The Biologics License Application (BLA)

Matthew Hegreness, J.D., Ph.D.
Covington & Burling LLP
October 15, 2020

FDLI

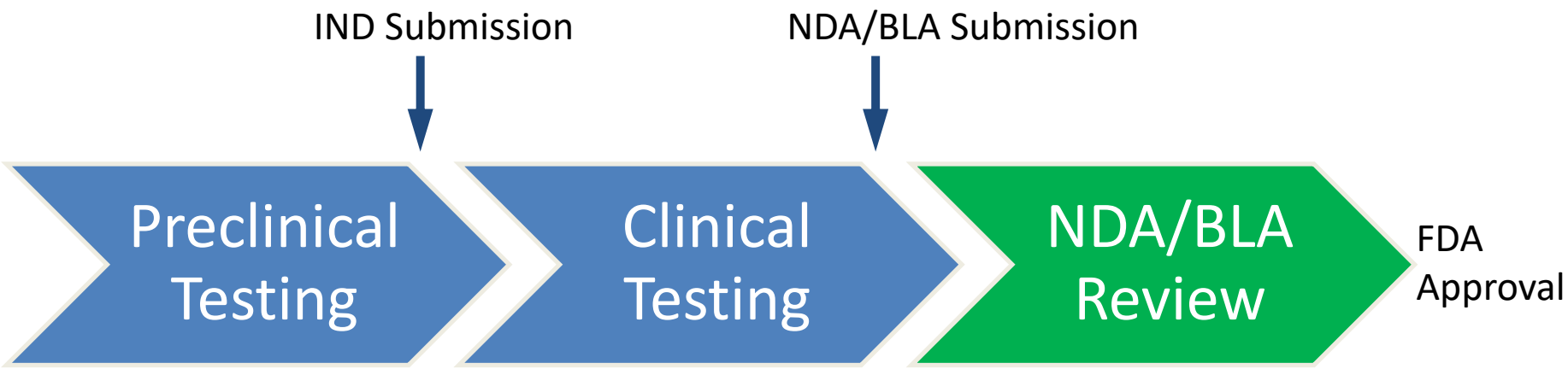
Learning Objectives

- What standard does FDA use to approve a Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHSA)?
- What goes in a BLA?
- What is FDA's process for reviewing a BLA?

Agenda

A. Approval standard
B. Content and Organization of a BLA
C. FDA Review
D. FDA's Decision
E. CBER Biologics: Selected Topics

The Journey of Drug Development



- Likelihood that a drug that enters clinical testing will eventually be approved: **12%**
- Average time from start of clinical testing to submission of NDA or BLA: **81 months**

DiMasi et al., *J. of Health Economics* (2016);47:20-33.

APPROVAL STANDARD

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Focus: Section 351(a) BLA

- Public Health Service Act describes two approval pathways:
  - Section 351(a): the full BLA
  - Section 351(k): the biosimilar BLA

42 U.S.C. 262

Standard for Approval Under 351(a)

- Standard = “safe, pure, and potent”
- PHSA 351(j):
  - The Federal Food, Drug, and Cosmetic Act (FDCA) “applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act.”

42 U.S.C. 262

Safe, Pure and Potent

- **Safety**: “relative freedom from harmful effect”
- **Purity**: “relative freedom from extraneous matter in the finished product”
- **Potency**: “specific ability or capacity of the product, as indicated by appropriate laboratory tests or by **adequately controlled clinical data** obtained through the administration of the product in the manner intended, to effect a given result”

21 C.F.R. 600.3

“Potency”: Guidance

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological 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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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*.

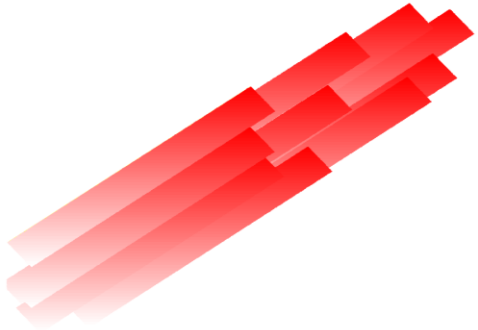
For questions regarding this draft document, contact (CDER) Ei Thu Lwin, Office of New Drug Policy, 301-796-0728 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010, ocod@fda.hhs.gov.

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

December 2019
Clinical/Medical

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



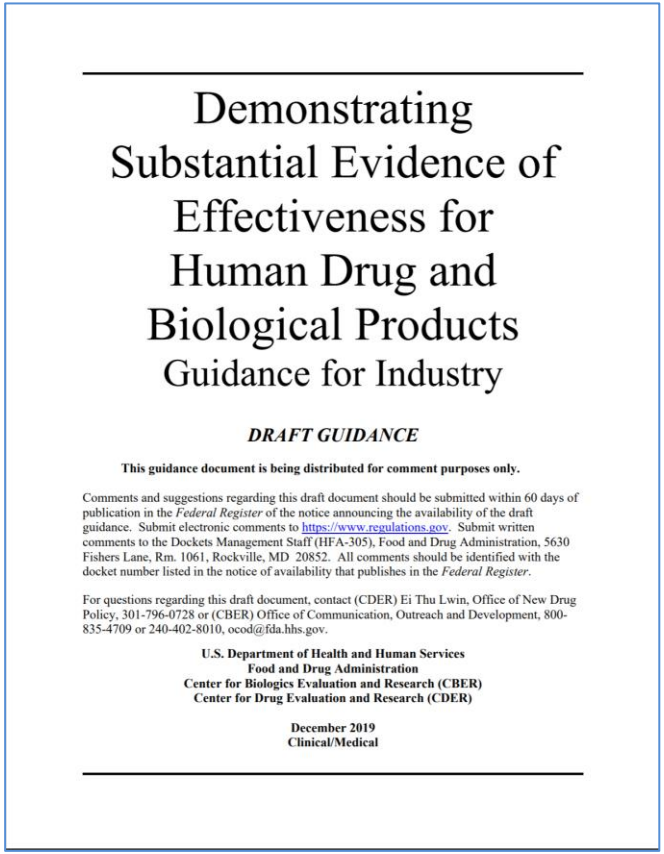
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
Clinical 6

“Potency”: Guidance

- *“*Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered ‘substantial evidence’ of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act.”

- “In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would, with limited exceptions, consist of controlled clinical investigations as defined in the provision for ‘adequate and well-controlled studies’ for new drugs (21 CFR 314.126).”

- Also, Congress directed FDA in 1997 (FDAMA) to “minimize differences in the review and approval” of BLAs and NDAs.



Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

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U.S. Department of Health and Human Services
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December 2019
Clinical/Medical

Applicability of FDCA to Biologics

- Investigational New Drug Application (and all related regulations) for investigational products apply
- Prescription Drug User Fee Act applies (to innovative products)
- Risk evaluation and mitigation strategy (REMS) authorities apply
- Mandatory post-approval study authority applies
- Orphan Drug Act applies

Content and Organization of a BLA

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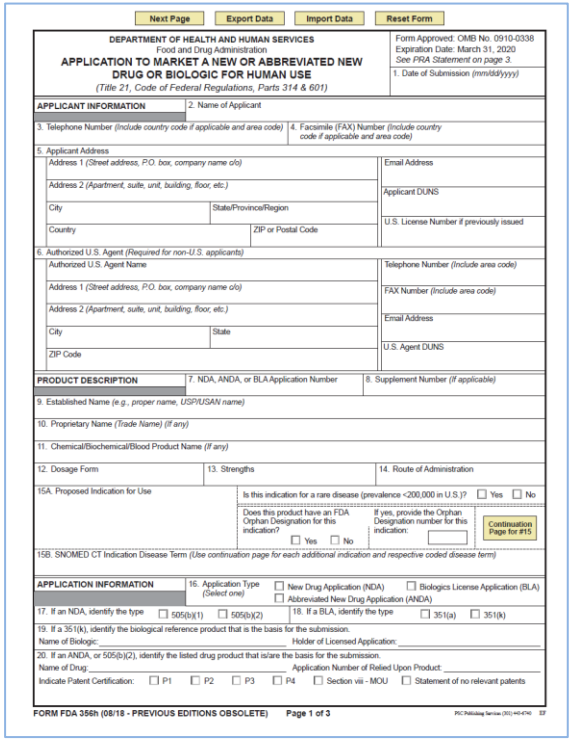
Form FDA 356h

- Form for both NDAs and BLAs



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2020
See PRA Statement on page 3.

1. Date of Submission *(mm/dd/yyyy)*

APPLICANT INFORMATION

2. Name of Applicant

3. Telephone Number *(Include country code if applicable and area code)*

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*

5. Applicant 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

Email Address

Applicant DUNS

U.S. License Number if previously issued

6. Authorized U.S. Agent *(Required for non-U.S. applicants)*

Authorized U.S. Agent Name

Address 1 *(Street address, P.O. box, company name c/o)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State

ZIP Code

Telephone Number *(Include area code)*

FAX Number *(Include area code)*

Email Address

U.S. Agent DUNS

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number

8. Supplement Number *(If applicable)*

9. Established Name *(e.g., proper name, USP/USAN name)*

10. Proprietary Name *(Trade Name) (If any)*

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form | 13. Strengths | 14. Route of Administration

15A. 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 #15

15B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*

APPLICATION INFORMATION

16. Application Type *(Select one)* ☐ New Drug Application (NDA) ☐ Biologics License Application (BLA) ☐ Abbreviated New Drug Application (ANDA)

17. If an NDA, identify the type ☐ 505(b)(1) ☐ 505(b)(2)

18. If a BLA, identify the type ☐ 351(a) ☐ 351(k)

19. If a 351(k), identify the biological reference product that is the basis for the submission.
Name of Biologic: _____ Holder of Licensed Application: _____

20. If an ANDA, or 505(b)(2), identify the listed drug product that is/are the basis for the submission.
Name of Drug: _____ Application Number of Relied Upon Product: _____
Indicate Patent Certification: ☐ P1 ☐ P2 ☐ P3 ☐ P4 ☐ Section viii - MOU ☐ Statement of no relevant patents

FORM FDA 356h (08/18 - PREVIOUS EDITIONS OBSOLETE) Page 1 of 3

BLA: Chemistry (or Quality)

- Chemistry Section
  - Chemistry, manufacturing, and controls information
  - Samples (Submit only upon FDA's request)
  - Methods validation package

21 CFR 601.2

BLA: Non-Clinical and Clinical

- Nonclinical pharmacology and toxicology section
- Human pharmacokinetics and bioavailability section
- Clinical data section

21 CFR 601.2

Chemistry

- Chemistry Section
  - Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)

Other Items in BLA

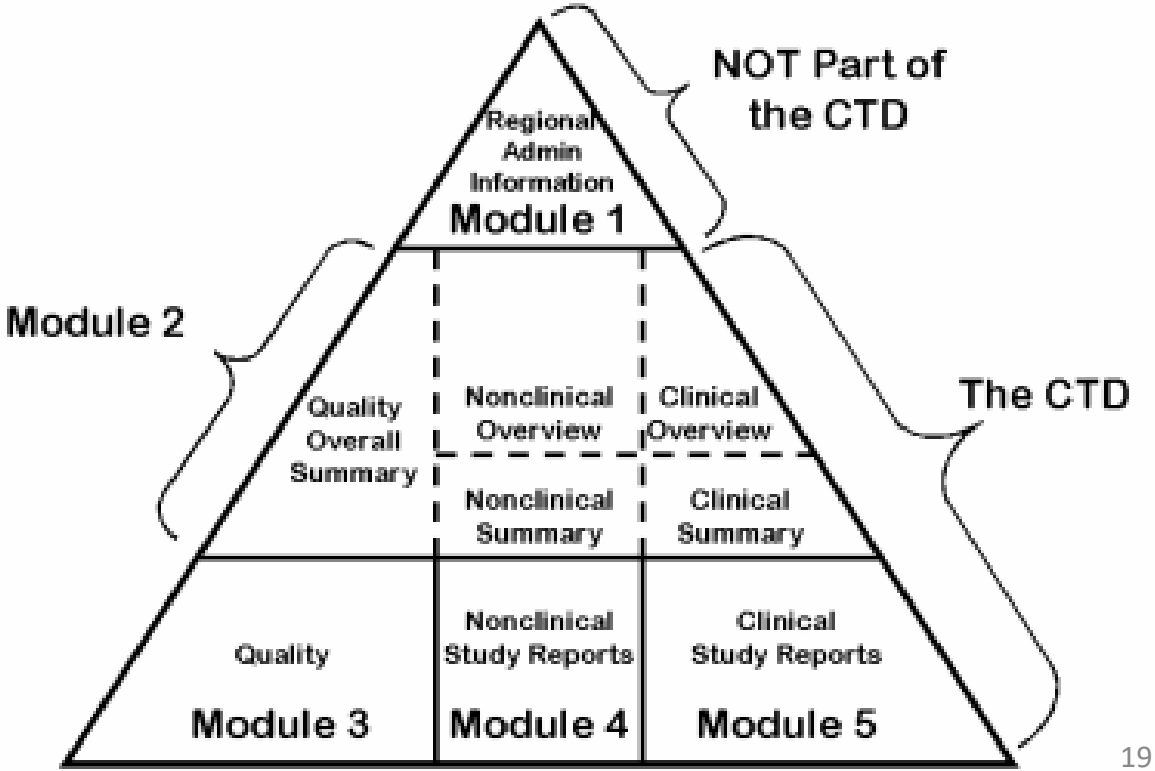
- Pediatric Research Equity Act assessments or deferral/waiver
- Debarment certification
- Investigator financial certification/disclosure
- Certification of compliance with 42 U.S.C. 282(j)(5)(B) on compliance with ClinicalTrials.gov requirements

Other Items Potentially in BLA

- Proposed REMS or postmarketing study requirements
- Request for reference product exclusivity
- Request for priority review voucher
- Proposed proprietary name and nonproprietary name
- Request for priority review

Electronic Common Technical Document (eCTD)

- Requirement to submit BLAs in eCTD format has gone into effect
- International Council for Harmonisation (ICH)



Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FORTEO safely and effectively. See full prescribing information for FORTEO.

