Accelerated development of monoclonal antibodies: an opportunity to meet the health needs in México

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ABSTRACT

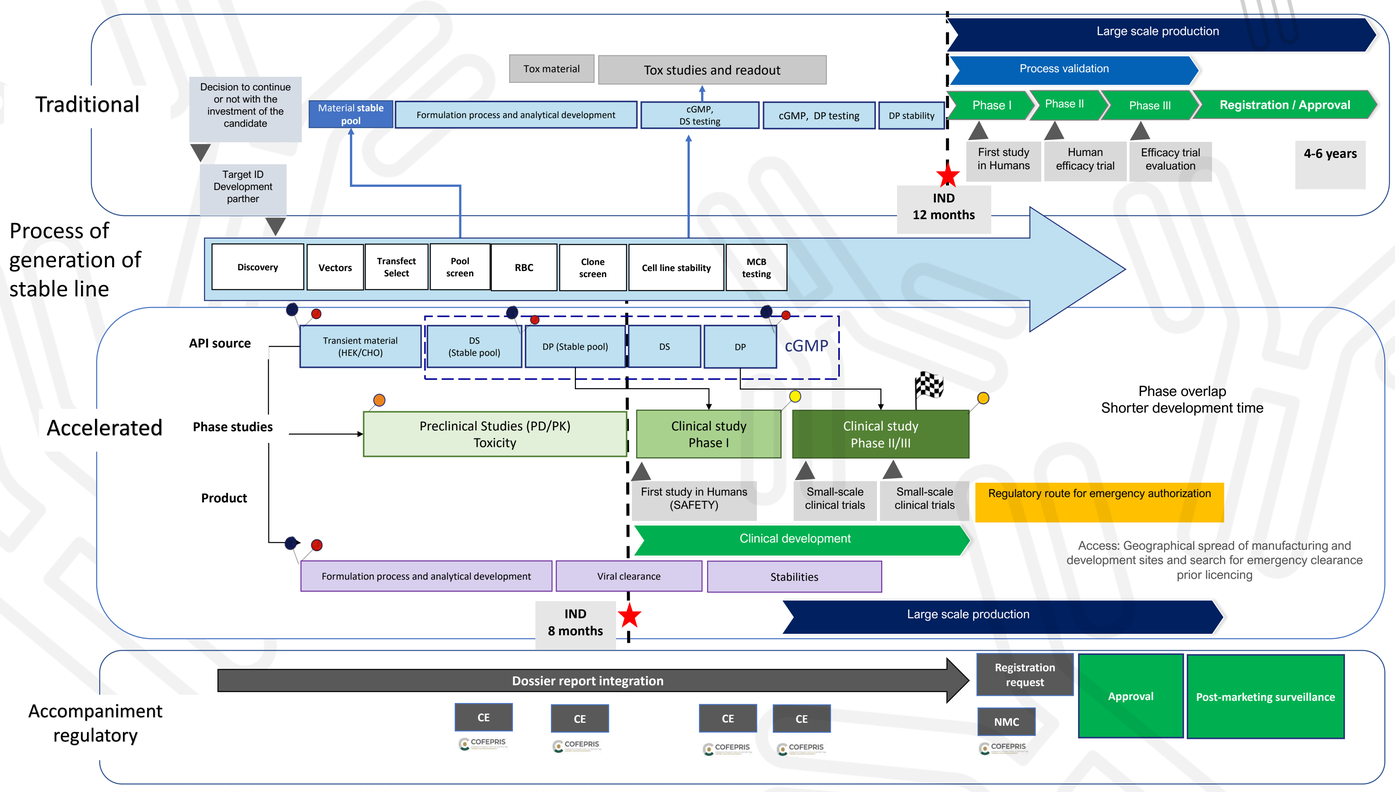
The development of therapeutic antibodies is a process of several sequential stages that start with basic research, followed by the development of a pharmaceutical form, preclinical studies, and clinical studies. However, there are other pathways for drug development, particularly promoted by regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) through the so-called "Expanded Access Programs" (EAP) that they are a "fast track" to making new drugs available for the treatment of serious or life-threatening diseases with no therapeutic alternatives. In this way, the FDA allows the pharmaceutical company lower standards than the regular procedure, as well as monitoring from early stages of drug development.

