

Introduction to the Technical Requirements in the Guidelines on Prophylactic COVID-19 mRNA Vaccines

**Center for Drug Evaluation of NMPA
Biologics CMC Division
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I. Profile of CMC Development of COVID-19 mRNA Vaccines

- ✓ **One of the five technical routes for the development of COVID-19 vaccines in China**
 - Inactivated vaccines, attenuated influenza virus vector vaccines, adenovirus vector vaccines, recombinant protein vaccines, and messenger RNA vaccines (mRNA vaccines)
- ✓ **Several COVID-19 mRNA vaccines have been approved for clinical trials in China**
 - Prototype strains and variant strains
 - Mainly based on LNP delivery system
- ✓ **Applicable to unified working procedures and technical standards related to COVID-19**
 - Specifications for such tasks as connected development and review, rolling review, and expert consultation
 - Technical guidelines on COVID-19 and mRNA vaccines
- ✓ **Several COVID-19 mRNA vaccines are under communication**



II. CMC Technical Guidelines on mRNA Vaccines in China and Abroad

- ✓ **Chinese Pharmacopoeia**
- ✓ **Relevant existing guidelines and principle guidelines on COVID-19 vaccines**
- ✓ **Technical guidelines on mRNA vaccines**
 - Guidelines on CMC Study of Prophylactic COVID-19 mRNA Vaccines (interim), 2020.8, CDE/ Guideline on the Chemistry, Manufacture and Control of Prophylactic COVID-19 mRNA Vaccines (Current Version), 2021.9, CCFDIE
 - Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations, 2021, WHO



II. CMC Technical Guidelines on mRNA Vaccines in China and Abroad

- ✓ Technical requirements are basically consistent between WHO and CDE technical guidelines
- ✓ Several stylistic differences

WHO TOC:	CDE TOC:	WHO quality control and verification:	CDE quality control and verification:
1. Introduction	1. Introduction	Identification	mRNA & lipid identification
2. <u>Purpose and scope</u>	2. Study data of template design, construction of transcription template plasmid and culture collection	mRNA content	mRNA content
3. Terminology	2.1 <u>Target antigen selection and DNA template design</u>	Lipid content	Content of delivered materials and related excipients
4. General considerations	2.2 <u>Construction and preparation of transcription template plasmid</u>	MRNA fragment size	mRNA sequence length
5. Special considerations	2.3 <u>Establishment and verification of seed banks</u>	mRNA integrity	Sequence integrity and accuracy
6. Manufacture and control of mRNA vaccines	3. <u>Production process</u>	Purity and impurities	Purity and impurities
6.1 <u>General manufacturing overview</u>	3.1 <u>General requirements</u>	Capping efficiency	Capping efficiency
6.2 <u>General information and description of vaccine construct and composition</u>	3.2 <u>Manufacture of mRNA bulk</u>	polyA tail size	polyA tail length and distribution
6.3 <u>Control of starting and raw materials and excipients</u>	3.3 <u>Formulation and production process</u>	Zeta potential and surface charge	Zeta potential
6.4 <u>Process development and in-process controls</u>	4. <u>Study on quality characteristics</u>	LNP encapsulation efficiency	LNP encapsulation efficiency
6.5 <u>Product characterization</u>	5. <u>Quality specifications</u>	Particle size distribution and particle size	Nanoparticle size and dispersion coefficient
6.6 <u>Consistency of manufacture</u>	6. <u>Stability study</u>	Potency and correct expression of antigen protein	Bioactivity (in vivo and in vitro potency)
6.7 <u>Manufacture and control of bulk purified mRNA (drug substance)</u>	7. <u>Study on sources of packaging materials and containers in immediate contact with products, basis for the selection and quality specifications</u>	Sterility, endotoxin, pH, etc.	Sterility, endotoxin, pH, etc.
6.8 <u>Manufacture and control of final formulated vaccine (drug product)</u>	8. <u>Phase consideration for CMC development under emergency state and changes during development</u>		
6.9 <u>Records</u>	9. <u>Glossary</u>		
6.10 <u>Retained samples</u>	10. <u>References</u>		
6.11 <u>Labelling</u>			
6.12 <u>Distribution and transport</u>			
7. <u>Nonclinical evaluation of mRNA vaccines</u>			
8. <u>Clinical evaluation of mRNA vaccines</u>			
Authors and acknowledgements			
References			



III. Guiding Ideology of Development and Evaluation

- ✓ **Risk identification and risk control as the core**
 - **Consider the safety risk and effectiveness risk of the product and then analyze mRNA part and nanoparticle part item by item**
 - Safety risk, mRNA part (split mRNA, etc.), and nanoparticle part (lipid excipient, impurities, etc.)
 - Effectiveness risk, mRNA part (capping, etc.), and nanoparticle part (encapsulation, particle size, etc.)
 - **What are the quality target product profile (QTTP), critical quality attributes (CQA), and hazardous impurities?**
 - Such as mRNA purity, capping efficiency, encapsulation efficiency, ability of delivery into cells, dsRNA residue, incomplete mRNA, DNA template residue, etc.



III. Guiding Ideology of Development and Evaluation

✓ **Risk identification and risk control as the core**

- **How to control the risks in product design, process development, manufacture verification and other links?**

For impurities with safety risks: study the generation, elimination, residue and verification of impurities

For capping related to effectiveness risks: study the type of caps, capping process, parameter range, etc.

