China Clinical Trial Requirements – CMC Specific

Mini Case Study

WCBP 2023

The Mayflower Hotel,
Washington, DC

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26 January 2023

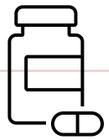
Agenda

- Introduction
- China requirements for clinical trial CMC dossiers
- Case Study 1 –Tabulated summary of CMC research for antibody drug CTA
- Discussion Points

Introduction

- China is a strategically important major market
- Improved regulatory environment promotes China innovation
- Many companies now integrate China into global development plan to enable early China registration
- Some CMC-specific obstacles are rate limiting factors in achieving simultaneous submission/approval of China CTA

CMC Dossier for China CTA



DRUG SUBSTANCE

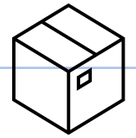
- 32S1-S7
- QoS
- Executed Production BR
- Batch Testing Record
- Stability Chromatograms
- CoA

DRUG PRODUCT

- 32P1-P7
- QoS
- Executed Production BR
- Batch Testing Record
- Stability Chromatograms
- CoA

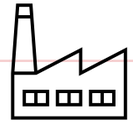
ANALYTICAL

- Full method copy
- Method validation reports



EXCIPIENT /PKM

- Excipient CoA
- Excipient PO/invoice
- PKM CoA
- PKM PO/invoice



GMP

- Excipient/PKM source statement
- GMP declaration
- TSE/BSE declaration

Case #1 – Tabulated Summary of CMC Research for Antibody Drug CTA

- Biologics only
- Summary table of entire M3 plus content outside of M3
- In addition to M2.3 QoS
- Pre-formatted
- Sequence of content not aligned with ICH M4Q for Quality

- Hard to estimate whether/when reviewer will request it
- Request received at different stages of review
- Quick turnaround time required ~ 5 working days
- Main document to review

What's Required for the Tabulated Summary

- **Summary information***
- Construction of upstream process
- **Raw materials for production***
- Manufacturing process for drug substance
- Manufacturing process for drug product

- Quality study
- Specification and batch release data
  - Specification and batch release for DS
  - Specification and batch release for DP
  - Justification of specification
  - Methodology and preliminary method qualification
  - Reference standard

- **Batch Records***
- Stability study
  - DS
  - DP
- **Container closure system in direct contact with the drug***

