GILEAD
Creating Possible

Navigating Global Regulations for Antibody Drug Conjugates (ADCs) *A CMC Perspective*

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Views expressed herein are my own and not representative of or attributable to Gilead.

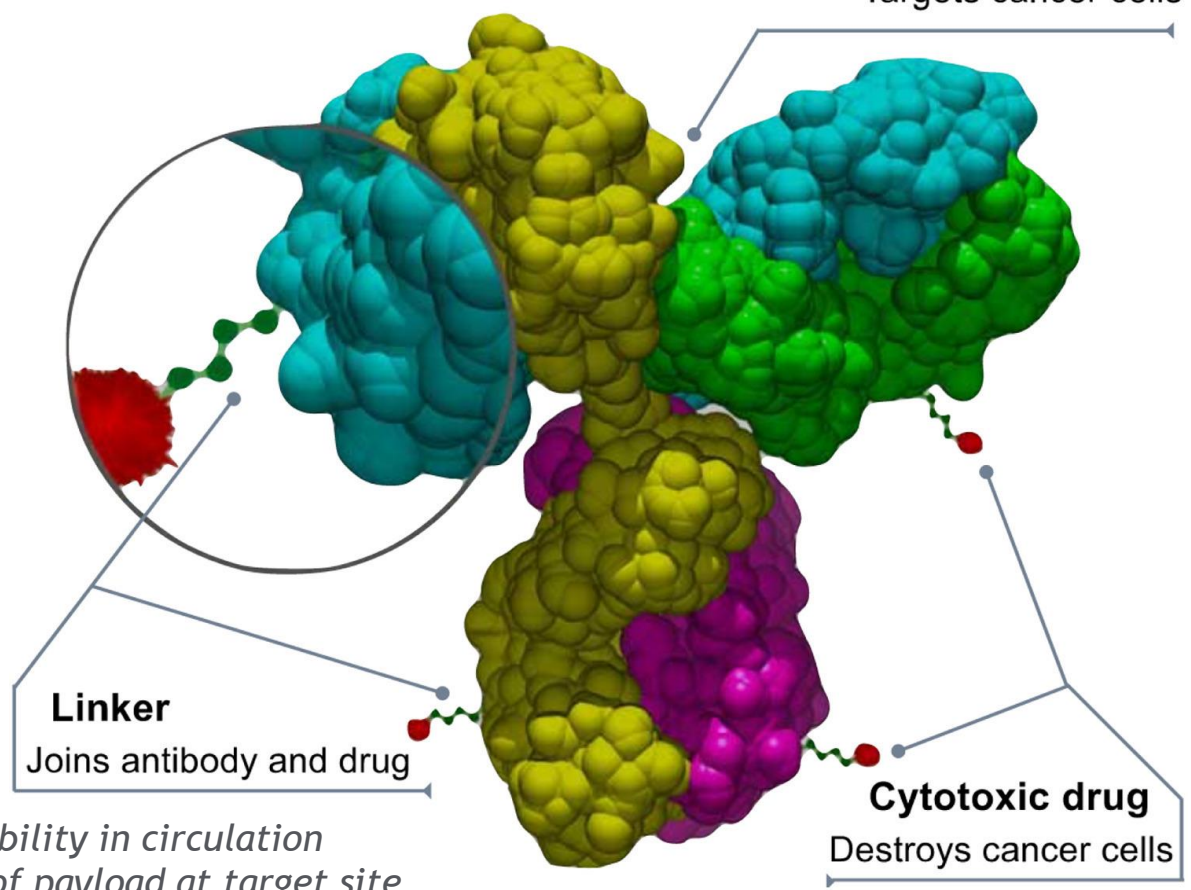
Agenda

- Introduction to ADCs and Current ADC landscape
- Global Regulatory Requirements and Points to Consider for ADCs
- Post Approval Change Management and Challenges
- Conclusions

Introduction to ADCs

Antibody
Targets cancer cells

High affinity for tumor antigen
Chimeric or humanized
High molecular weight
Long half life