FORTEO (teriparatide [rDNA origin] injection) for subcutaneous use
Initial U.S. Approval: 2002

WARNING: POTENTIAL RISK OF OSTEOSARCOMA
See full prescribing information for complete boxed warning.

- **In rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor. (5.1, 13.1)**
- **Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO only for patients for whom potential benefits outweigh potential risk. (5.1)**
- **FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma (e.g., those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton). (5.1)**

RECENT MAJOR CHANGES

Indications and Usage, Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis (1.3)	MM/200X
Dosage and Administration, Treatment of Men and Women with Glucocorticoid-Induced Osteoporosis (2.3)	MM/200X

INDICATIONS AND USAGE

FORTEO is recombinant human parathyroid hormone analog (1-34), [rhPTH(1-34)] indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1)
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture (1.2)
- Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture (1.3)

DOSAGE AND ADMINISTRATION

- Recommended dose is 20 mcg subcutaneously once a day (2.1, 2.2, 2.3)
- Administer as a subcutaneous injection into the thigh or abdominal wall (2.4)
- Administer initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (2.4)
- Use of the drug for more than 2 years during a patient's lifetime is not recommended (2.5)

DOSAGE FORMS AND STRENGTHS

Multi-dose prefilled delivery device (pen) containing 28 daily doses of 20 mcg (3)

CONTRAINDICATIONS

- Patients with hypersensitivity to teriparatide or to any of its excipients (4)

WARNINGS AND PRECAUTIONS

- Patients with Paget's disease of bone, pediatric and young adult patients with open epiphyses, and patients with prior external beam or implant radiation involving the skeleton: Should not be treated with FORTEO (5.1, 8.4)
- Treatment duration: Use of FORTEO for more than 2 years during a patient's lifetime is not recommended. (5.2)
- Patients with bone metastases, history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or hypercalcemic disorders: Should not be treated with FORTEO (5.3, 5.4, 5.5)
- Laboratory alterations: FORTEO may increase serum calcium, urinary calcium, and serum uric acid (5.5, 5.6)
- Urolithiasis: Use with caution in patients with active or recent urolithiasis because of risk of exacerbation (5.6)
- Orthostatic hypotension: Transient orthostatic hypotension may occur with initial doses of FORTEO (5.7)

ADVERSE REACTIONS

Most common adverse reactions (>10%) include: arthralgia, pain, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Digoxin: Use FORTEO with caution in patients receiving digoxin. Transient hypercalcemia may predispose patients to digitalis toxicity (5.8, 7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal studies, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue nursing or FORTEO, taking into account the importance of treatment to the mother (8.3)
- Pediatric Use: FORTEO should not be used in pediatric and young adult patients with open epiphyses due to increased baseline risk of osteosarcoma (5.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: MM/20XX

FULL PRESCRIBING INFORMATION: CONTENTS*

Master Files

- Optional submission to FDA of information concerning facilities, processes, or ingredients for a drug
- Method for supplying information in a confidential manner
- May be referenced by holder or others (with permission) in an application w/letter of authorization

Expedited Programs for Serious Conditions

	Criteria for Designation	Features of Programs
Fast Track	Nonclinical or clinical data "demonstrates the potential to address unmet medical needs"	• Actions to expedite development. • Rolling review.
Breakthrough Therapy	"preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints"	All the benefits of Fast Track plus: • Intensive guidance on efficient drug development, beginning in Phase 1 • Organizational commitment involving senior managers
Regenerative Medicine Advanced Therapy	A "regenerative medicine therapy" and "preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition"	All the benefits of Fast Track and Breakthrough plus: • Potential ways to support accelerated approval and satisfy post-approval requirements

Two others: **Accelerated Approval** and **Priority Review**

Accelerated Approval

	Criteria	Features of Programs
Accelerated Approval	Generally provides a meaningful advantage over available therapy ("taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments") Demonstrates an effect on: • **Surrogate endpoint** that is "reasonably likely to predict clinical benefit" or • **Intermediate clinical endpoint** ("clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit")	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint • Promotional materials • Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal

Priority Review

	Criteria	Features of Programs
Priority Review	• An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR • An application for a drug that has been designated as a qualified infectious disease product OR • Any application or supplement for a drug submitted with a priority review voucher	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review) • Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