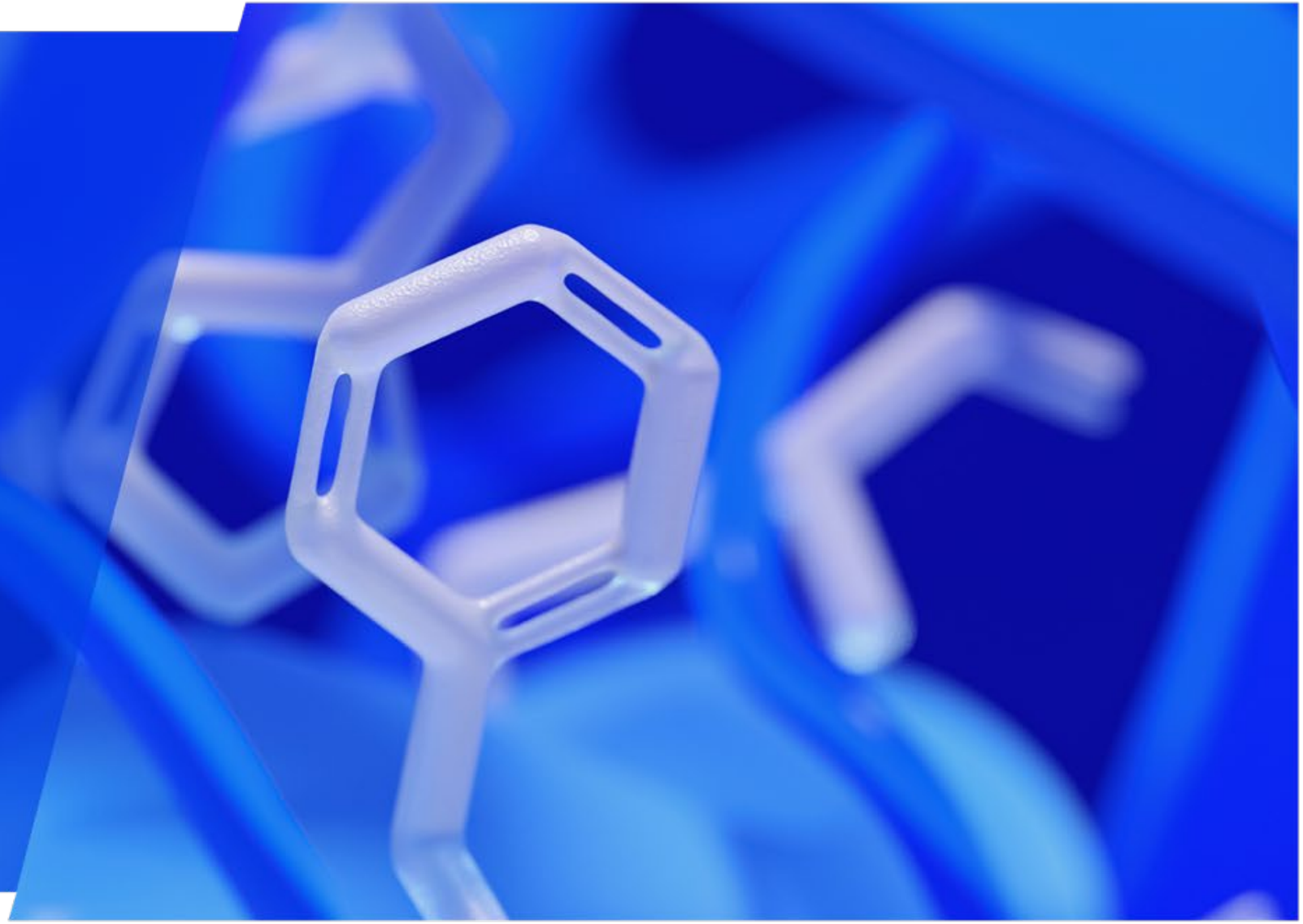
*** require content outside of M3**

Microsoft Word Document

Discussion Points

- What are the challenges your company encounter during China CTA submission?
- What are your solutions/proposals?
- What are examples of “push-back”?
- What are examples of “lean” submission package?

China Clinical Trial Requirements – CMC Specific



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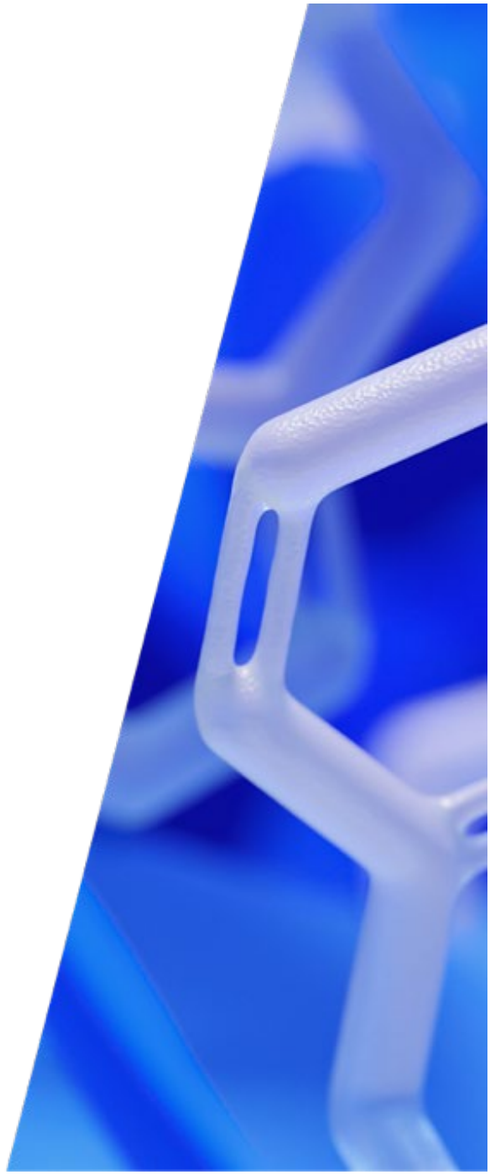
26 January 2023

