Regulatory Considerations for Bioconjugates from the Small Molecule Perspective

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Disclaimer

This presentation reflects the view of the presenter and should not be construed to represent the FDA's views or policies.


Everyone deserves
confidence in their *next* dose
of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

Outline

- Bioconjugates Overview
- Review process for bioconjugates at the FDA
- Key considerations from the small molecule perspective
    - ADC example
        - Drug-linker intermediate
        - Drug substance
        - Drug product
- Post-approval drug-linker changes and comparability
- Structure of submission (eCTD) and cross-referencing
- Engaging with the FDA

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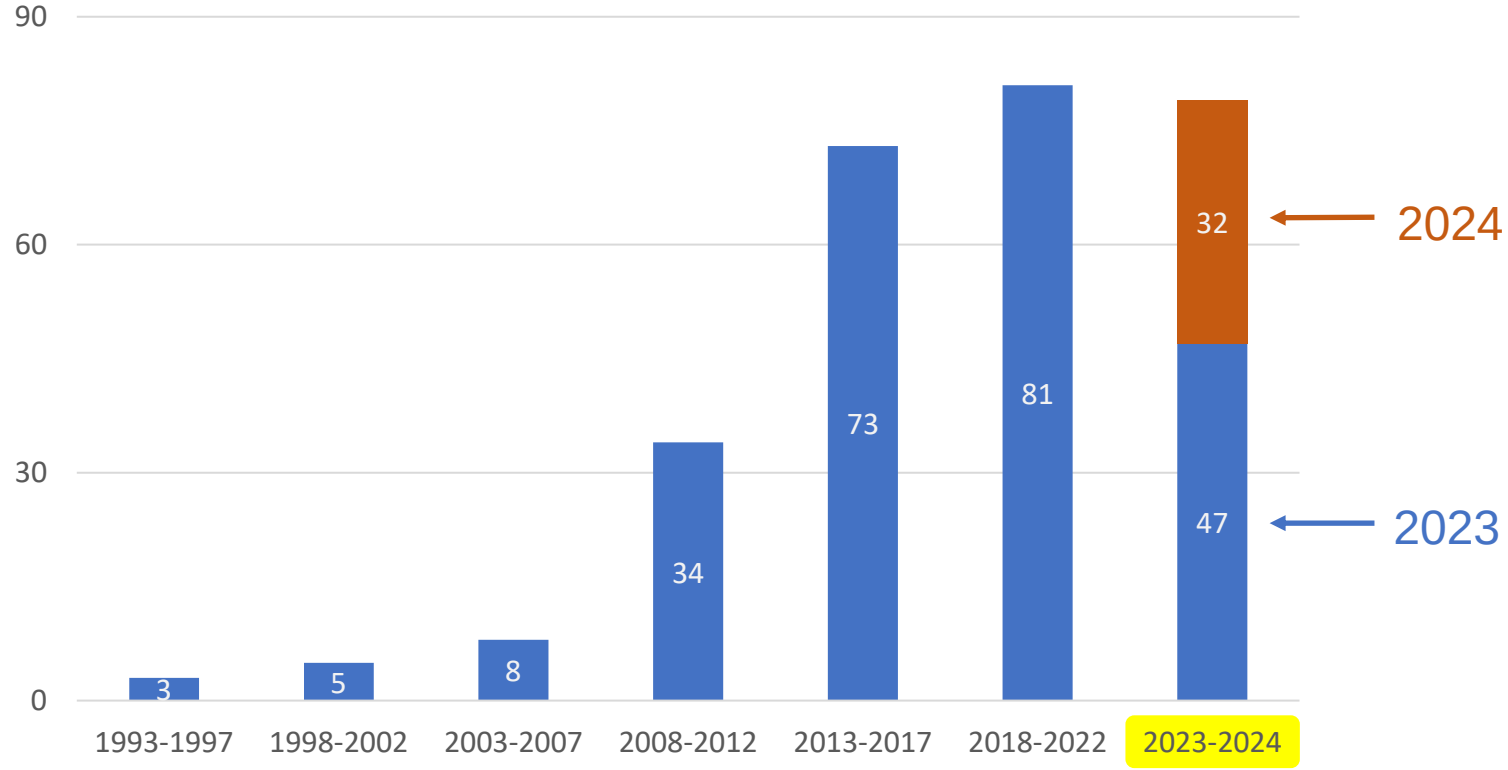
Commercial ADC IND Submissions



