Introduction of CMC Review Practice for China COVID-19 vaccines

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I. Background Information

II. Laws, Regulations and Technical Evaluation Standard System

III. Early Stage CMC Requirements and Staged Considerations in Emergency

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I. Background Information

✓ Technical Roadmap:

- Use of Novel Adjuvants
- Development of Novel Viral Vectors
- Application of Novel Drug Delivery System
- Use of Novel Drug Delivery Devices
II. Laws and Regulations

Vaccine Administration Law (Issued in 2019)

For vaccines which are used to respond to major public health emergencies or other vaccines which are urgently needed as identified by the competent health department under the State Council, the drug regulatory department under the State Council may grant conditional approval to registration application if benefits of those vaccines outweigh risks based on evaluation. When particularly major public health emergencies or other emergencies which seriously threaten public health occur, the competent health department under the State Council shall propose recommendations on the urgent use of vaccines based on the need of infectious disease prevention and control, and after evaluation organized by the drug regulatory department under the State Council, the permission for the urgent use within certain scope and period shall be granted.

Special Review and Approval Procedure for Drug Registration (SFDA Decree No.21)

- According to the principle of unified leadership, early involvement, expeditiousness and efficiency, and scientific review and approval
- Carry out special review and approval of drugs for handling public health emergencies

Supporting documents by CDE for Decree No.21

One program, two procedures, and one good practice
1. CDE Working Program for Special Review and Approval of Anti-Covid 19 Medicines
2. Working Procedure for Review of Application for Project on Anti-Covid 19 Medicines
3. Working Procedure for Assessment and Review by the Ad Hoc Expert Group on Anti-Covid 19 Medicines
4. NMPA Good Practice on Expert Meetings on Anti-Covid 19 Medicines
II. Establishment of a standard system for the development, review and approval of COVID-19 vaccines

More targeted technical guidelines (interim) and requirements for application submission in response to COVID-19 pandemic

- Technical Guidance for CMC Studies of Prophylactic mRNA Vaccines for Covid-19 (Interim)
- Technical Guidance for Clinical Studies of Prophylactic Vaccines for Covid-19 (Interim)
- Guidance for Clinical Evaluation of Prophylactic Vaccines for Covid-19 (Interim)
- Requirements for the Dossiers for Clinical Trial Application of Prophylactic Vaccines for Covid-19 (Interim)
- Essentials for Technical Review of Prophylactic Vaccines for Covid-19 (for internal use)

In view of the rapid development of new biomedical technologies and the limited understanding of the biological characteristics of Covid-19, these technical guidelines will be continuously improved and updated in due course with the deepening of research and the accumulation of relevant research data.
## Initiatives for Accelerating Research and Development

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<th>Working Mechanisms</th>
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| **1. Technical standards first**          | • The technical guidelines guiding technical research and the preparation of application dossiers have been drafted.  
• The essentials for technical review of common changes have been drafted.                                                                                                                                                                                                                   |
| **2. From “orderly” to “simultaneously”** | • Simultaneously conduct testing, inspection and review  
• Simultaneously conduct MAH’s release testing and registration testing (by the national lab (NIFDC)) to complete drug testing required by China’s Regulations within 21 days                                                                                                                                                   |
| **3. Continuous communication**           | • Establish a dedicated review team and a dedicated contact system  
• Enhance communication with applicants; CDE’s involvement at early stage; regular follow-up; and feedback to applicants' questions within 24 hours                                                                                                                                                           |
| **4. Rolling submission of dossiers**      | • Applicants can submit updated data and responses to supplementary questions about dossiers on a rolling basis, and timely feedback can be given on dossiers submitted through rolling submissions to achieve "end of review at the end of research and development"  
• Some study data may be submitted after on-site inspection/testing                                                                                                                                                                                                                   |
| **5. Accelerated clinical trials**         | • Changes in clinical trial modes and design: seamless design, etc.  
• Clinical interim analysis is supportive of conditional approval for marketing                                                                                                                                                                                                                    |
| **6. Regulatory flexibility and post-marketing requirements based on risk assessment** | • Post-marketing risk management plan and continued monitoring, timely update of IPC, stability study data, etc.  
• Risk management and control of post-marketing changes                                                                                                                                                                                                                                         |
| **7. Formation of the ad hoc expert group** | • Form an ad hoc expert group composed of academicians and experts in the fields of CMC, pharmacology and toxicology, and clinical sciences to provide solid technical support for review and approval in emergency |
Technical review in the service of R&D