Case #2 - Problem Statement

- China appears to be less familiar with Modular (Generic) Viral Clearance strategies
    - ❖ Pfizer typically uses a platform manufacturing process for a standard monoclonal antibody which is supported with a Modular (Generic) Viral Clearance package
- China is a new member to ICH and is currently gaining knowledge regarding Modular Viral Clearance
- ICH Q5A(R2) draft guideline has been released for public comment / review in China (as an ICH member)
- To date, China has not accepted Modular Viral Clearance data for early phase clinical submissions

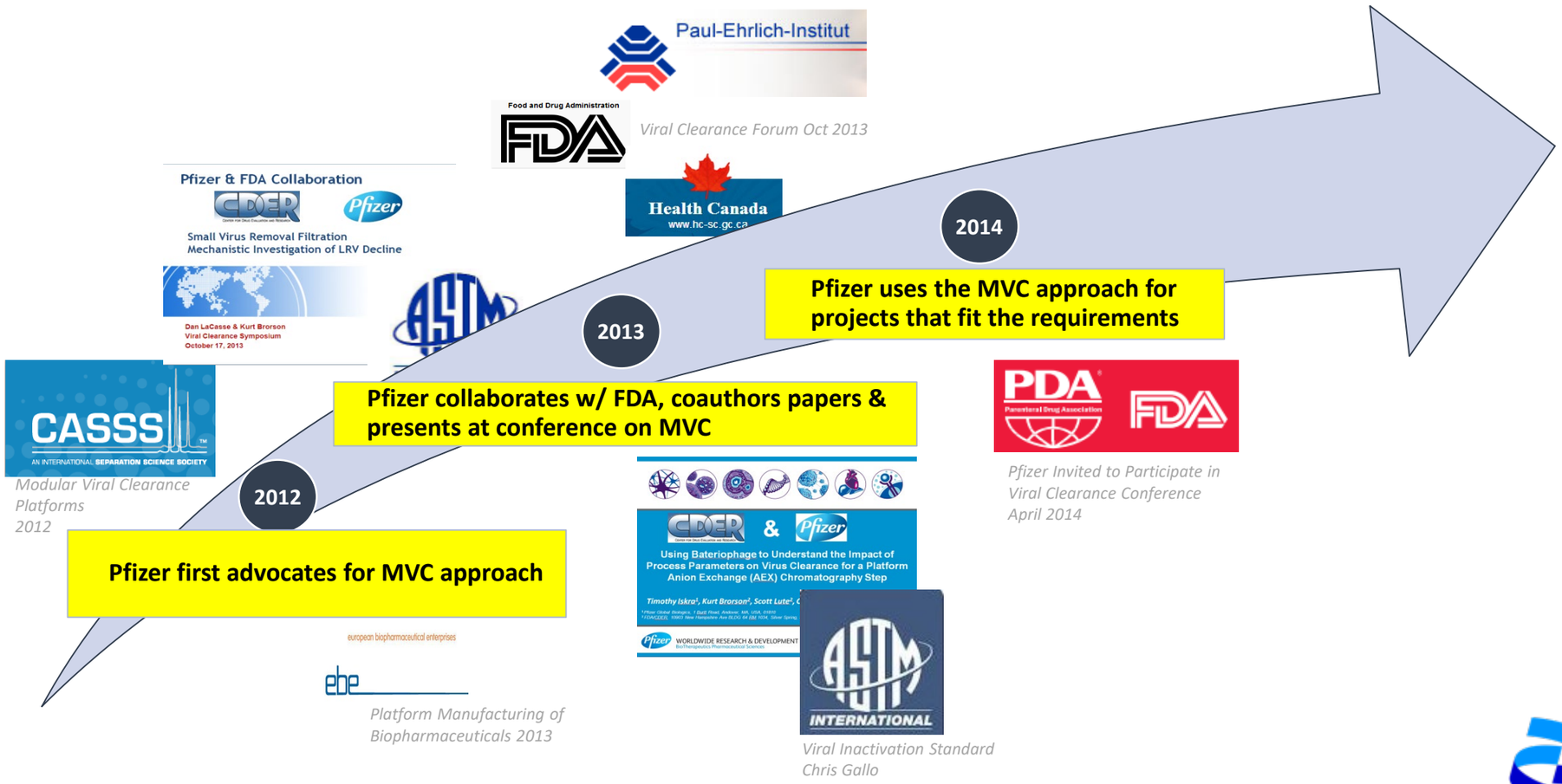


What is a “Modular Viral Clearance Package”?

- Modular Viral Clearance (MVC) or “Generic VC” is a package of data that demonstrates virus removal and/or inactivation across bracketed unit operations, allowing similar processes to apply the MVC performance across similar process steps

