Platform and Prior Knowledge in the Development of Neutralizing Monoclonal Antibodies: A Regulatory Perspective

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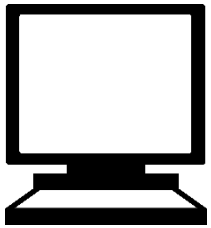
Advancing Quality & Technology of Future Pharmaceuticals
Accelerating Development:
Fast Tracking Critical Treatments, Antibody Platforms, and Quality Standards for Emerging Modalities
Dec 2, 2021

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.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Patients expect safe and effective medicine with every dose they take.
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FDA
Pharmaceutical quality is
assuring *every* dose is safe and effective, free of contamination and defects.
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FDA
It is what gives patients confidence in their *next* dose of medicine.
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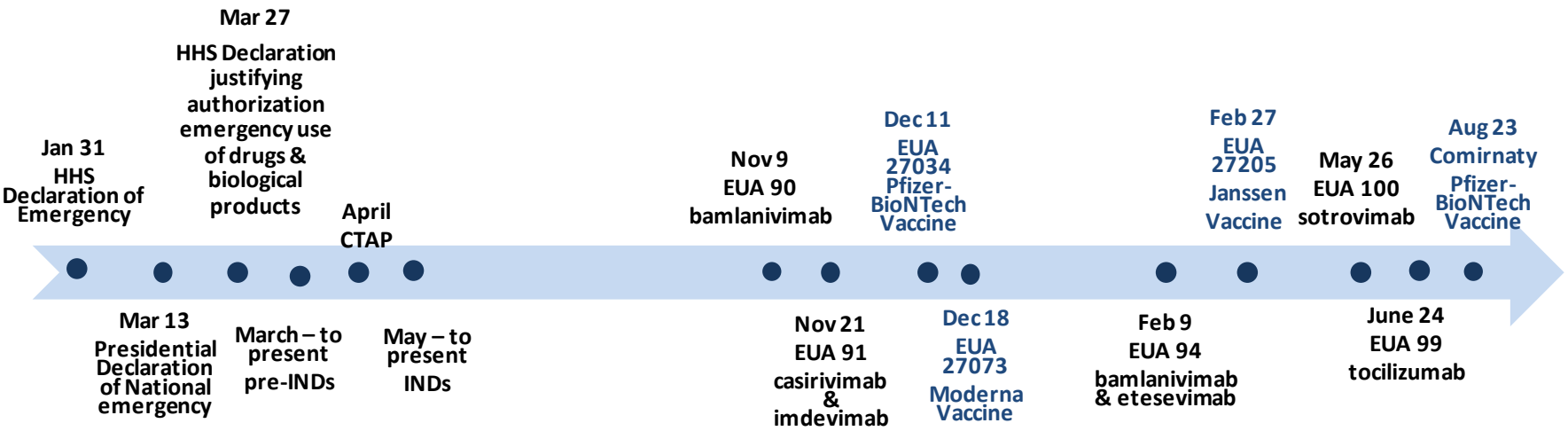
Disclaimer

Please refer to any cited guidance, as this talk only refers to them at a high level. Specific regulatory issues need to be addressed with the relevant assessment team.

COVID-19

Some Biological Products Key Milestones as of November 2021



Note: *Vaccine EUA information on this slide is presented for context only. Vaccine development is out of the scope of this presentation.*

60+ Neutralizing antibodies are being studied for COVID-19

Active Pre-INDs

670+

Drug development programs in planning stages[1]

11

COVID-19 treatments currently authorized for Emergency Use[3]

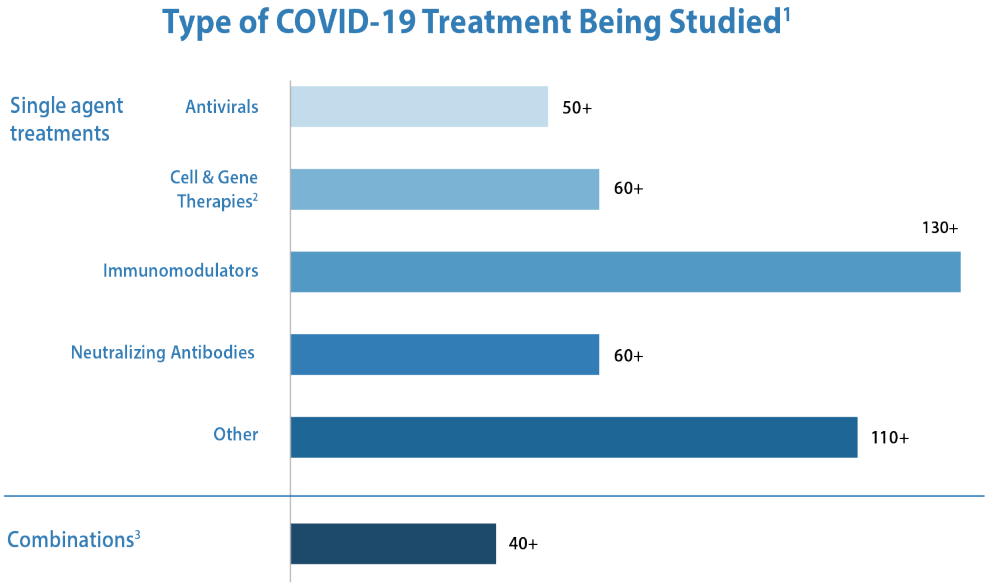
Safe to proceed INDs

470+

Trials reviewed by FDA[2]

