Managing Post-Approval Changes In Gene Therapy Products

Post-Approval Commercialization Workshop

Post-Approval Change Management and Overall Impact on Commercialization

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Ramjay S. Vatsan, Ph.D., CQA
Gene Therapy Team Leader
Division of Cellular and Gene Therapies
Office of Tissue and Advanced Therapies
Center for Biologics Evaluation and Research/FDA

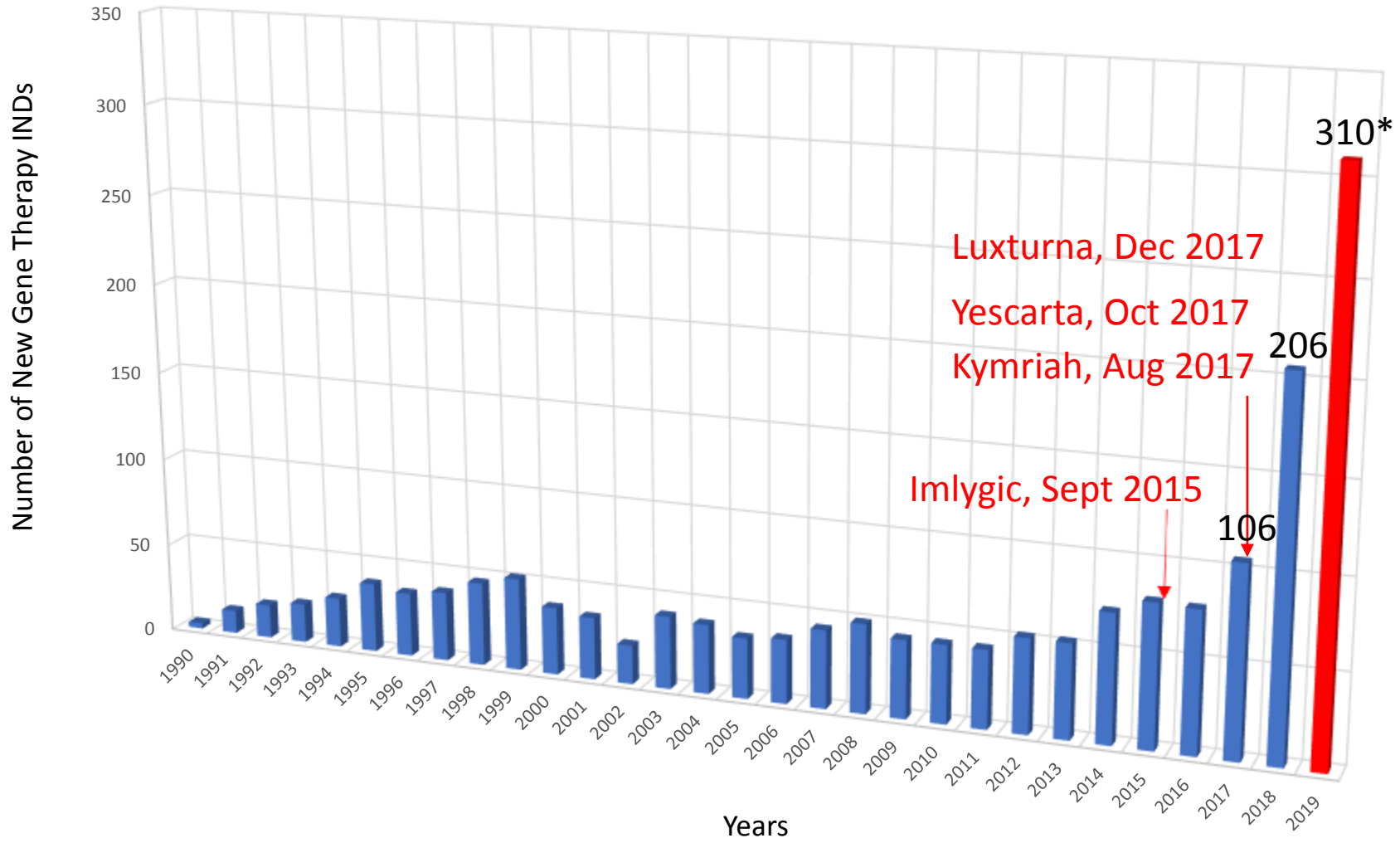
Outline

- Introduction
- Reasons for Post-Approval CMC Changes to GT products
- Reporting the changes to FDA
- Evaluating changes
- Summary
- Contact info and additional resources