Antibodies have become a frequently used therapeutic alternative to combat different diseases, whether infectious or chronic-degenerative. During the development of these, in a traditional way, it is necessary to generate stable clones derived from eukaryotic expression systems such as CHO cells to produce monoclonal antibodies in sufficient quantities to carry out phase I preclinical or clinical studies, all with the aim of guaranteeing safety and minimizing risks. However, in parallel, transiently expressed cultures can be used to produce the necessary material to support the formulation process and analytical development. The availability of this raw material weeks or months before obtaining the material from the stable clones can speed up the schedule and reduce the costs of drug development.

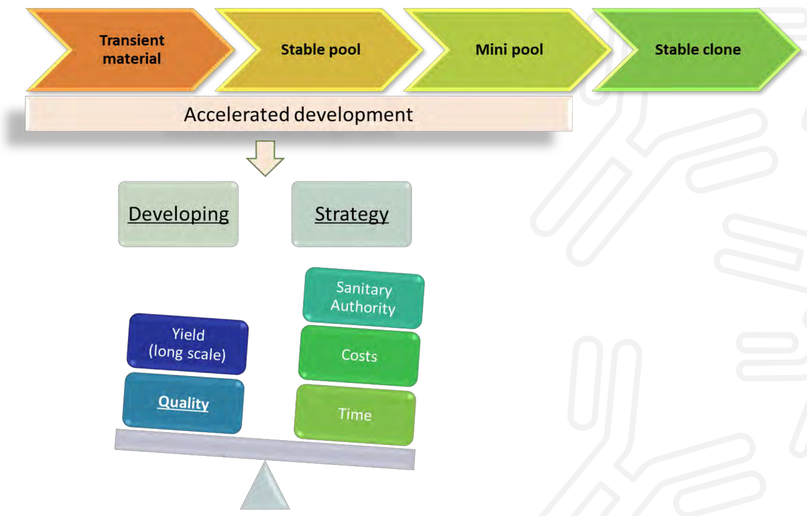
In this regard, the use of stable pools, mini-pools or transient expression systems to produce material for preclinical toxicology studies has already been reported, such practice is supported by the quality of the product obtained, which allows its release and subsequent comparisons to through expanded characterization testing with the material for clinical use, reducing the critical pathway to submit an investigational new drug (IND). Also, understanding of the heterogeneity of populations derived from CHO cell clones, the use of a clinically proven IgG1 isotype with low risk profiles for quality and safety, as well as production experience with current good manufacturing practices (cGMP) established for this type of biotherapeutic, supports the use of these alternative methods for rapid, inexpensive and safe evaluation of therapeutic antibodies during preclinical safety studies and early phase clinical trials.

The clearest example of the aforementioned was given by the urgency of having neutralizing antibodies (NAbs) to treat COVID-19, which led the FDA to establish strategies to accelerate the development and commercialization of NAbs against SARS-CoV-2, in which it is possible to expedite the development of products during the pandemic, by considering the use of a "stable cell pool" and transitory material instead of a bank of clonally derived cells for the first clinical batches. Additionally, rapidly developed therapeutic antibodies therefore have a clear advantage over vaccines or antivirals due to its availability to treat a pandemic disease outbreak such as COVID-19.

Regulatory strategy for the generation of innovative Mexican mAbs



MCB: Master cell bank, **RCB:** Research cell bank, **cGMP:** Good manufacture practices, **NMC:** New Molecules Committees, **IND**: Investigation New Drug.
API: active pharmaceutical ingredient, **DS**: drug substance, **DP**: drug product.