FDA Review

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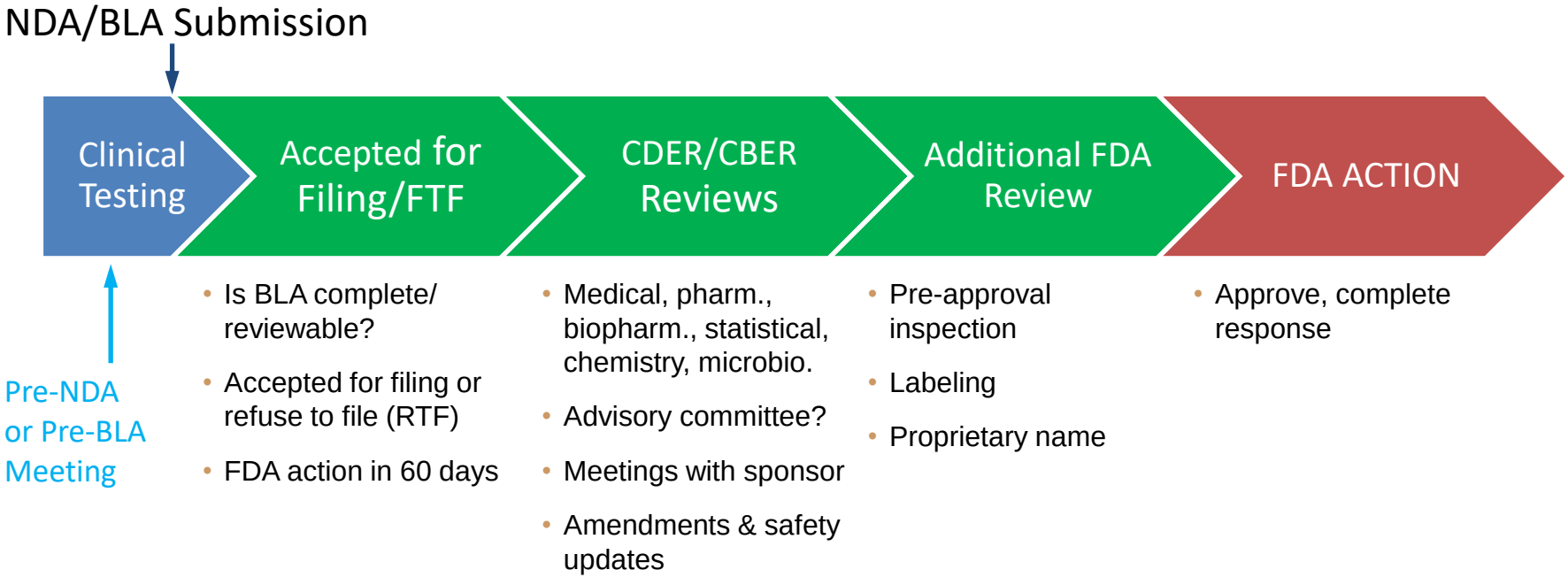
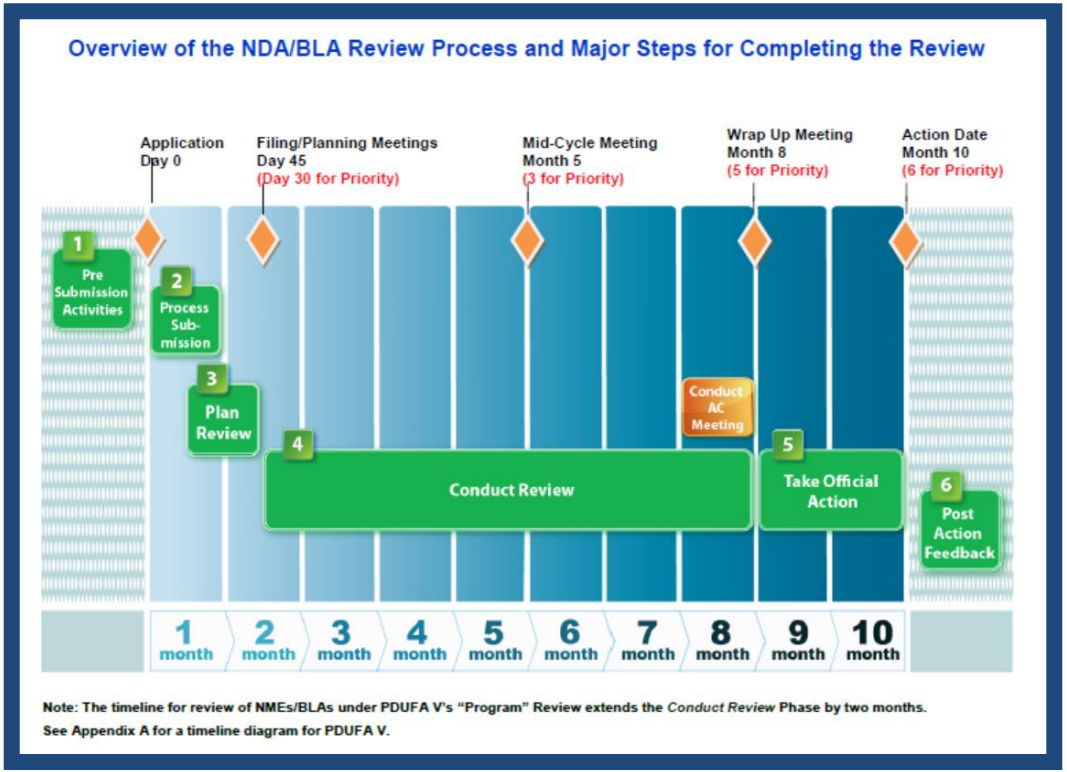
NDA/BLA Review Process



CDER 21st Century Review Process Desk Reference Guide



Types of Meetings

- Type A: for stalled development or to address an important safety issue
- Type B:
  - Specific developmental meetings such as pre-BLA, pre-IND
  - Includes Type B (EOP), e.g., End-of-Phase 2 meetings
- Type C: other meetings

Pre-Filing Meetings

- Goal: Ensure submission is well-organized and readily reviewable by FDA
- Purposes
  - Acquaint FDA reviewers with information to be submitted in BLA
  - Agree on format and content of application
  - Discuss appropriate methods for statistical analysis of the data
  - Identify any major unresolved problems

Filing Decision

"An application for a biologics license shall not be considered as filed until all pertinent information and data have been received by the Food and Drug Administration."

21 C.F.R. 601.2

Refuse-to-File Decision

- Made w/in 60 days after FDA receives BLA
- FDA makes threshold determination if BLA is sufficiently complete to permit a substantive review

The User Fee Framework

- Industry pays $$ to support drug review
- FDA performance goals
  - In “side letter”
- Recently reauthorized in 8/17
  - PDUFA VI
  - Reauthorized for 5 years

PDUFA VI Fees

- New fee structure
  - Eliminate establishment and supplement fees
  - Greater contribution from program fees (formerly product fees)
- FY 2021 user fees
  - Application with clinical data: $2,875,842
  - Application without clinical data: $1,437,921
  - Program fee: $336,432
- Reauthorized the “Program”

PDUFA VI Performance Goals

	New Molecular Entity (NME) or Original BLA: "the Program"	Non-NME NDA	Supplement
Priority	8 Months	6 Months	6 months
Standard	12 Months	10 Months	10 months

- Commitment = date by which FDA commits to "review and act on" 90% of applications
- Review goal on Class 2 resubmission = 6 months
- Review goal on Class 1 resubmission = 2 months