FDA Approved Oncolytic and GT Products

- Imlygic (Amgen- HSV- Approved 2015)
  - Genetically modified oncolytic viral therapy
  - For the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
- Luxturna (Spark- AAV-GT Approved 2017)
  - For the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.
- Kymriah (Novartis- Lentivirus- Approved 2017)
  - CD19-directed genetically modified autologous T cell immunotherapy
  - For up to 25 year old with acute lymphoblastic leukemia (ALL)
  - For adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL)
- Yescarta (Kite- Retrovirus- Approved 2017)
  - CD19-directed genetically modified autologous T cell immunotherapy
  - For adult patients with relapsed or refractory large B-cell lymphoma (DLBCL)

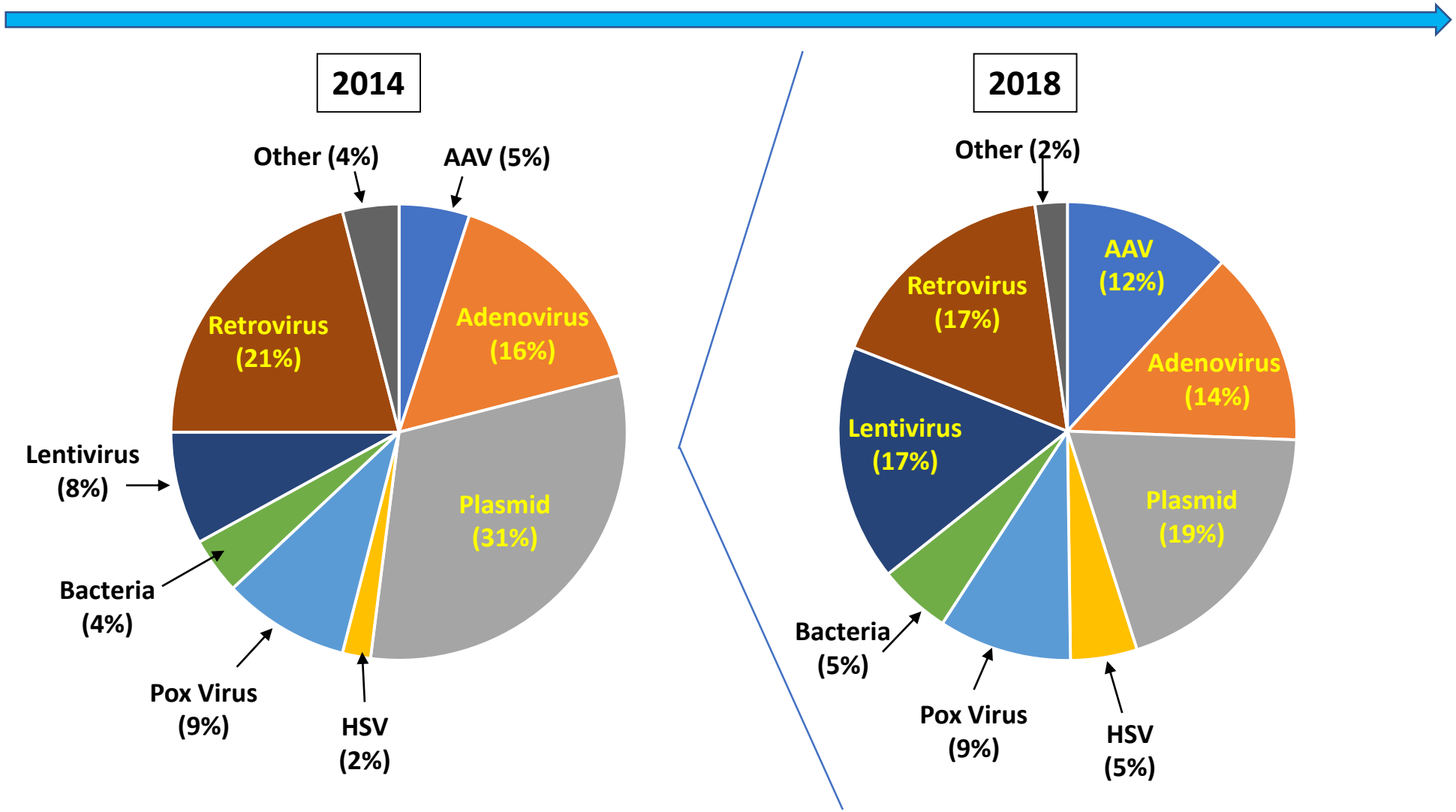
Rapid Growth in Annual GT IND Applications