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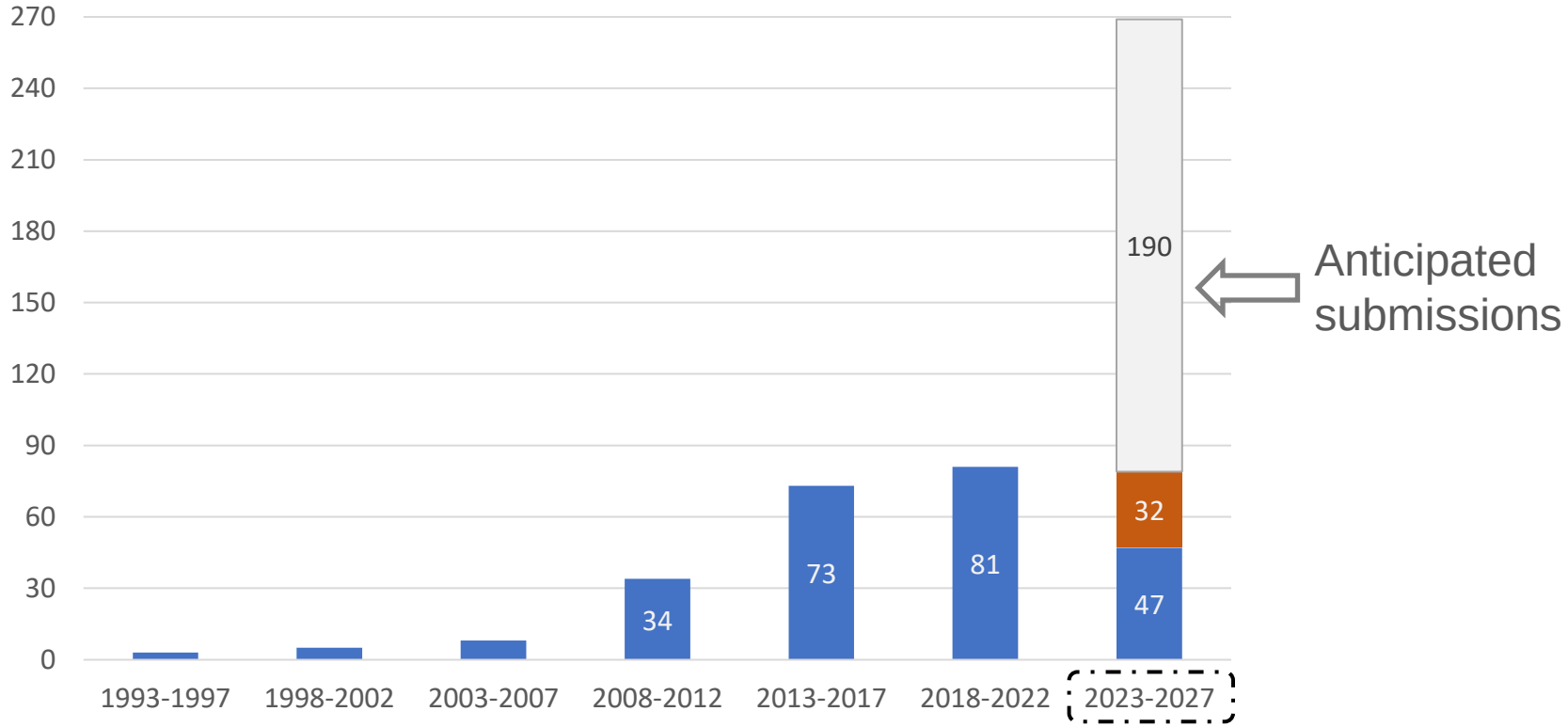
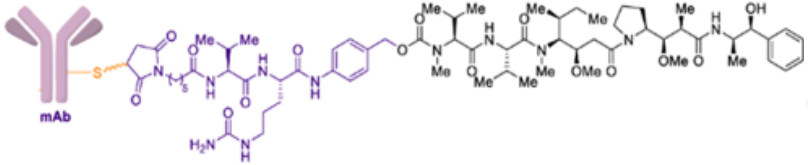
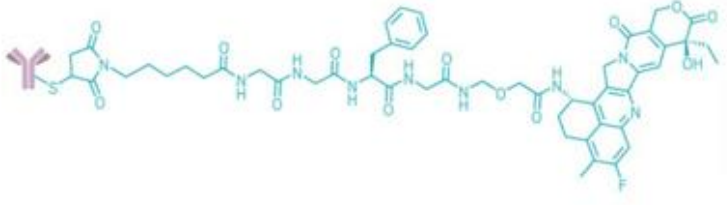