Linker
Joins antibody and drug

Maintains ADC stability in circulation
Efficient release of payload at target site
Minimal cross reactivity and immunogenicity

Cytotoxic drug
Destroys cancer cells

Effector component of the ADC
Chemically synthesized
Highly potent and cytotoxic

Image From Journal of Pharmaceutical Sciences

Current ADC Landscape

- As of 2022 there are ~ 14 ADC drugs on the market worldwide.
- USA Approved ADCs: There are up to 12 ADC drugs on the market in USA.
- Europe Approved ADCs: There are eight ADC drugs on the market in Europe.
- Canada Approved ADCs: There are eight ADC drugs on the market in Canada
- The indications for ADC drugs are all focused on the oncology field. Among the drugs that have been marketed, 6 drugs target solid tumors (breast cancer, bladder cancer, gastric cancer, etc.) and 7 drugs target hematologic tumors.
- A number of these approved ADC drugs have followed expedited regulatory pathways to approval.

ADCs Submissions are Inherently Complex

- **Mixed modality** of a large and a small molecule makes **ADCs more complex** from both a product development and regulatory expectations perspective.
- ADCs are **regulated as biologics**: CMC components of these submissions are **reviewed collaboratively** by both small and large molecule experts at Health Authorities.
- Health Authorities **draw from existing guidance** for large and small molecule to guide the review process.
- It is an expectation for Sponsors to follow the currently established ICH and local Health Authority guidance and expectations.
- Globally there is some ambiguity in requirements for mAb and drug-linker intermediates as it relates to ADC manufacturing.
- **Post approval change management is more challenging** due to multiple manufacturing and control steps in the process.
- There is a small number of facilities manufacturing ADCs and these facilities require additional control due to manufacturing of cytotoxic materials.

US FDA | ADC CMC Requirements

Highlights

- No ADC specific guidance
- mAb, DS conjugate & DP follow biologics guidance
- Drug linker follows pharmaceuticals guidance
- Submission sent to OPQ where review is performed by both Biologics and small molecule experts
- Product is considered a biologic for life cycle management.
- Stability data for N+1 step downstream of change is expected

Biologics Requirements/Expectations

- PAI may be required on mAb, DS conjugate, DP and any testing sites during review in support of BLA approval
- Additional records: SOPs, executed batch records
- Annual stability batch is expected.
- **For a mAb intermediate change, a DS batch on stability is expected**

SM Requirements /Expectations (Drug Linker)

- **DL follows final API requirements (rather than DS intermediate).**
- For a DL intermediate change, a DS batch on stability is expected

Health Canada | ADC CMC Requirements

Highlights

- No ADC specific guidance
- mAb, DS conjugate & DP follow biologics guidance
- Drug linker follows pharmaceuticals guidance
- Submission sent to Biologics Bureau, linker reviewed by Pharmaceutical Bureau
- Product listed as biologics (not Advanced Therapeutic Products)

Biologics Requirements/Expectations

- On-site Evaluation may be required on mAb, DS conjugate & DP sites during review in support of NDS approval
- **Samples and reference standards submission during review of NDS.**
- Additional records: SOPs, executed batch records
- **Lot Release requirements**
- **Yearly Biologic Product Report (APQR with additional details)**

SM Requirements /Expectations (Drug Linker)

- DL follows final pharmaceutical DS requirements (rather than DS intermediate), i.e., site require listing on Drug Establishment license

EMA | ADC CMC Requirements

Highlights

- No ADC specific guidance
- mAb, DS conjugate & DP follow biologics guidance
- Drug linker follows pharmaceuticals guidance
- Submissions are coordinated through EMA with a rapporteur and co-rapporteur assigned per usual process
- Final DP testing testing to be performed in the EU.
- QP responsible for final product release.