- Objective: Develop a robust orthogonal Parvovirus and Retrovirus modular Viral Clearance package for global applicability of Ph1 & Ph2 platform antibody manufacturing processes

Implementing a Modular Viral Clearance Approach for Phase 1 and Phase 2 Platform Antibody Clinical Submissions



Pfizer

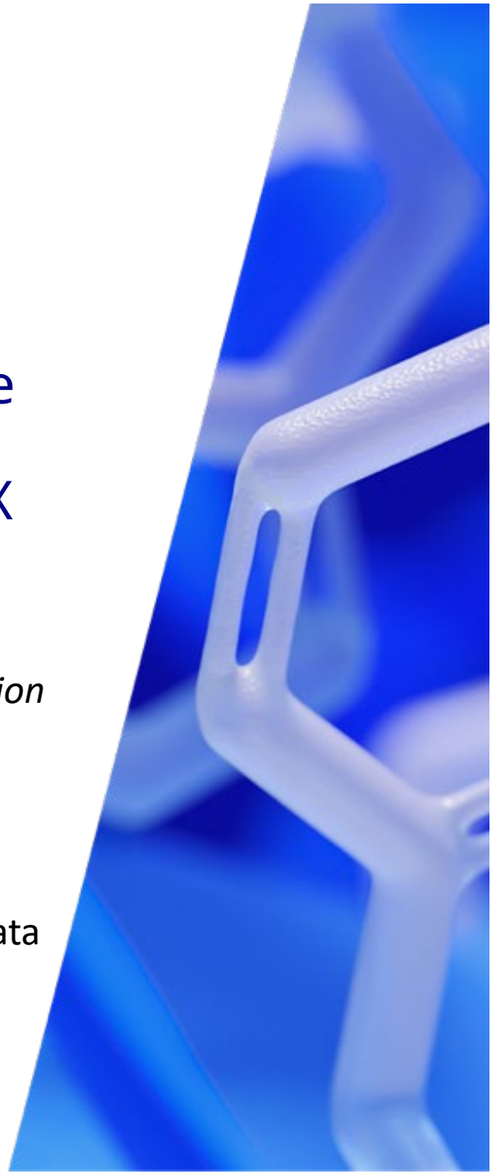
Pre-CTA meeting dialogue & CDE feedback

- Pfizer requested a F2F pre-CTA meeting to discuss the MVC approach with follow-up feedback provided by the CDE
- Pfizer has established a MVC approach which has been used globally for early phase platform antibody clinical manufacturing processes since 2014. Does the CDE agree with the scientific advances to leverage data and knowledge gained from extensive VC studies and experience to apply a MVC approach for PF-XXXX in early clinical development in China?
  - **CDE Feedback**

    Considering China has joined ICH, we would acknowledge the modular viral clearance approach after ICHQ5A (revision version) including the requirements of MVC approach.
  - **Pfizer Clarification**