Structures of FDA Approved ADCs

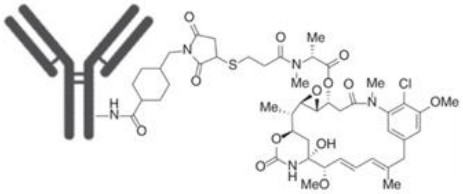
Brentuximab vedotin (2011), Enfortumab vedotin (2019), Tisotumab vedotin (2021), Polatuzumab vedotin (2023)



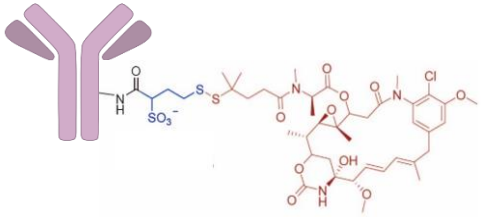
Trastuzumab deruxtecan (2019)



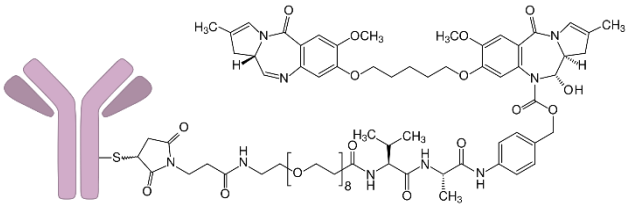
Trastuzumab emtansine (2013)



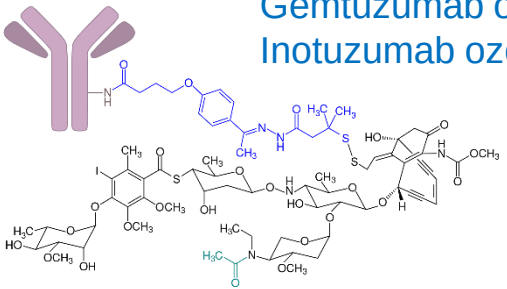
Mirvetuximab soravtansine (2022)



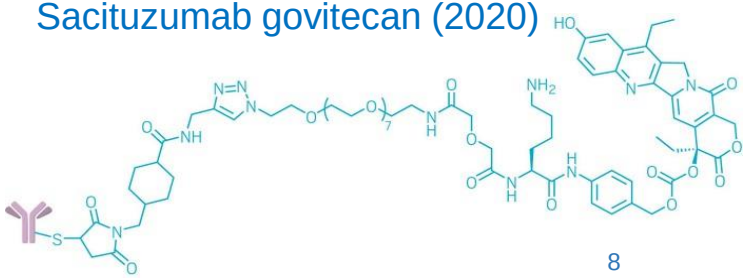
Loncastuximab tesirine (2021)



Gemtuzumab ozogamicin (2000), Inotuzumab ozogamicin (2017)



Sacituzumab govitecan (2020)



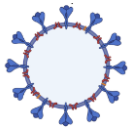
Innovations in Bioconjugates from Literature

Biomolecule/Carrier Molecules

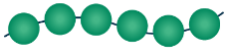
Antibodies
(fragments, probodies)

Proteins/Peptides

SiRNAs



Virus-like particles

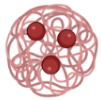


Polymers

Payloads

Small Molecules

Oligonucleotides



Nanoparticles

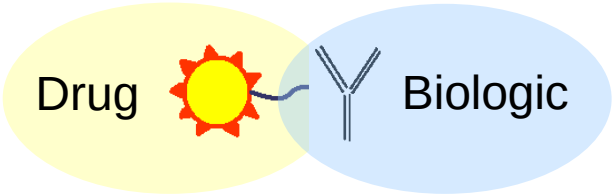
Peptides

Radioconjugates

- **Advances in Linker & Conjugation Chemistry**
- **Targets & Payloads outside of Oncology**

Bioconjugates Review Challenges

- Considered a drug/biologic combination product per 21 CFR 3.2(e)[1]
  - Drug and biologic components assessed per respective regulations



- Challenging manufacturing processes
- Minimal ICH, FDA, or other regulatory guidance documents
- Ensure quality using science and risk-based regulatory approaches on a **case-by-case** basis

Engage Early with FDA

[1]For details on combination products, refer to https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types