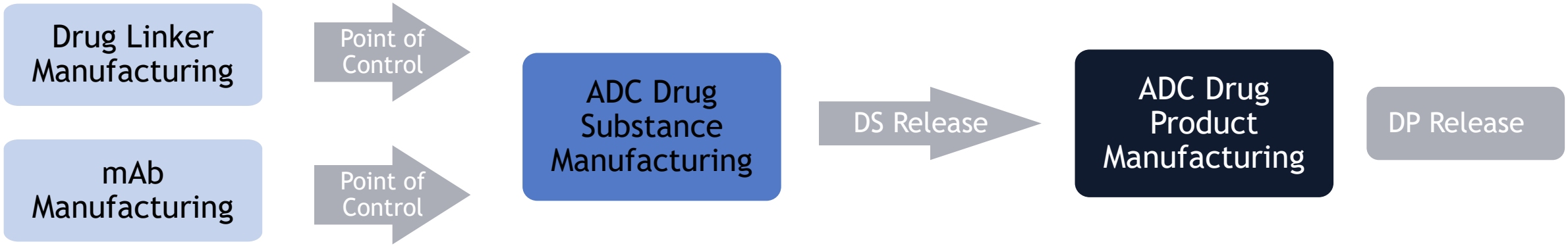
Biologics Requirements/Expectations

- An inspection may be required on mAb, DS conjugate and DP sites during review in support of MAA approval
- mAb and DS section should have the level of detail expected in a biologics MAA

SM Requirements /Expectations (Drug Linker)

- DL follows final API requirements (rather than DS intermediate).

Dossier Expectations for ADCs

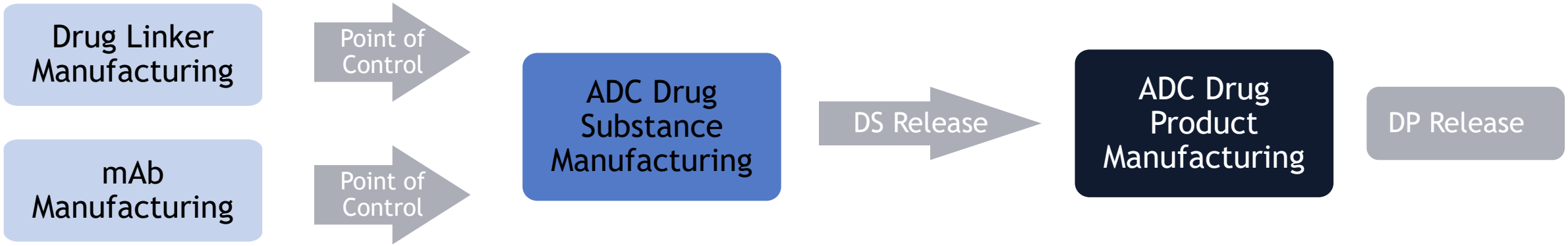


- mAb and Drug Linker (DL) are classified as intermediates.
- Expectation is to have a stand-alone DS dossier section for both these components, but other options have also been found acceptable.
- Level of detail expected to be similar to DS/API.

- Drug Substance CTD section should follow the structure as described in M4Q.

- Drug Product CTD section should follow the structure as described in M4Q.