* Projected based on 108 INDs received by April 2019

Gene Therapy Vectors

Rapid growth in AAV and Lentivirus as vectors of choice in GT



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Expedited Product Development

Various expedited product development programs offered by FDA

- Fast Track (FT) Designation
- Breakthrough (BT) Designation
- Regenerative Medicine Advanced Therapy (RMAT) Designation
- Accelerated Approval
- Priority Review

Engagement with FDA

- Prepare for change
- Initiate dialogue with the Agency
- Discuss change management protocols early

Potential Causes for Post-Approval Changes to Gene Therapy Products

Gene Therapies are frequently designed to cure rare diseases

- Small trial sizes
- Small batch sizes
- Limited manufacturing experience

Other Reasons for Post-Approval CMC Changes

- Changes to the reagents
- Changes to the assay methods/availability of new, more sensitive assay methods
- Process improvements
- Additional facilities (scale-out)
- Changes to Lot sizes (Scale-up)

The Regulations

- **21 CFR 601.12: Changes to an approved application**

An applicant must inform the Food and Drug Administration (FDA) about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).

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Types of Supplements Related to Changes

Prior Approval Supplement (PAS) – Major (601.12 (b))

Changes requiring supplement submission and approval prior to distribution of the product made using the change

Changes Being Effected in 30 days (CBE-30) – Moderate (601.12(c))

Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change

Changes Being Effected (CBE) – (601.12(c)(5))

Based on experience with a particular type of change, …on particular assurances that the proposed change has been appropriately submitted (to the Agency)…. the product made using the change may be distributed immediately upon receipt of the supplement by FDA

Annual Report Reportable Changes – Minor Changes (601.12(d))

Changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product

Other Reportable Changes

Labeling Changes (601.12(f))

FDA must be informed before distribution of the product with the labeling changes

- *Labeling changes that require supplement submission and prior approval before distribution* ***(601.12(f)(1))***
- *Labeling changes that require supplement submission but may be distributed prior to approval* ***(601.12(f)(2))***
- *Labeling changes requiring submission in an annual report* ***(601.12(f)(3))***
  Examples: Editorial changes
- *Advertisements and promotional labeling* ***(601.12(f)(4))***

Major Changes (PAS): Examples*

- **Process Changes including but not limited to:**
  - Changes to culture growth time leading to increase in number of cell doublings; recovery procedures; change in a column; change in processing steps
- **Changes to Analytical Methods:**

  Establish a new method, changes to specifications, eliminate a test, etc
- **Changes to Excipients**
- **Changes to Reference Standards**
- **Significant manufacturing changes or addition of new manufacturing sites**
  - **Scale up or Scale out of the manufacturing process**
- **Facility changes that could introduce contaminations or cross-contaminations**

* Examples are general considerations- categories may vary based on the product

Moderate Changes (CBE-30): Examples

- Change in the site of compendial tests from one facility to another (e.g., Sterility/Endotoxin tests from an existing contract lab to a new contract lab; from the applicant to a new contract lab).
- Change in a supplier of trypsin or serum used in the manufacture of viral vaccine products.
- Change in the structure of a legal entity that would require issuance of a new license(s), or change in name of the legal entity or location that would require reissuance of the license(s).

Minor Changes (CBE): Examples

Any previously agreed upon changes to the manufacturing process or testing as a part of the BLA review

- **Addition of release tests and/or specifications**
- **Addition of in-process tests**
- **Tightening of specifications for intermediates**

- *FDA can, upon a review of the submission, change the submission category*
  - *In the event of a recategorization of the application, the applicant will be notified.*

Annual Report Reportable Changes: Examples

- Changes to the supplier of manufacturing reagents
  - Without changing the type of reagents or quality (Example: Buffers, non-animal derived reagents).
- Minor changes to manufacturing equipment (replacement of centrifuges, laboratory equipment, biosafety safety hoods, etc.).
- Administrative changes (changes to the management/technical teams)
- The report shall also include all information related to each change made during the annual reporting period.