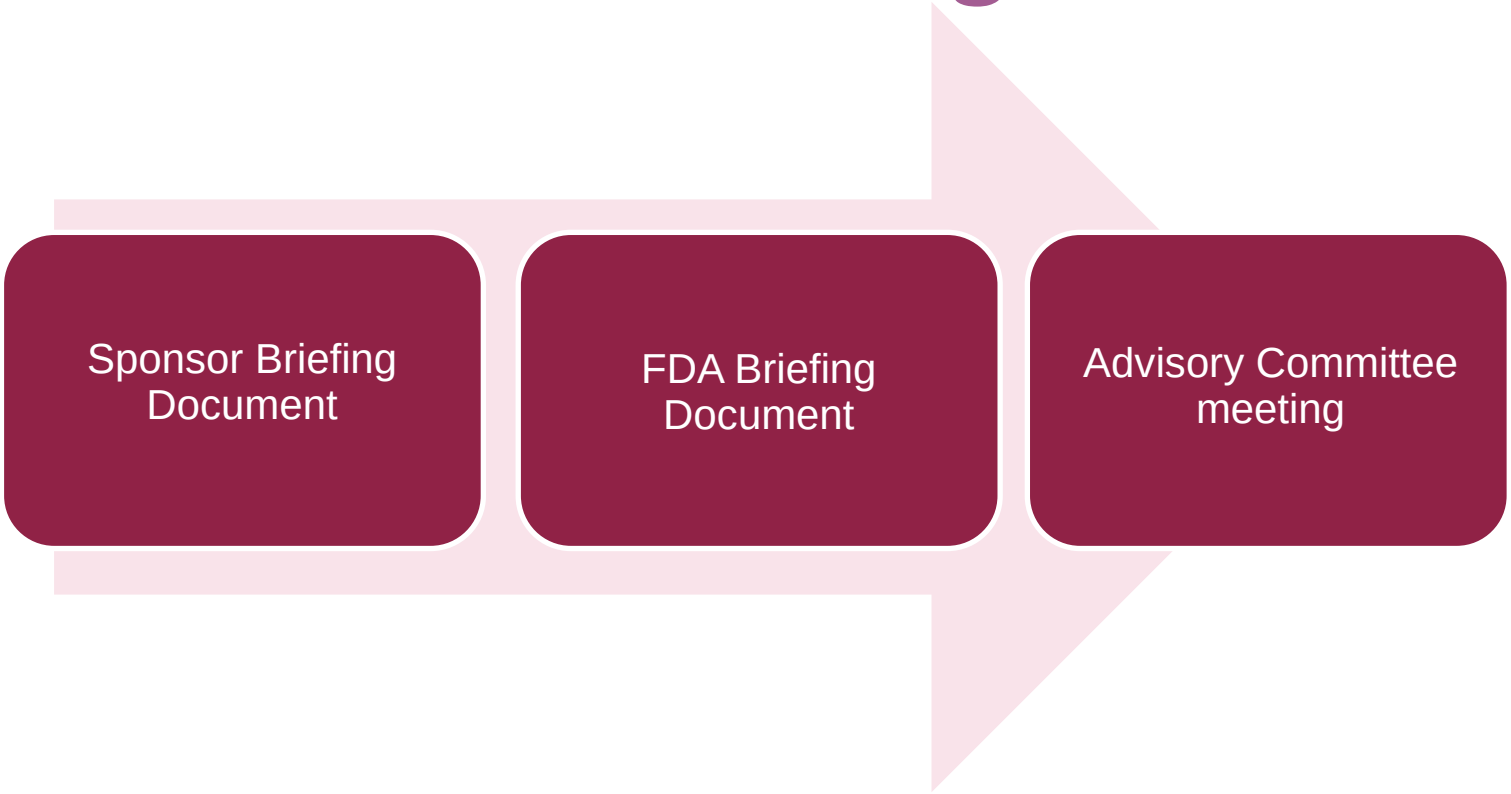
Amendments

- Amendment: submission of additional information to pending BLA or supplement
- Raises issue of whether FDA's goal date will be extended
- 3-month extension of goal date for "major" amendment to original BLA

Major Amendments

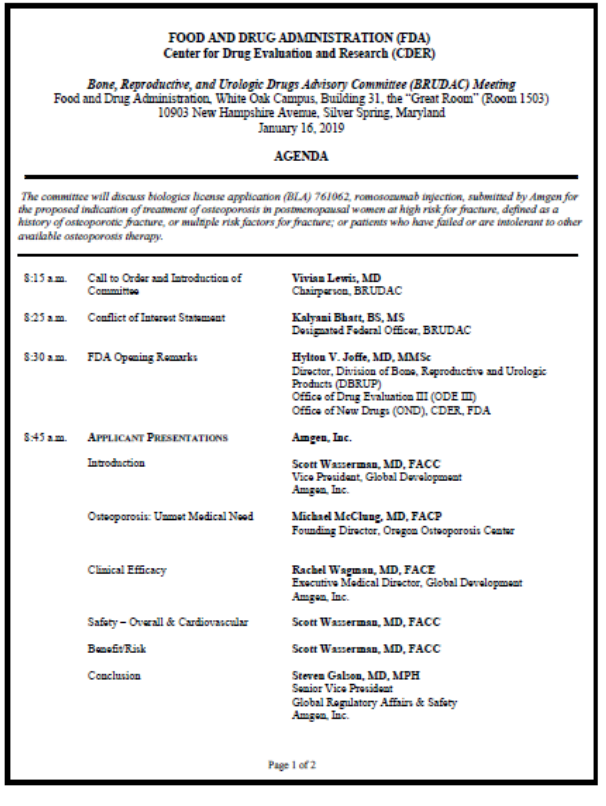
- Examples of major amendments (per PDUFA VI commitment letter)
  - Major new clinical safety/efficacy study report
  - Major re-analysis of previously submitted study
  - Submission of a REMS with ETASU not included in the original application or significant amendment to a previously submitted REMS with ETASU

AdComm Briefing Process



AdComm: Typical Agenda

- Sponsor presentation
- FDA presentation
- Open public hearing
- Questions to the Committee
- Discussion and Voting



FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting
Food and Drug Administration, White Oak Campus, Building 31, the "Great Room" (Room 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
January 16, 2019

AGENDA

The committee will discuss biologics license application (BLA) 761062, romosozumab injection, submitted by Amgen for the proposed indication of treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

8:15 a.m.	Call to Order and Introduction of Committee	**Vivian Lewis, MD** Chairperson, BRUDAC
8:25 a.m.	Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, BRUDAC
8:30 a.m.	FDA Opening Remarks	**Hylton V. Joffe, MD, MMSc** Director, Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) Office of New Drugs (OND), CDER, FDA
8:45 a.m.	APPLICANT PRESENTATIONS	**Amgen, Inc.**
	Introduction	**Scott Wasserman, MD, FACC** Vice President, Global Development Amgen, Inc.
	Osteoporosis: Unmet Medical Need	**Michael McClung, MD, FACP** Founding Director, Oregon Osteoporosis Center
	Clinical Efficacy	**Rachel Wagman, MD, FACE** Executive Medical Director, Global Development Amgen, Inc.
	Safety – Overall & Cardiovascular	**Scott Wasserman, MD, FACC**
	Benefit/Risk	**Scott Wasserman, MD, FACC**
	Conclusion	**Steven Galson, MD, MPH** Senior Vice President Global Regulatory Affairs & Safety Amgen, Inc.

Page 1 of 2

AdComm Procedure: Voting

3. **VOTE**: Is the overall benefit/risk profile of romosozumab acceptable to support approval?

   A. Yes, for Amgen's proposed indication (treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy)

   B. Yes, but for a different indication

   C. No

   Provide a rationale for your vote. If you voted for (B), describe the patient population in whom the benefits outweigh the risks.

   Votes submitted into the system/record

   Vote Result: ***A: 15*** ***B: 3*** ***C: 1***

Pre-Approval Inspections (PAIs)

- Assess:
  - Readiness for Commercial Manufacturing
  - Conformance to Application
  - Data Integrity
- Actions
  - Recommend approval
  - Recommend withholding approval

Many PAIs delayed in 2020 due to COVID-19

FDA's DECISION

FDA Actions: Approval

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761062

BLA APPROVAL

Amgen Inc.
Attention: Molly Salyers
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320

Dear Ms. Salyers:

Please refer to your Biologics License Application (BLA) dated and received July 19, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Evenity (romosozumab-aqqg) injection.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Evenity is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Evenity drug substance at [redacted]. The final formulated drug product will be manufactured and filled at [redacted] and labeled and packaged at Amgen Manufacturing Ltd, Juncos, Puerto Rico. You may label your product with the proprietary name, Evenity, and market it in 105 mg/1.17 mL single-use prefilled syringes.

