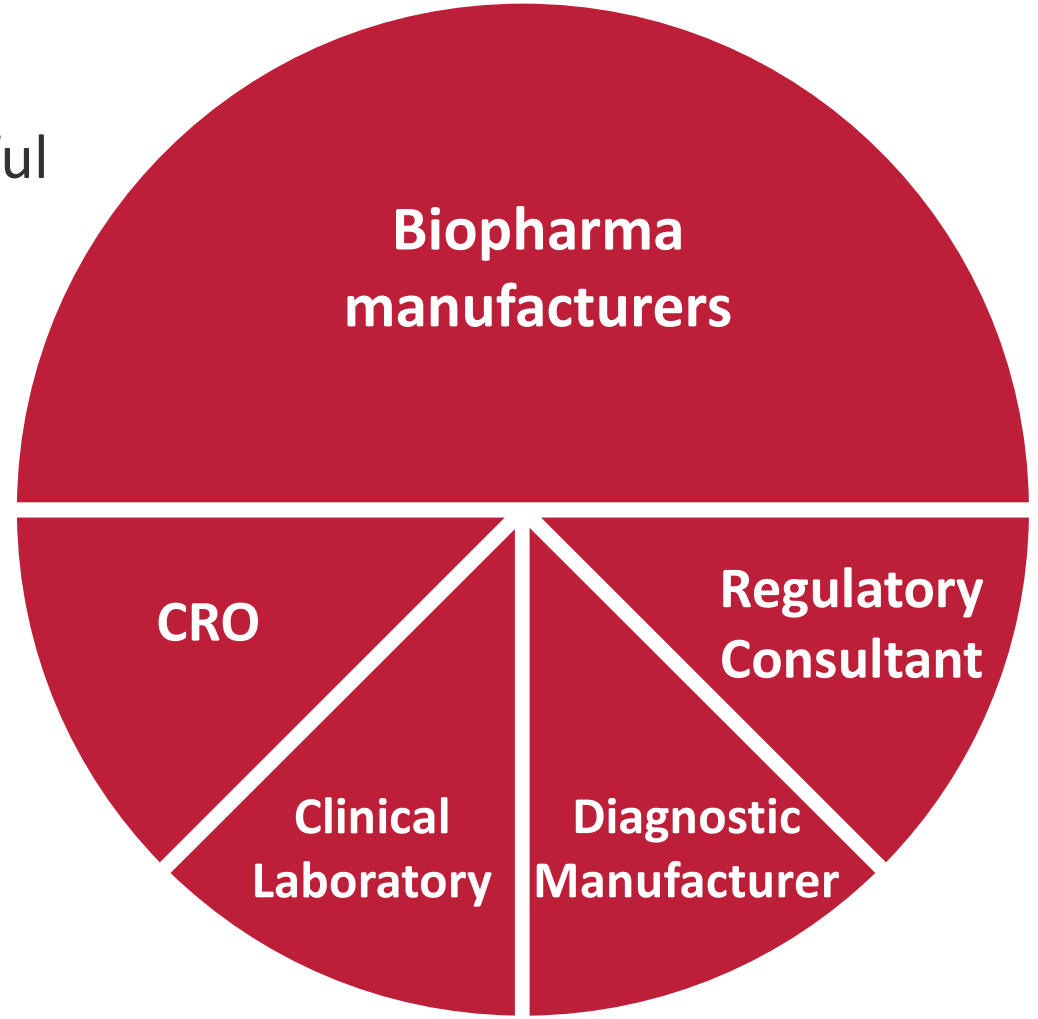
The best target population involves a combination of screening biomarkers or characteristics

Control supply chain and revenues, i.e. if an IVD is required for therapy or monitoring, CDx development ensures manufacturer control of availability

Make patient selection and administration more friendly and streamlined for end users

Biopharma brings half the solution

Selecting the right partners early is essential to successful co-development



Interactive – Vendor Group Discussion

List several partners/vendors you work with.

What challenges have you seen in selecting and working with vendor partners? How do you overcome them?

Strategy Recap

- Streamlined co-development options exist in oncology, looking to the future these may also be developed for gene therapy
- In rare disease, co-development can ensure access to necessary IVDs and is encouraged by regulators
- Existing companion products for biologics (BLA) are primarily for HER-2 detection in oncology
- The first companion PMA to a BLA application in gene therapy was submitted by Biomarin this year
- Opportunities exist to partner in growing genetic testing market

Keys to Successful CDx Development

- Clear aim for IVD/device product (e.g. patient selection)
- Identification of similar products (if exist) and regulatory pathway, typically PMA
- Early regulatory engagement to streamline parallel development of IVD/device and biologic
- Clear development partnerships vs decision to develop in-house
- Development of necessary QSR, ISO 13485, and cGMP manufacturing processes, including design controls for devices

Interactive – Group Discussion and Q&A

What opportunities do you see in co-development?

Time for Q&A

Thank You

Angela N. Johnson, MSE, PMP, RAC
Angela@angelanjohnson.com