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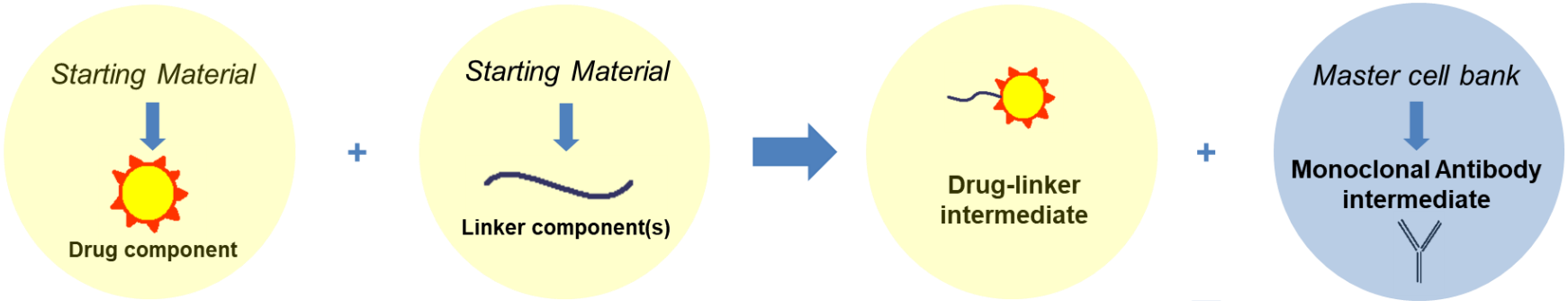
Bioconjugates (ADCs) Review Responsibilities



Office of Product Quality Assessment III (OPQA III)

Small Molecule Team | Biologics Team

Office of Pharmaceutical Manufacturing Assessment (OPMA)

Microbiology and Facilities

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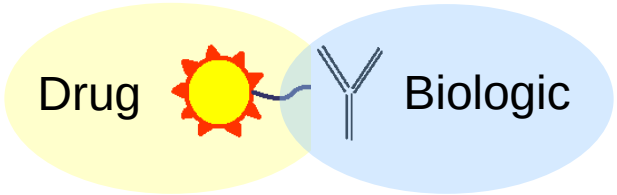
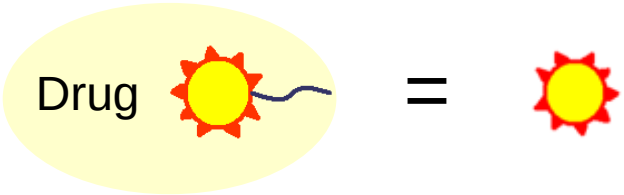
Key Considerations: Drug-Linker Intermediate

- ADC is a drug/biologic combination product



- Drug-linker intermediate is drug component of combination product

Evaluation criteria are **the same** for a drug-linker intermediate as a small molecule final drug substance



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Drug-Linker Intermediate: Starting Materials

Follow recommendations of ICH Q11 and ICH Q11 Q&A

- Chemically synthesized compounds
  - Stable and appropriately characterized molecules
  - Multiple chemical transformation steps preferred
  - Starting material impurities do not impact quality of drug-linker
- Fermentation/Natural and semi-synthetic compounds
  - Microbial strains/biological origin, etc.
- Peptides
  - Amino acids and their derivatives

Recommend discussing starting materials designation in an End-of-Phase 2 CMC-focused meeting

Drug-Linker Intermediate: Characterization/Controls

- Chiral characterization/controls, as appropriate
- Impurities
  - IND stage:
    - Impurity profile
      - Impurities in the clinical batch(es) should be adequately justified relative to data from toxicology studies
    - Structure of known impurities
    - Whether impurities have potential to conjugate with mAb intermediate
  - BLA stage:
    - **Impurity control follows principles of ICH Q3A**
    - Recommend determining structures of individual impurities per principles of ICH Q3A prior to pivotal clinical trials
- Expectations for specification/stability consistent with small molecule drugs
  - Ensure the identity, quality, strength and purity of drug-linker

Key Considerations: Drug Substance

- Small molecule relevant DS quality attributes
  - **Drug-to-Antibody ratio (DAR)**
    - Adequate controls & consistent DAR in tox and clinical batches
  - **Drug Loading Distribution (DLD)**
    - Homogeneity of DAR species in ADC
  - **Purity**
    - Conjugation process-related impurities
      - Excess unconjugated drug, reducing agents, quenching agents, residual solvents
    - Free drug related substances (e.g., free drug, drug-linker fragments, drug-linker degradation products)
      - Impurities in the clinical batch(es) should be qualified or adequately justified relative to data from toxicology studies