- **Multi-batch manufacture validation and quality analysis**

Avoid the risks of non-robust process and intra-batch quality inconsistency

- **Support of necessary non-clinical study data**

Investigate the safety and effectiveness of the product on animals



IV. Main Content of Technical Requirements

- ✓ According to the conventional development and evaluation ideas, the CMC part mainly includes the main raw materials and excipients for manufacture, production process, study on quality characteristics, quality specifications, stability study, etc.
- ✓ Gradually improve the CMC study during clinical trials.



CDE

IV. Main Content of Technical Requirements

✓ Main raw materials and excipients for manufacture

➤ mRNA part

Various enzymes, 5'-cap analogs, nucleotides, organic solvents, buffer systems, and purified materials: Pay attention to the source, character, purity, impurities, quality specifications, removal conditions and other relevant information, and establish internal inspection and release; and carry out quality control of DNA transcription templates and the raw materials used to prepare DNA transcription templates

➤ Nanoparticle part

Organic solvents, various lipid excipients, and stabilizer sucrose: Focus on the quality of lipid excipients and provide detailed source and quality information, especially purity and impurity detection (establish characterization detection)

Self-made excipients: Carry out robustness study on the preparation process of excipients

Pay attention to the quality differences of excipients from different suppliers and their impact on the quality of mRNA vaccines



CDE

IV. Main Content of Technical Requirements

✓ **Production process**

- **Propose technical requirements with a focus on the process development and process control**

Key indicators that should be paid attention to when the process is established

Process operation parameters and the proposed ranges

Performance parameter control standards for intermediates

- **The preparation process of delivery material and its compound with mRNA and particle forming process are core processes**

Various process parameters of the preparation of mRNA and lipid solution and particle encapsulation process and the equipment used

- **Process validation**

Such as the consistency of implementation parameters, continuous batch release testing, impurity clearance rate of each process step, quality inspection of intermediates, etc.



IV. Main Content of Technical Requirements

✓ Study on quality characteristics

- Analysis on quality characteristics of mRNA
- Analysis on quality characteristics of nanoparticles
- Interaction between mRNA and delivery system (loading of mRNA and lipid and release of mRNA from particles)

Characteristic analysis usually includes

- Structural features (especially structural attributes related to the functions of mRNA and delivery system)
- Purity
- Impurity analysis (process related impurities and product related impurities)
- Study on bioactivity and immunological characteristics

The characteristic analysis for the products at different stages has different focuses



IV. Main Content of Technical Requirements

✓ Quality specifications

- **DNA transcription template**
- **mRNA bulk (involving submission for testing)**

Such as physical and chemical properties, mRNA sequence quality control (length, concentration, purity, polyA tail, capping, etc.), impurity quality control (dsRNA, DNA residue, protein residue, etc.), activity quality control (antigen expression), etc.

- **Intermediates of preparation**
- **Finished products (involving submission for testing)**

Such as physical and chemical properties, mRNA quality control (sequencing, sequence length, content, mRNA purity, etc.), particle quality control (encapsulation efficiency, particle size, PDI, Zeta potential, lipid content, etc.), impurity quality control (lipid impurities and process impurities), potency quality control (in vivo potency), etc.

Verification items of current quality specifications and technical requirements:

Based on the consensus of all parties
It is the basic requirement of clinical trial risk control and the key consideration of clinical trial admission
Consideration for establishing valence quality standard

- **Based on the consensus of all parties**
- **Keep consistent with foreign quality control requirements**
- **Basic requirement for risk control of clinical trials and key consideration of clinical trial access**
- **Consideration for establishing potency quality specification**



IV. Main Content of Technical Requirements

✓ **Stability study**

- **Follow the relevant guidelines for stability studies of biologics**
Pay attention to temperature change, pH change, repeated freezing and thawing, stability in use, etc.
- **The stability of mRNA and nanoparticles is the key point and difficulty of mRNA vaccine development**
Ensure the functionality of Endogenous mRNA expression and nanoparticle delivery during the manufacture, storage and transportation of finished products
- **The stability study can be considered from two aspects: physicochemical indexes and biological indexes, and the sensitive indexes which can reflect the overall quality of the product should be adopted**
Such as encapsulation efficiency, content of active ingredients (mRNA content and lipid content), mRNA purity and integrity, particle size and distribution, Zeta potential, etc.; In vivo potency, antigen expression activity, etc.



IV. Main Content of Technical Requirements

- ✓ **Changes during clinical trials and continuous improvement of CMC content**
 - **For CMC changes, detailed description, analysis and risk assessment before and after the changes should be conducted, and sufficient comparability study should be carried out to assess potential impact of the changes on product quality**
 - **For major changes during clinical trials, it is suggested to carry out comparative analysis on the comprehensive efficacy studies before and after the changes**
 - **Continuously accumulate sufficient and comprehensive product production and quality control data during clinical trials**

Such as using advanced methods to carry out complex study on quality characteristics, carrying out methodological verification, optimizing and adjusting the process according to production experience, improving quality control standards according to batch data, etc.
 - **Make overall arrangement in advance and pay attention to representative problems of retained samples in each development stage**

Such as facilitating comparability study, establishing and tracing reference materials, continuous stability investigation, etc.

Thanks for Listening

内部资料仅作参考
Reference Only