Reference ID: 4416809

FDA Actions: Complete Response Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206843

COMPLETE RESPONSE

Bristol-Myers Squibb Company
Attention: Charles D. Wolleben, PhD
Group Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

April 29, 2014	July 9, 2014	August 29, 2014
May 2, 2014	July 10, 2014	September 11, 2014
May 20, 2014	July 14, 2014	October 9, 2014
June 10, 2014	July 23, 2014	October 23, 2014
June 20, 2014	July 29, 2014	November 19, 2014

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. You submitted two NDAs, NDA 206843 for daclatasvir and NDA 206844 for asunaprevir. The proposed indication for both NDAs was for the treatment of chronic hepatitis C virus infection. The pivotal data to support safety and efficacy for each drug came from three Phase 3 trials which evaluated the combination of daclatasvir and asunaprevir or the combination of daclatasvir and asunaprevir in combination with pegylated interferon alpha and ribavirin (P/R). Thus, both NDA's shared the same three pivotal phase 3 trials. On October 6, 2014, you withdrew the asunaprevir application. As a result, the daclatasvir NDA does not contain adequate evidence to establish the safety and efficacy of daclatasvir without asunaprevir for the treatment of chronic hepatitis C virus infection.

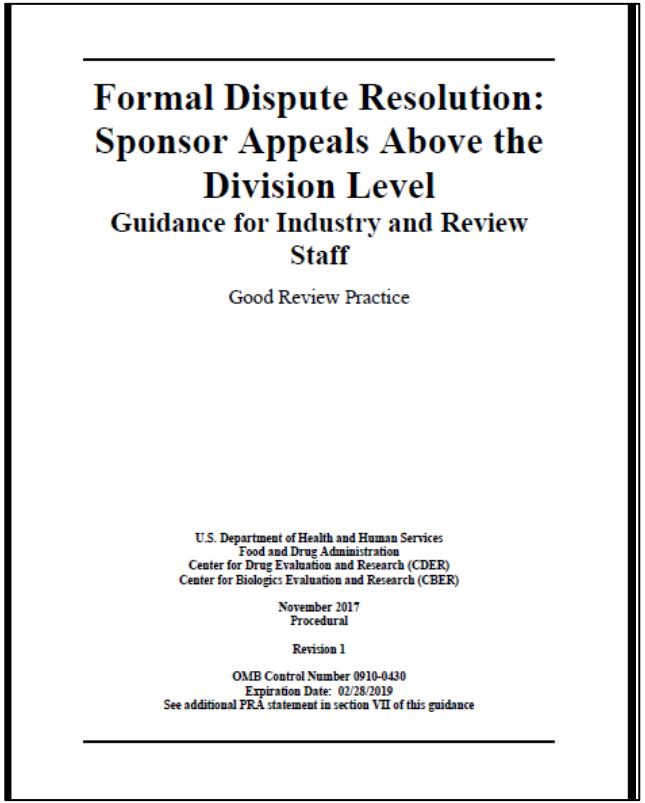
Reference ID: 3662226

Major Dispute Resolution PDUFA VI Goals

- Scope: For procedural or scientific matters involving review of human drug applications that cannot be resolved at signatory authority
  - Including request for reconsideration by signatory authority
- Goal: FDA response to appeal within 30 calendar days of receipt
- Responses “should ordinarily be to either grant or deny the appeal”
  - Potential for FDA to need “further data or further input from others”
  - Potential for Advisory Committee review
  - Effect on timing

Formal Dispute Resolution (FDR)

- Final guidance released Nov. 2017
- States narrower scope of disputes eligible for FDR than PDUFA VI goals



Formal Dispute Resolution: Sponsor Appeals Above the Division Level

Guidance for Industry and Review Staff

Good Review Practice

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)

November 2017
Procedural

Revision 1

OMB Control Number 0910-0430
Expiration Date: 02/28/2019
See additional PRA statement in section VII of this guidance

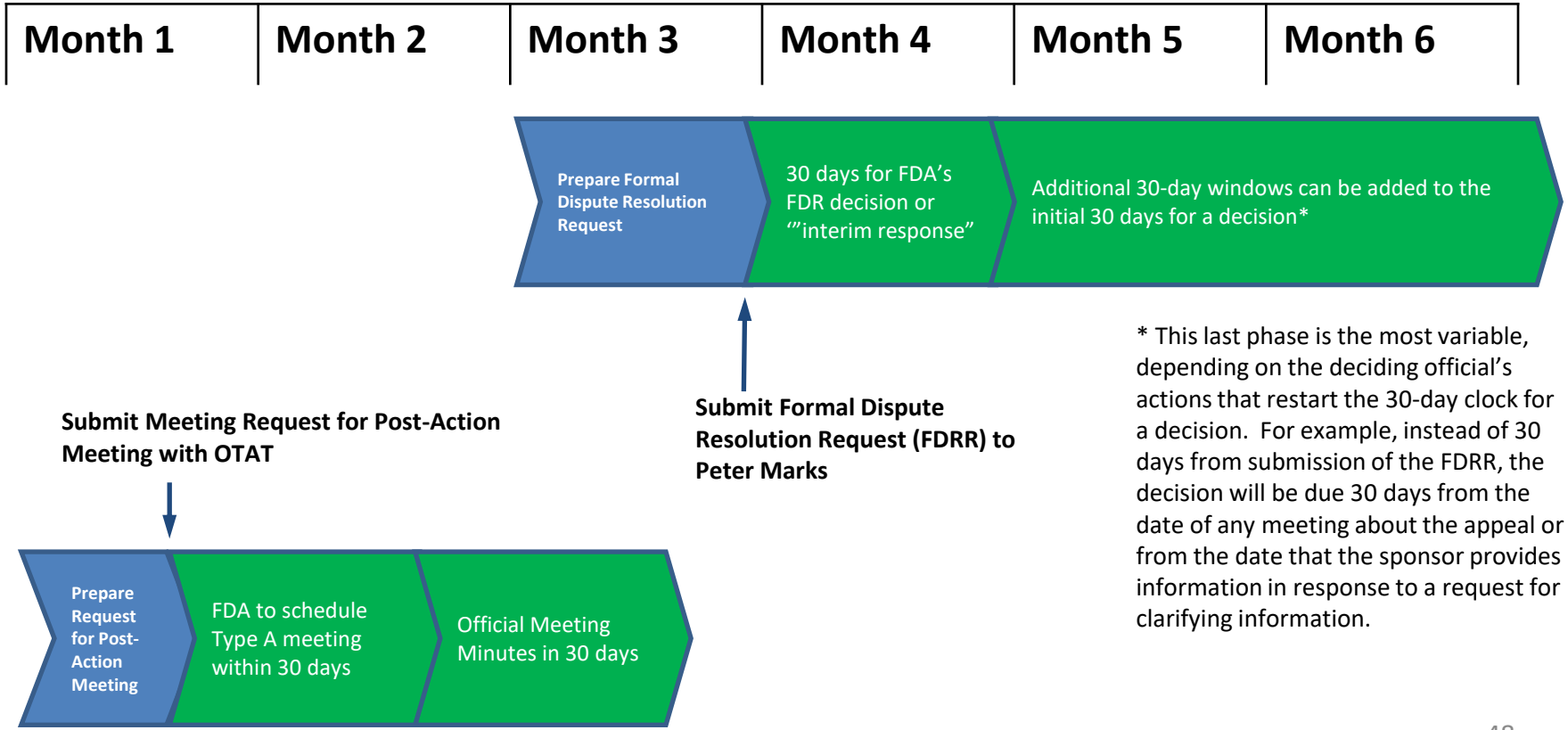
Disputes Eligible for FDR (Guidance)