1

Treatments currently approved by FDA for use in COVID-19



From Data as of 11/21/2021. Excludes vaccines

Coronavirus Treatment Acceleration Program (CTAP) | FDA

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Expedited Development of Neutralizing Antibodies

- Strategies
- Platform and Prior knowledge
  - Examples applied to COVID-19 mAb development
- Opportunities for drug development

STRATEGIES

Key FDA Guidances

- 1997 Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use
  - Reduced safety testing for feasibility clinical trials in serious or life-threatening conditions
  - Generic/modular virus clearance studies or
  - Two orthogonal robust virus clearance steps

- Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency, Feb, 2021
  - Strategies for limited early phase development to enable FIH
  - ***Leveraging experience from mAbs in development and licensed***
  - Critical elements of the development program

STRATEGIES FOR LIMITED EARLY PHASE DEVELOPMENT TO ENABLE FIH

Examples of Strategies for Limited Early Phase Development to Enable FIH

Strategy	Risks	Regulatory Considerations & Mitigation strategies

Stable bulk culture in lieu of clonally derived cell bank	• Lot-to-lot consistency
	• Comparability risks
	  ○ Impact on relevance and interpretation of data generated with pre-change product
	  ○ Impact on product supply
		• Full safety testing (ICHQ5A)
		• Enhanced control strategy; e.g. process description and specifications
		• Comprehensive comparability when e.g., transitioning to clonal cell line
		• Limited duration for approach (i.e., few batches)

Flexibility in quantity of initial stability data submitted	• May not be applicable to all products • May not correlate or be predictive	• Leverage formulation development data • Robust stability protocols • Additional stability timepoints – to obtain data earlier/in a timely manner • Supported by accelerated stability data

This information constitutes examples of risks, mitigation strategies, and regulatory considerations. Different approaches may be needed on a case-by-case basis.
https://www.fda.gov/media/146173/download

Examples of Strategies for Limited Early Phase Development to Enable FIH

Strategy	Risks	Regulatory Considerations & Mitigation strategies
Interim results from limited safety testing (e.g., cell banks, UPB) • Full study reports at a negotiated time	• Safety	• Negotiated timing for data submission (e.g., Data needed prior dosing patients)
Two robust orthogonal virus clearance steps (no available modular/generic virus clearance data)	• Safety	• Principles from Points to Consider in the Manufacture and Testing of Monoclonal Antibodies for Human Use guidance • Limited batches
Use of mixing and diluting with sterile filtration employing aseptic technique	• Safety	• Expectations for aseptic technique: CGMP for Phase 1 Investigational Drugs (July 2008) • Additional controls • Immediate use • Limited duration for approach (i.e., few batches)

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STRATEGIES LEVERAGING EXPERIENCE FROM MABS IN DEVELOPMENT AND LICENSED

Examples of Strategies Leveraging experience from mAbs in development and licensed

Strategy	Risks	Regulatory Considerations & Mitigation strategies
Platform knowledge • Process • Specifications • Methods • Formulation • Stability	• May not be applicable to all products • Challenging for molecules other than antibodies	Applicability to new product • Similar properties (e.g., pI, antibody isotype, etc.) • Specs: may be adequate for e.g., process-related impurities • Stability: same formulation & similar product properties
Limited Tech Transfer activities for Facilities	• Product quality • Consistency • Supply	• Experience in manufacturing biotech products • History of recent inspection

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Examples of Strategies Leveraging experience from mAbs in development and licensed

Strategy	Risks	Regulatory Considerations & Mitigation strategies
Modular data for viral and impurity clearance	• Safety	• Applicability to the new product (e.g., product properties)

Leveraging development data
• Formulation & accelerated stability
• Process development & characterization
	• May not be applicable to all products
	• May not correlate or be predictive
		• May support
		  • Product stability
		  • In-use stability
		  • Compatibility
		• May support control strategy

Rapid methods	• Inadequate control of product quality	• Similar or superior performance as typical methods, or • Confirmatory results with typical method

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STRATEGIES - CRITICAL ELEMENTS OF THE DEVELOPMENT PROGRAM

Examples of Strategies -Critical elements of the development program

Strategy	Risks	Regulatory Considerations & Mitigation strategies
Prospective Comparability plans, e.g. • Scale up • Transition to MCB • Site transfer	• May only include anticipated manufacturing changes	• Discussion with Agency and agreement on expectations for comparability – lower regulatory risk. • Important to consider facility(ie's) compliance history
• Strategy to propose shelf life	• Stability • Safety and efficacy	May leverage all available stability data at different conditions as well as other studies such as formulation development data