Key Considerations: Drug Product

- Small molecule relevant DP quality attributes
  - **Drug-to-Antibody ratio (DAR)**
  - **Drug Loading Distribution (DLD)**
  - **Purity**
  - **In-use compatibility study**
    - In-use stability data to support any proposed hold-times for reconstituted and/or further diluted DP solutions
      - DAR
      - Free-drug related substances
  - **Elemental impurities**

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Post-Approval Changes in Drug-Linker

Recommendations for drug-linker related post-approval changes:

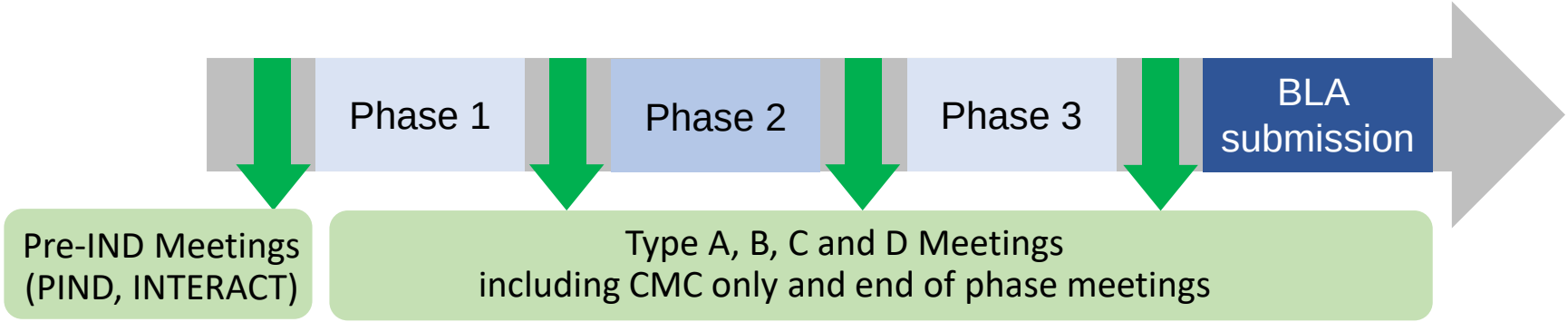
- Drug-linker Intermediate
  - Demonstrate quality equivalence (e.g., impurity profile and any critical drug-linker physical properties) of at least 3 consecutive pilot or commercial scale batches of pre- and post-modification materials (e.g., isolated intermediate or final drug-linker)
- Drug Substance
  - Batch data of drug substance manufactured with post-change drug-linker, as appropriate, to demonstrate quality equivalence based on risk of change
- Stability
  - At least 3 months of long-term and accelerated stability data for drug-linker
  - Commitment to place the first commercial-scale batch of drug substance on stability
  - Additional stability data in certain cases (e.g., to support drug-linker specification changes or address stability concerns)

Structure of Submission

- Application structure (Electronic Common Technical Document Structure)
  - Prefer 3 separate [3.2.S] modules for drug substance, drug-linker intermediate, and mAb intermediate

- Strongly encourage cross-referencing **drug-linker info** to drug master files (DMFs) or other applications (i.e., designate a parent application), as appropriate
  - Avoid submitting and updating duplicative info
  - In each application, indicate which drug-linker batch will be used to support nonclinical and clinical studies and provide supporting data as needed

Discussions with Agency



- Discussions related to starting materials, manufacturing, specifications, impurity controls, batch data, stability program, etc.

Discussions with Agency are strongly encouraged throughout clinical development!

Some Relevant Guidance Documents

- **Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products.**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-and-format-investigational-new-drug-applications-inds-phase-1-studies-drugs-including-well
- **INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information Guidance for Industry.**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/inds-phase-2-and-phase-3-studies-chemistry-manufacturing-and-controls-information
- **Exploratory IND Studies Guidance for Industry, Investigators, and Reviewers.**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exploratory-ind-studies
- **Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-q7a-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients
- **Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products.**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products
- **Q11 Development and Manufacture of Drug Substances & Questions and Answers (Chemical Entities and Biotechnological/Biological Entities).**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q11-development-and-manufacture-drug-substances
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q11-development-and-manufacture-drug-substances-questions-and-answers-chemical-entities-and
- **Clinical Pharmacology Considerations for Antibody-Drug Conjugates Guidance for Industry.**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-considerations-antibody-drug-conjugates-guidance-industry
- **Postapproval Changes to Drug Substances, Draft Guidance for Industry.**
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-changes-drug-substances-guidance-industry

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