Changes to the Drug Substance/Drug Product

A drug that is different from that approved under the Biological License Application can not be introduced in the market based on 601.12.

- If the biological product changes substantially and is no longer the same drug, then a new BLA will be required.
- Discuss with FDA to determine if the proposed change will change the drug to require a new BLA application.
- Develop change management protocols

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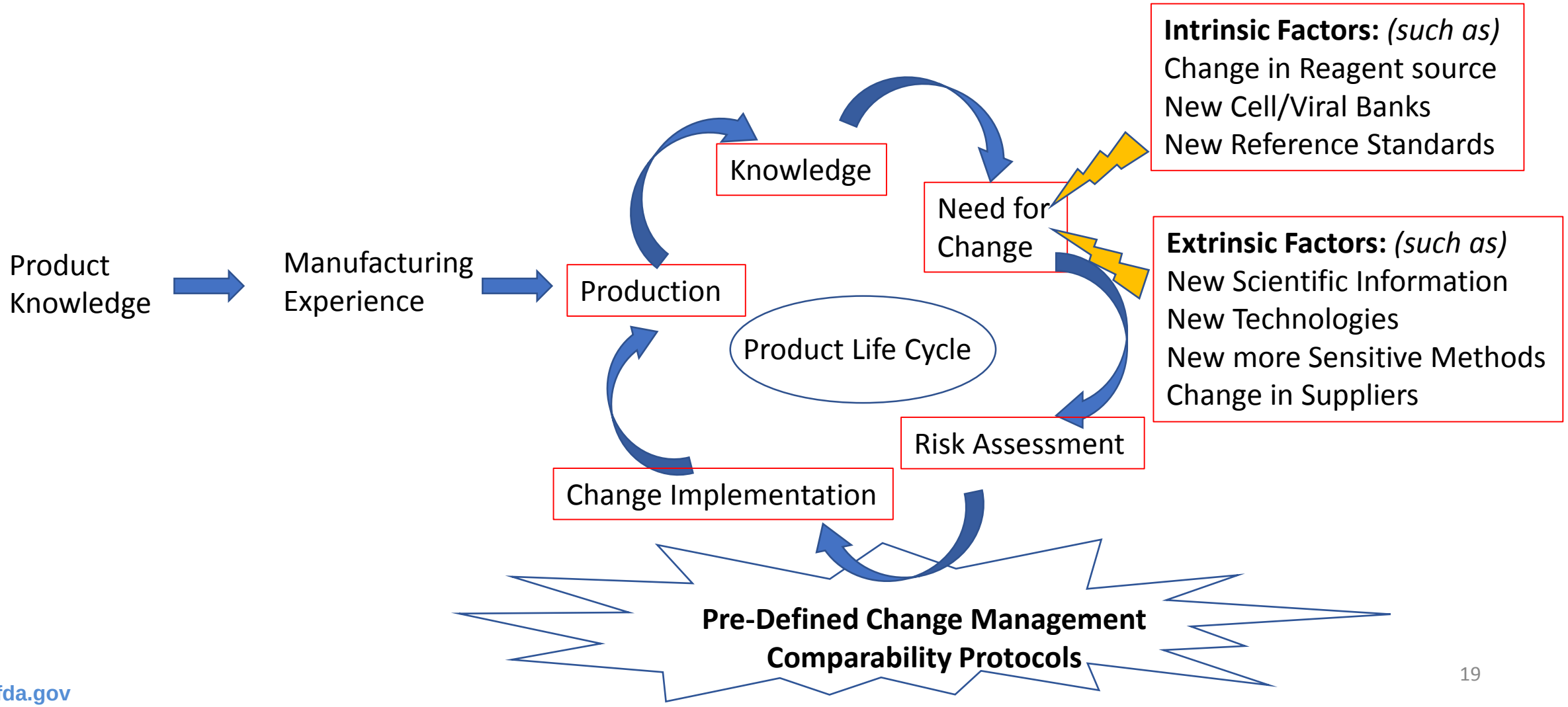
Managing Product Life Cycle: Defined Change Protocols



Change Management: Comparability Protocols

A comparability protocol is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC change(s) on product quality.