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PLATFORM AND PRIOR KNOWLEDGE

Platform Technologies

General Platform Definition

- *A group of technologies that are used as a base upon which other applications, processes or technologies are developed (techopedia)*
- *A set of actions or ideas that forms the basis for future development (Cambridge dictionary)*
- May be considered a subset of "prior knowledge" per ICH Q10
- May include "modular" unit operations where the considerations are independent of connection to other operations
  - ➢ Individual companies may develop their own platform(s)

Examples of Platform Approaches- mAbs

Discovery, Design & Optimization

- Target development & engineering
  - Lead selection (e.g. screening platforms)

Pharmaceutical Development

- Formulation & stability

Control Strategy

- Specifications (methods and acceptance criteria)
  - e.g., process-related impurities

Manufacturing Process

- Downstream Purification Design
- Modular impurity clearance
- Modular viral clearance

ICHQ11: Platform Manufacturing

The approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture ***other drugs of the same type*** *(e.g., as in the production of monoclonal antibodies using predefined host cell, cell culture, and purification processes, for which there already exists considerable experience)*

- A-mab case study applies the concept of platform and prior knowledge
  - e.g. Molecule design, formulation, manufacturing (upstream and downstream) process deign

Examples of Platform Approaches Applied to COVID-19 Neutralizing mAbs

Lead identification

- e.g. collection of fully human antibodies generated by using humanized mice and convalescent plasma

Formulation & stability

- Most sponsors leveraged their own formulation studies from other antibodies
  - e.g. studies from previous molecules of the same isotype (e.g. IgG1)
  - Used a "platform formulation"
  - Accelerated stability studies (product-specific and other mAbs) were used to assess degradation profile and support real-time stability

Hansen et al., *Science* **369**, 1010–1014 (2020)
Taylor et al., *Nat Reviews Immunology* **21**, 382-393 (2021)
Kelly B. *Nat Biotechnol* **38,** 540–545 (2020)

Examples of Platform Technologies Applied to COVID-19 Neutralizing mabs

Manufacturing

- Most sponsors used mab platform manufacturing with little optimization
- Modular viral and modular impurity clearance was applied

Control strategies

- Most sponsors used a combination of product-specific and mAb platform methods
- Generally accepted acceptance criteria (e.g. process-related impurities) were applied
- Specs justification & risk assessment considered low probability of off-site target effects because the spike protein is a foreign target

Hansen et al., *Science* **369**, 1010–1014 (2020)
Kelly B. *Nat Biotechnol* **38,** 540–545 (2020)

How Did Platform Technologies help expedite development?

- Sponsors applied their own in-house technologies, platforms & knowledge in formulation, manufacturing processes, and analytical methods
- Platform manufacturing processes were used with little additional optimization
- In some cases, platform manufacturing processes start from in-house cell line to platform unit operations – no cell-line specific process development was applied
- In some cases, limited new technologies were created & applied for COVID - no time to experiment

How Did Platform Technologies help expedite development?

- Some sponsors conducted parallel development "at risk, up-front investments" - **no risk to patient safety**
  - e.g. using parallel processes expanding clonally-derived cell banks and non-clonal cell pools
  - Scale up and transfers were conducted in parallel
    - Worked closely with CMOs with experience manufacturing mAbs
  - High business risk tolerance

- Process optimization is not intended, or it is deferred for the BLA

  ➢ Agency's flexibility is contingent on this adequacy of the knowledge provided; not merely "less information"

Opportunities for drug development?

Yes, platform approaches were possible and worked for COVID-19 because we have been applying them already!

But

- Applicability of platform and prior knowledge is limited by the data and information submitted in an application
- There are opportunities for leveraging industry's knowledge and this should be provided in the application
  - It is not sufficient to just say e.g., it is the same formulation or same process, etc.
- Industry needs to be willing to do the work up front and willing to share it (we don't know what you don't tell us)

Closing Remarks

- Strategies for accelerated development of COVID-19 neutralizing antibodies may be useful for addressing, for example, SARS-CoV2 variants and other life-threatening conditions
- Platform and prior knowledge have been and can continue to be applied; however,
  - Industry should provide the data, information, and rationale of the applicability of such knowledge to a particular product
- The approaches taken for COVID-19 have and will continue to consider benefit/risk
- This experience allowed us to test strategies and identify new opportunities

THANK YOU FOR YOUR ATTENTION

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FDA Guidance

- Emergency Use Authorization of Medical Products and Related Authorities Guidance for Industry and Other Stakeholders January 2017
- Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) Medical Countermeasure (MCM) Authorities: FDA Questions and Answers for Public Health Preparedness and Response Stakeholders. January 2014
- Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency Guidance for Industry February 2021
- COVID-19: Potency Assay Considerations for Monoclonal Antibodies and Other Therapeutic Proteins Targeting SARS-CoV-2 Infectivity Guidance for Industry. January 2021
- Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers October 2019
- Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, February 1997

FDA Guidance

- COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products, May 2020

- COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers Guidance for Industry, March 2021

https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19