Control Strategy: Dossier Expectations for ADCs



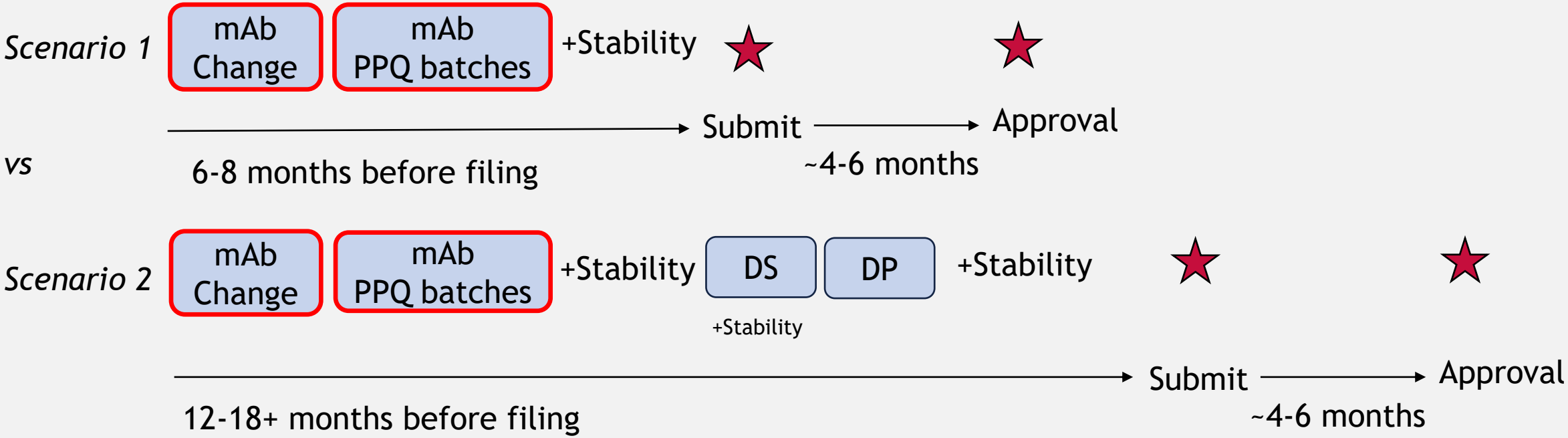
- Control over quality attributes that are needed to support quality of DS and DP

- Requirements for release and stability follow established ICH guidance
- Should ensure safety and efficacy for patients

- In each part of the submission there is expectation to discuss the controls in place (both in-process and release).
- Discussion of Overall Control Strategy Module 2 is important to provide the story about your product.
- **While the expectations for drug product and the drug substance are clear in regulatory guidance for small & large molecules, the expectations for control over the drug-linker or the monoclonal antibody i.e. drug intermediates (DI), are less well defined.***

*Statement from Journal of Pharmaceutical Sciences

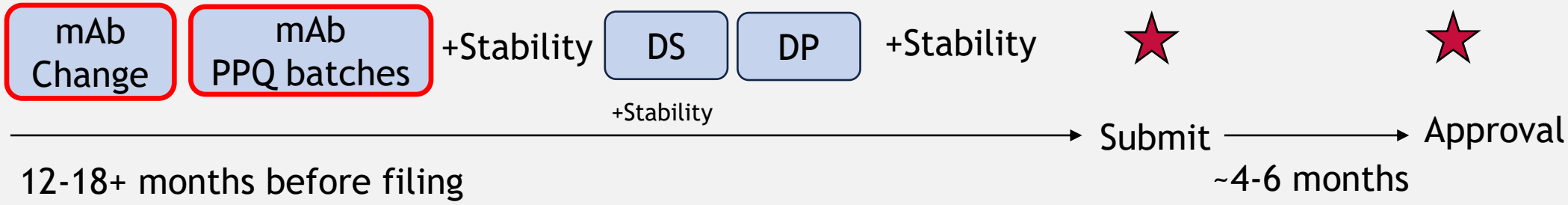
Post Approval Change Management:
Downstream Evaluation and Stability Requirements



- Downstream evaluations and stability studies for the assessment of antibody and drug-linker changes lengthens the approval time of changes.
- Requirement for downstream data and stability studies should be based on the level of risk posed by the change.
- Can we manage the downstream evaluations as post-approval commitments ? We may also use PACMPs to accelerate the final evaluation.

Use of PACMPs as A Tool for Faster Approvals

NORMAL SUBMISSION PATHWAY



2-STEP APPROACH WITH A PACMP

PACMP as a regulatory tool provides predictability and transparency in terms of the requirements and studies needed to implement a change.

Conclusions

- ADCs are inherently complex: Development, regulatory submission, post approval change management and supply chain.
- Health Authorities draw from existing guidance for large and small molecule to guide the review process.
- Globally there is some ambiguity in requirements for mAb and drug-linker intermediates as it relates to ADC manufacturing.
- Global implementation of PACMPs can help with faster implementation of changes and get proactive alignment on data requirements for certain changes.