- An applicant can submit one or more Comparability Protocols
- Comparability protocols may be submitted in the original BLA or as a PAS
- The comparability protocols should describe the **specific tests, validation studies, and acceptance criteria to be achieved** in order to demonstrate the lack of adverse effect(s) for specified types of manufacturing changes, on product quality.

Submission and approval of a Comparability Protocol may enable:

1. Greater predictability regarding the timing of implementation of CMC changes
2. Placing the product into distribution sooner than without the use of a protocol
3. More effective planning of the product supply chain

Evaluation of Reportable Changes

Basic requirements for all change Categories:

- In addition to the requirements in 21 CFR 601.12, an applicant making a change to an approved application must conform to other applicable laws and regulations, including the current good manufacturing practice (cGMP) requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in **21 CFR parts**
- **210, 211 (cGMP regs)**
- **600 through 680 (Biologics Regs)**
- **820 (Quality Systems Regs)**

Evaluating Changes: Tools For Change Management

- Comparability Studies
- Risk Evaluation
- Use of Standards
- Bridging studies
- Post-marketing commitments (e.g., Assessment of long term effects of the changes)

Emerging Concepts in Managing Change

- **ICH Q12 : Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management**

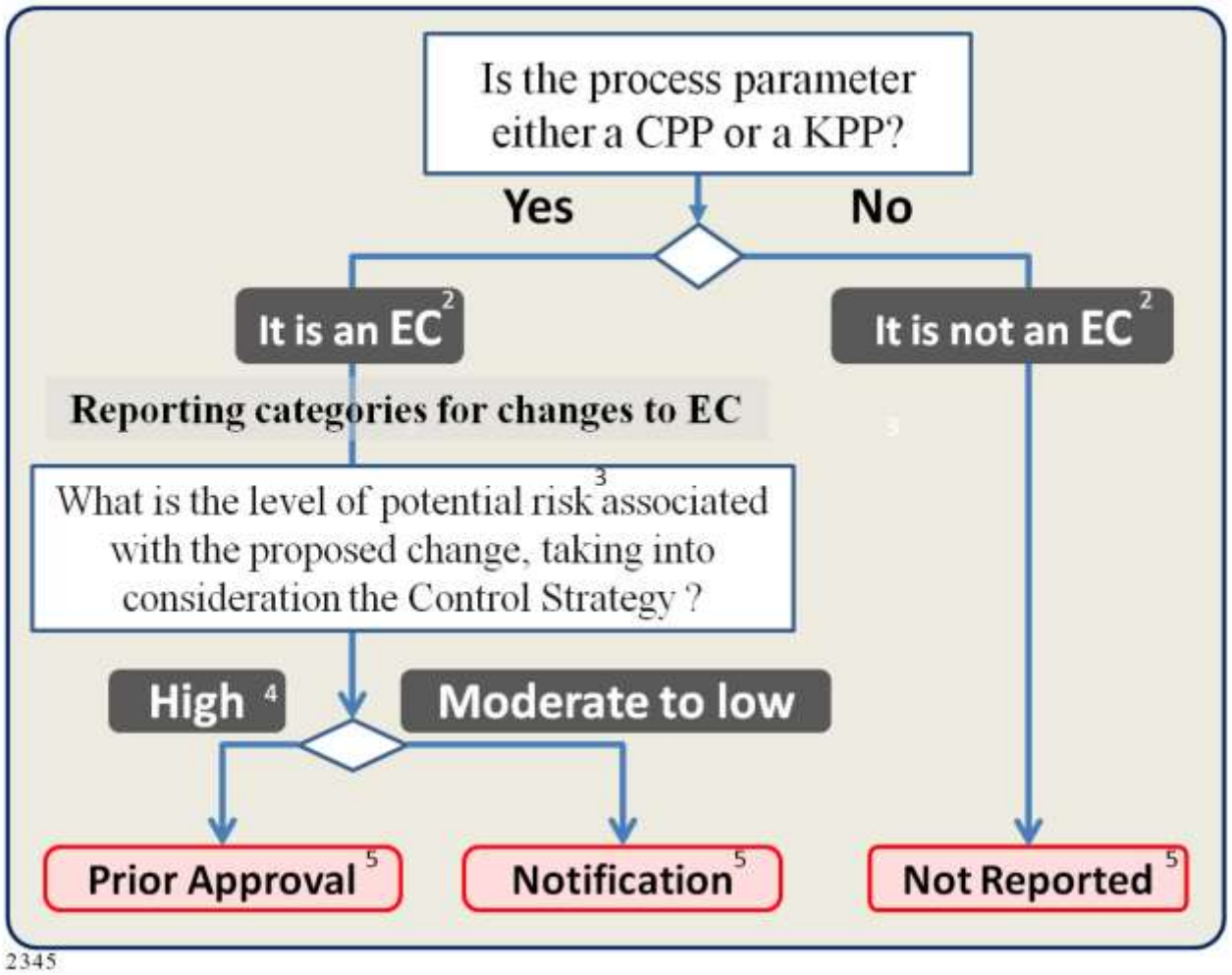
(DRAFT Guidance November 16, 2017)