➢ Communication on CMC-related issues
  ➢ 35 expert consultation meetings were held
  ➢ More than 100 meetings/panel discussions of senior reviewers across review functions
  ➢ More than 2,000 consultations in various forms

Scientific research data is the basis for effective communication
III. Early Stage CMC Requirements and Staged Considerations in Emergency

- Staged, progressive considerations
- Overall coordination
- Good identification at R&D stage
- Advance comparability study design and sample retention

- **Seed banks**: primary seed banks may be used for clinical trial sample preparation; consider the use of accelerated testing methods

- **Manufacturing process**: platform-based process development; it is recommended to study as many process control parameters as possible to accumulate product knowledge and process knowledge, and to lay a foundation for possible issues in the scale-up and their comparability studies; the reduction of control parameters would not be considered until adequate accumulation and validation work is completed.

- **Quality characteristics study**: staged submission

- **Specifications**: focus on the comprehensiveness of testing items; progressive confirmation of standard limits
III. Early Stage CMC Requirements and Staged Considerations in Emergency

Other aspects

✓ Encourage integration of platform technology with innovative R&D

➢ Whether established as platform technology
➢ Maturity of the platform technology
➢ The extent to which the platform technology can be used for reference
➢ Demonstration and necessary supporting data
➢ Specific studies are to be conducted on characteristic processes and quality attributes
IV. CMC Considerations for Conditional Approvals

- Adjustments to the review and approval process
- General CMC requirements
- Considerations for determining shelf life
- Post-marketing considerations
IV. CMC Considerations for Conditional Approvals

Adjustments to the review and approval process

Traditional mode

✓ Initiate review and approval after acceptance of all required dossier
✓ Conduct review, inspection and testing in an orderly manner
✓ There may be a possibility of multiple submissions of supplementary materials

Conditional approval

✓ Prioritize allocation of resources to synchronize with vaccine development and clinical trials
✓ Resolve key technical issues in advance and discuss in advance the CMC data to be submitted for conditional approval for marketing
✓ Conduct simultaneously the review, inspection and registration testing
✓ Initiate manufacturing site inspection after confirmation of the process and specification, etc., and dynamic inspection batches can be taken as validation batches
✓ Consider conducting front-loaded registration testing
IV. CMC Considerations for Conditional Approvals

General CMC requirements

✓ The formulation and manufacturing process should be feasible, the specification should be reasonable, and the CMC data can support marketing approval of the vaccine

➢ According upgrade and improvement achieved during the clinical stage
➢ Production continuity
➢ Quality controllability
➢ Comparability study
➢ Pass on-site inspections and specification verification
➢ Continued improvement after marketing, e.g., continued stability study, etc.
V. Post-marketing Changes

➢ Focus on post-marketing accessibility of the vaccines and encourage increase in production capacity for vaccine through multiple approaches
  ➢ Addition of production lines
  ➢ Scale-up
  ➢ Addition of suppliers of critical materials
  ➢ …

➢ Working procedures
Post-Marketing Change Process for Addition of Production Lines and Increase in Production Capacity for COVID-19 Vaccines
✓ Rolling review of change plans and comparability study protocol
✓ Front-loaded inspection and testing

➢ Technical Review System
✓ Essentials for Technical Considerations for Studies on Post-Marketing Changes to COVID-19 Vaccines with Guaranteed Quality and Supply
✓ Essentials for Technical Considerations for Addition of Multiple-dose Package of COVID-19 Vaccines
✓ Technical Requirements for Post-Conditional Marketing Change in the Source of Raw Materials, Excipients, and Primary Packaging Materials of COVID-19 Vaccines
✓ …
VI. Conclusion

✓ Challenges and breakthroughs arising from the emergency

✓ Ensuring the safety, efficacy and quality controllability of the vaccines in emergency

✓ Based on scientific risk analysis, assessment and control

✓ **Focus on the planned, staged and progressive characteristics in vaccine development**

✓ Focus on post-marketing changes in production capacity expansion, vaccines against mutant strains and other changes
Thank you!