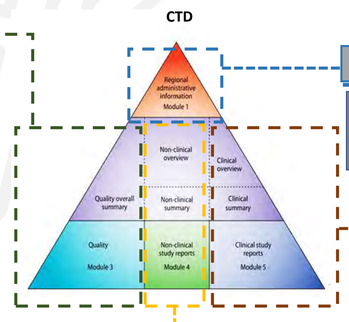


Regulatory compliance for the development of innovative Mexican mAbs

Use of transient material and stable pool

	Quality				
	Manufacture	Characterization	Validation	Specification	Stability
WHO	-Guideline for the safe production and quality control of monoclonal antibodies for use in humans (2021). -Guidelines on Validation-Appendix 4. Analytical Method Validation (2018)				
FDA	-Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997). -Analytical Procedures and Methods Validation for Drugs and Biologics. Guidance for Industry (2015).				
FEUM	-Productos biotecnológicos. Páginas 1989-1996. Duodécima edición (2018).				
EMA	-Guideline on development, production, characterization and specification for monoclonal antibodies and related products (2008).				
ICH	-Specifications: test procedures and acceptance criteria for biotechnological/biological products Q6B (1999). -Topic Q2 (R1) Validation of Analytical Procedures. Text and Methodology (1995). -Guideline M10 Bioanalytical Method Validation (2019).				
USP	-Chapter <1032> Development and Design of Bioassays; USP 35-NF-30, 2017. -Chapter <1033> Biological Assays Validation; USP 35-NF-30, 2017. -Chapter <1034> Analysis of Biological Assays; USP 35-NF-30; 2013.				

CTD: Common Technical Document
WHO: World Health Organization
FDA: Food and Drug Administration
FEUM: Farmacopea de los Estados Unidos Mexicanos
EMA: European Medicines Agency
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
USP: United States Pharmacopeia
COFEPRIS: Comisión Federal para la Protección contra Riesgos Sanitarios



National regulation

COFEPRIS	NORMA Oficial Mexicana NOM-257-SSA1-2014, En materia de medicamentos biotecnológicos.

Clinical studies

	Security	Efficacy	Tolerability	PK
FDA	- Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (2020). - COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (2021). -Safety Assessment for IND Safety Reporting. Guidance for the Industry (2015). -Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Guidance for Industry (2019).			
EMA	- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (2017).			
ICH	-General considerations for clinical studies E8 (R1) (2021).			

Non-clinical information

	Pharmacodynamics (PD)	Toxicology (Tox)	Pharmacokinetics (PK)
FDA	-Development of Monoclonal Antibody Products Targeting SARS-CoV-2, Including Addressing the Impact of Emerging Variants, During the COVID-19 Public Health Emergency (2021). -Nonclinical Considerations for Mitigating Nonhuman Primate Supply Contraints Arising from the COVID-19 Pandemic. Guidance for the Industry (2022).		
ICH	-Guidance for industry S6 (R1) preclinical safety evaluation of biotechnology-derived pharmaceuticals (2012). -CTD for the Registration of Pharmaceuticals for Human Use-Safety (2003). Guideline S9 on nonclinical evaluation for anticancer pharmaceuticals (2010). -Topic S7 A Safety Pharmacology Studies for Human Pharmaceuticals (2001).		
WHO	-Annex 4 Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology.		

Conclusion

The “fast track” that the regulatory entities have for the EAP is based on the conservation of the quality attributes of the therapeutic antibodies for use in humans that are used for the prophylaxis and therapy of various types of diseases, despite the fact of producing the biotherapeutic in eukaryotic systems that not necessarily express stably the antibody in all stages of the development. This route is also favored if IgG1 isotype is used and produced under GMP.

The most recent direct precedents of accelerated development are anti-SARS-CoV-2 therapeutics, which demonstrates the feasibility and usefulness of this strategy that could be repeated for other types of diseases.

All of the previously mentioned, as well as early monitoring by COFEPRIS, will allow for innovative and accessible treatments for the Mexican population through a strategy for the accelerated development of mAbs for the treatment of diseases of public health interest, including various types of cancer, autoimmune, metabolic and infectious diseases.

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