(Public commenting period ended in December 2018; Expected to complete step 4 in the 2nd half of 2019)

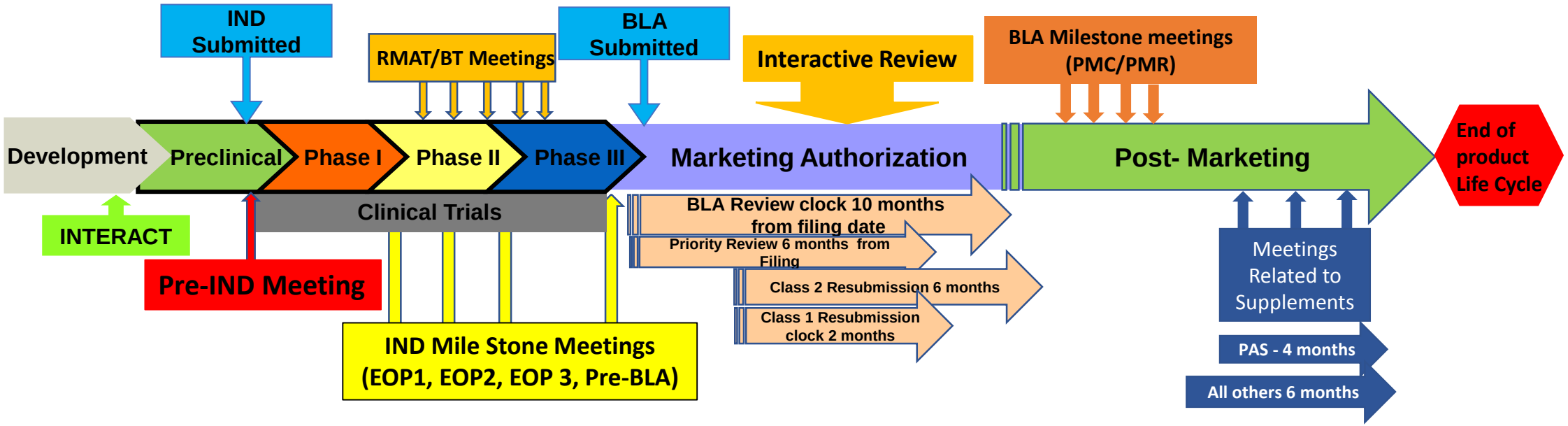
  - **Established conditions**
    - ECs are legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority
    - Implicit and Explicit Established Conditions
    - Identification of Established Conditions
    - Revision of Established Conditions

Established Conditions Decision Tree

Figure 1. Decision Tree for Identification of ECs and Associated Reporting Categories for Manufacturing Process Parameters[1]



Opportunities for Interaction with FDA



Summary

- Expect change
- Post-approval changes should be made with caution
- Prior approved comparability protocols can help managing changes
- Nature of the change determines the reporting category
- Early interactions with the FDA will help in designing comparability studies
- Appropriate use of change management tools may increase regulatory predictability

Contact Information and Resources

Ramjay Vatsan PhD (Ramjay.Vatsan@fda.hhs.gov)

Regulatory Questions:

OTAT Main Line – 240 402 8190

Email: OTATRPMS@fda.hhs.gov and Lori.Tull@fda.hhs.gov

Cell and Gene Therapy Guidance documents:
https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/default.htm

OTAT Learn Webinar Series:
http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm
Phone: 1-800-835-4709 or 240-402-8010
Consumer Affairs Branch: ocod@fda.hhs.gov

Manufacturers Assistance and Technical Training Branch:
industry.biologics@fda.gov