    It is anticipated ICH Q5A(R2) step 3 sign-off and step 4 adoption would be complete by Nov 2023. Pfizer plans to submit a CTA in May 2022, prior to finalization of the Q5A revision, to ensure China can join the global clinical development simultaneously. Will CDE currently accept the scientific advances of the MVC approach to leverage data and knowledge gained from extensive viral clearance studies and experience outlined in the briefing document for early phase CTA applications?
  - **CDE Feedback**

    Considering the consistency of review principle and requirement, it is not recommended to use MVC approach to support clinical trial application before the ICHQ5A (R2) effective (Nov 2023), otherwise there is potential risk of CTA rejection.
- **Issue:** Finalized guidance is currently years away – how do we handle Phase 1 platform antibody CTA submissions to CDE in 2023 and 2024?



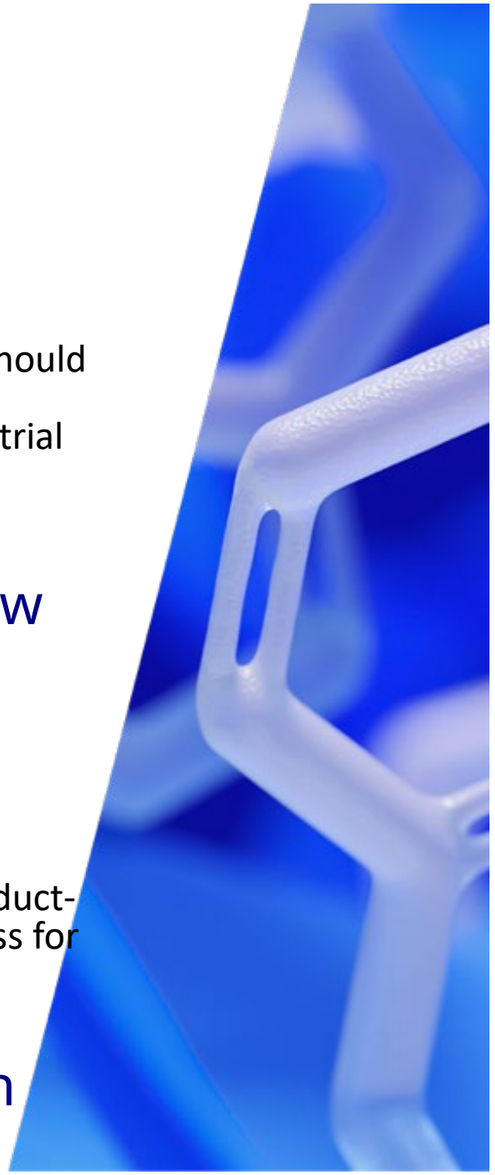
CDE dialogue and feedback

- Pfizer provided the following position on the ICHQ5A guideline which was referenced in their response
  - **Pfizer Clarification**

    As stated in ICH Q5A (R1) Guideline, the document is concerned with testing and evaluation of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin and outlines the data that should be submitted in the marketing application or registration package. Thus, although the ICH Q5A (R1) Guideline was leveraged during development of the MVC approach, the scope of this guidance does not directly extend to clinical trial applications.
- Pfizer submitted a CTA while product specific data was being generated in parallel as a “backup” which could be introduced if needed during the review cycle
  - **CDE Response to CTA**

    Submit the solid and comprehensive product specific viral clearance data.
  - **Pfizer Clarification**

    The level of safety margin calculated using retroviral clearance values from the MVC approach compared to the product-specific values further demonstrates that the MVC values are a conservative evaluation of the manufacturing process for viral clearance. The safety margin using the MVC approach serves as an acceptable alternative to product-specific clearance values while still continuing to ensure patient safety from a viral clearance perspective.
- Based on CDE feedback, the CTA was withdrawn and re-submitted with both MVC and product specific data, which was subsequently approved after 2.5 months
- **Issue:** Guidance is still currently years away – how do we handle Phase 1 CTA submissions in 2023 and 2024?



Questions /Discussion Points

- Are there examples or strategies that have been successful in gaining acceptance of the MVC approach for early clinical phase submissions to China?

- Are there examples of other countries that insist on similar requirements as China? If so, what has been the approach?