- "Scientific and/or medical disputes"
  - FDA considers this to encompass procedural matters that may arise in the context of a larger scientific and/or medical dispute
- Over a "regulatory action" regarding a user fee product with "scientific and/or medical significance," such as:
  - Complete response letter
  - IND clinical hold (partial or full)
  - Request for breakthrough therapy designation denied
  - Request for proprietary name review denied
- "Advice communicated in meeting minutes and other correspondences is not a regulatory action"

Formal Dispute Resolution Request (FDRR)

- FDRR submission is a brief-like document with a more measured and scientific tone
- Cannot introduce new information in an FDRR
- Can request a Type A meeting in connection with FDRR
- Also can request advisory committee input
- Further appeals

Sample Timeline: FDRR after CRL



* This last phase is the most variable, depending on the deciding official's actions that restart the 30-day clock for a decision. For example, instead of 30 days from submission of the FDRR, the decision will be due 30 days from the date of any meeting about the appeal or from the date that the sponsor provides information in response to a request for clarifying information.

Risk Evaluation and Mitigation Strategies

When can FDA require a REMS?

- Pre-approval
  - If FDA determines that a REMS is needed to ensure that drug benefits outweigh the risks
- Post-approval
  - If FDA learns of "new safety information" and determines that a REMS is needed to ensure that drug benefits outweigh the risks

FDCA 505-1

Potential REMS Elements

- Timetable for REMS assessments
- Medication guide
- Patient package insert
- Communication plan: May include HCP letters and disseminating:
  - REMS info to encourage implementation or explain safety protocols
  - Info through professional societies on serious risks or protocols to assure safe use
  - Info to HCPs about “drug formulations or properties,” including their limitations or patient care implications and how they relate to SAEs

Potential REMS Elements (cont'd)

- Packaging and disposal
  - Dispensing in unit dose packaging, packaging providing set duration, or another packaging system that may mitigate a serious risk
  - Dispensing to certain patients with safe disposal packaging or system for purposes of rendering drugs nonretrievable
- Elements to assure safe use (ETASU)

Elements to Assure Safe Use

- FDA may require ETASU only if:
  - Drug has been shown effective, but is associated with a serious adverse drug experience and can be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific, labeled serious risk
  - For a drug initially approved w/o ETASU, other permissible REMS elements are insufficient to mitigate serious risk
- Must be shaped to be commensurate with labeled risks, minimize burden, assure access

Elements to Assure Safe Use

- Potential ETASU:
  - Prescribers must have specialized training, experience, or certification
  - Required dispenser certification
  - Limited dispensing settings (*e.g.*, hospitals)
  - Evidence/documentation of safe use conditions before dispensing (e.g., lab results)
  - Patient monitoring
  - Patient registries
- May include an "implementation system"
  - "Reasonable steps" to monitor compliance by HCPs
  - "Work to improve implementation of such elements by such persons"

REMS Enforcement

- FDCA 505(p) – no introduction of drug into interstate commerce if not complying with REMS
  - Triggers violation of FDCA 301
- FDCA 502(y) – Misbranding
- Civil monetary penalties, FDCA 303(f)(4)

Postmarketing Studies & Trials

- FDA may require NDA/BLA applicant or holder to conduct a postmarketing study or trial to:
  - Assess known serious risk or signals of serious risk; or
  - Identify unexpected serious risk where data indicate the potential for a serious risk
- Requirement based on “scientific data deemed appropriate” by FDA, including regarding drug class
- If drug already approved, FDA can impose study or trial requirement only if FDA becomes aware of new safety information

ClinicalTrials.Gov

- Regulations (42 CFR Part 11)
- Required registration and results submission information for “applicable clinical trials,” regardless of whether study product is approved
  - Previously, results required only for approved products

CBER BIOLOGICS: Selected Topics

FDLI

Special Issues: CBER Biologics

- Vaccines
- Cellular Therapy
- Gene therapy products

CDER v. CBER

CDER	CBER
Monoclonal antibodies Most proteins for therapeutic use Therapeutic immunotherapies Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo	Cellular products Gene therapy Blood, blood products Vaccines Antitoxins, antivenins, and venoms Allergenic extracts

“Biological Product”

- **Biological Product (PHSA 351(i)):** A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide) or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

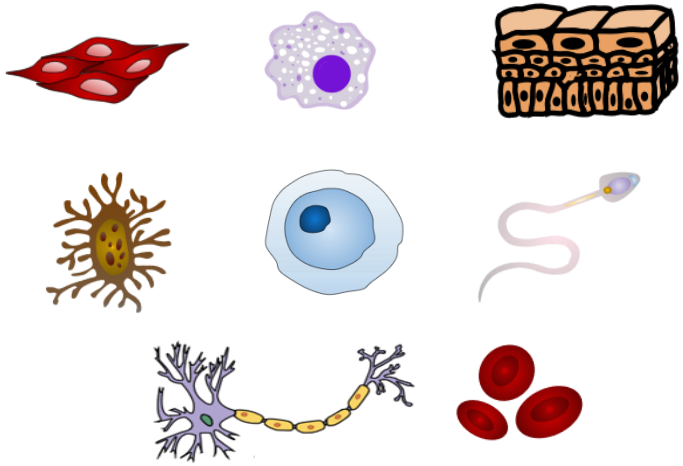
Vaccines

- Special considerations include:
  - Immunological effects
  - Establishing standards of potency
  - Linking standards to some measure of clinical effect

Vaccines for COVID-19 may be authorized through the Emergency Use Authorization (EUA) before or instead of BLA approval.
In 2020 FDLI annual conference (October 2020), CBER officials emphasized that the standards will be closer to BLA than to other EUAs (because of exposure to healthy persons)

What Is Cell Therapy?

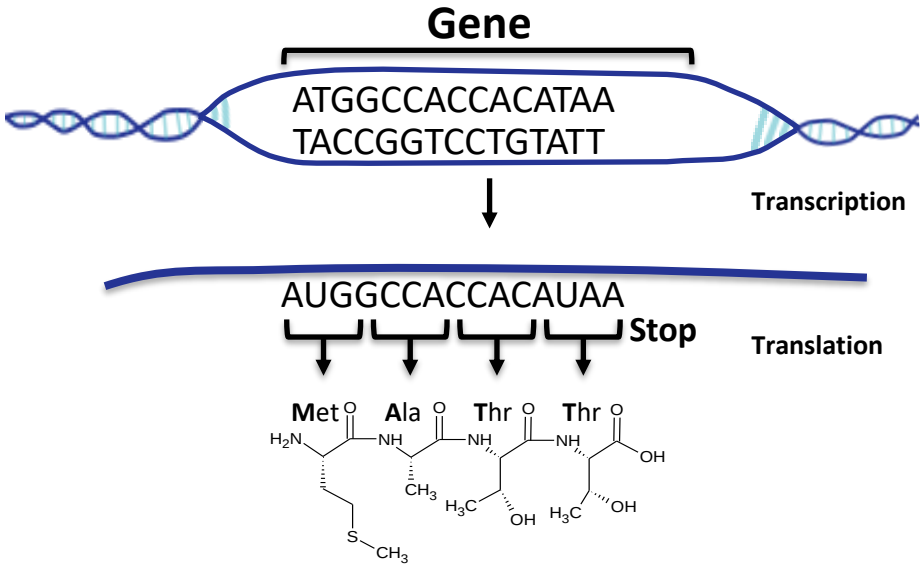
- "Cell therapy" is the therapeutic use of living cells
  - From the patient: **autologous**
  - From donors: **allogeneic**
  - From other species: **xenogeneic**
- Advanced cell therapies:
  - Investigational new drug application (IND)
  - Biologics license application (BLA)
  - CBER's Office of Tissue and Advanced Therapies (OTAT)



Contrast: Classic cell therapies used in practice of medicine ("361 HCT/P's")

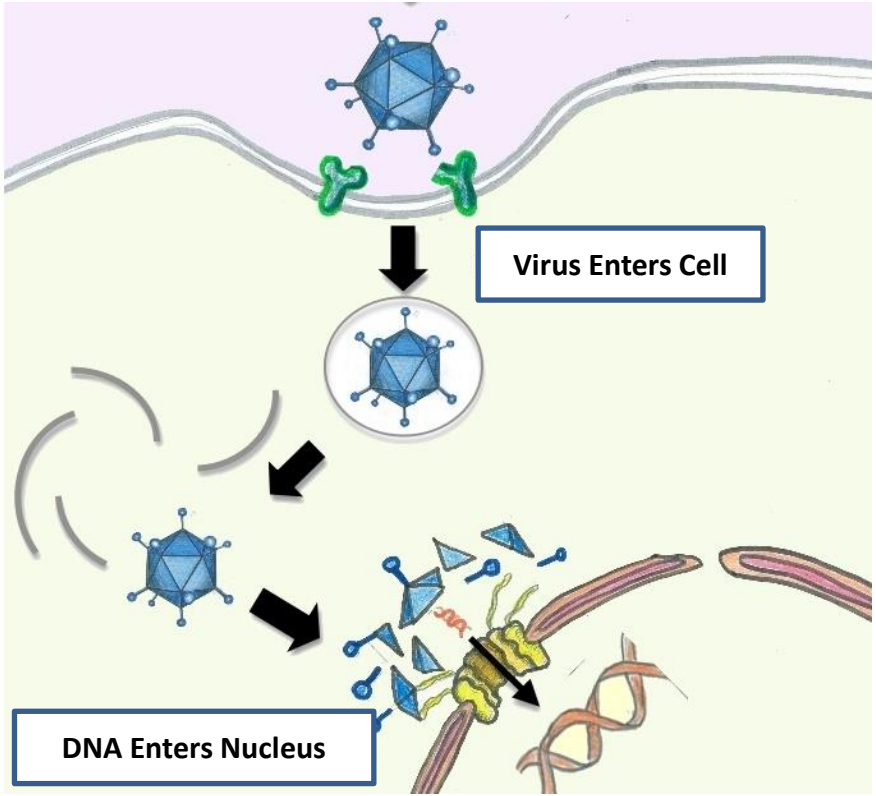
What Is Gene Therapy?

Gene Therapy: "modifies a person's genes to treat or cure disease," by **transcription** or **translation** of new or altered genes.



Contrast: **antisense therapies,** which **prevent translation** of **native mRNA**

Vector-Based Gene Therapy



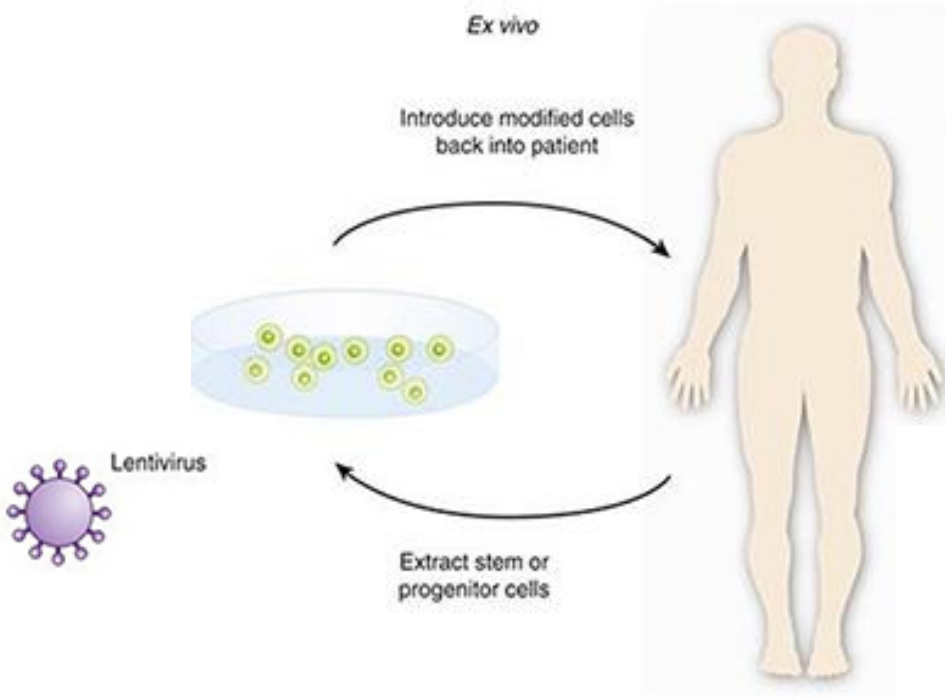
Vector Types:

Viruses

Adeno-Associated Virus (AAV)

- Non-pathogenic
- Single-stranded DNA
- LUXTURNA and ZOLGENSMA

Cellular Gene Therapy Products



- Gene therapy also includes genetically modified cells.
- Examples: CAR T-Cells (KYMRIAH and YESCARTA).
- Cells are removed, modified, put back.

Special Issues for Gene Therapies

- Emphasis on manufacturing process: Process is the product
- CMC reviewer often chairs the review committee and authored the summary basis for regulatory action
- Long-term follow-up
- CAR-T: REMS with ETASU, traceability
- Orphan-drug issues

Questions?

Matthew Hegreness, J.D., Ph.D.

Covington & Burling LLP

mhegreness@cov.com

202.662.5418