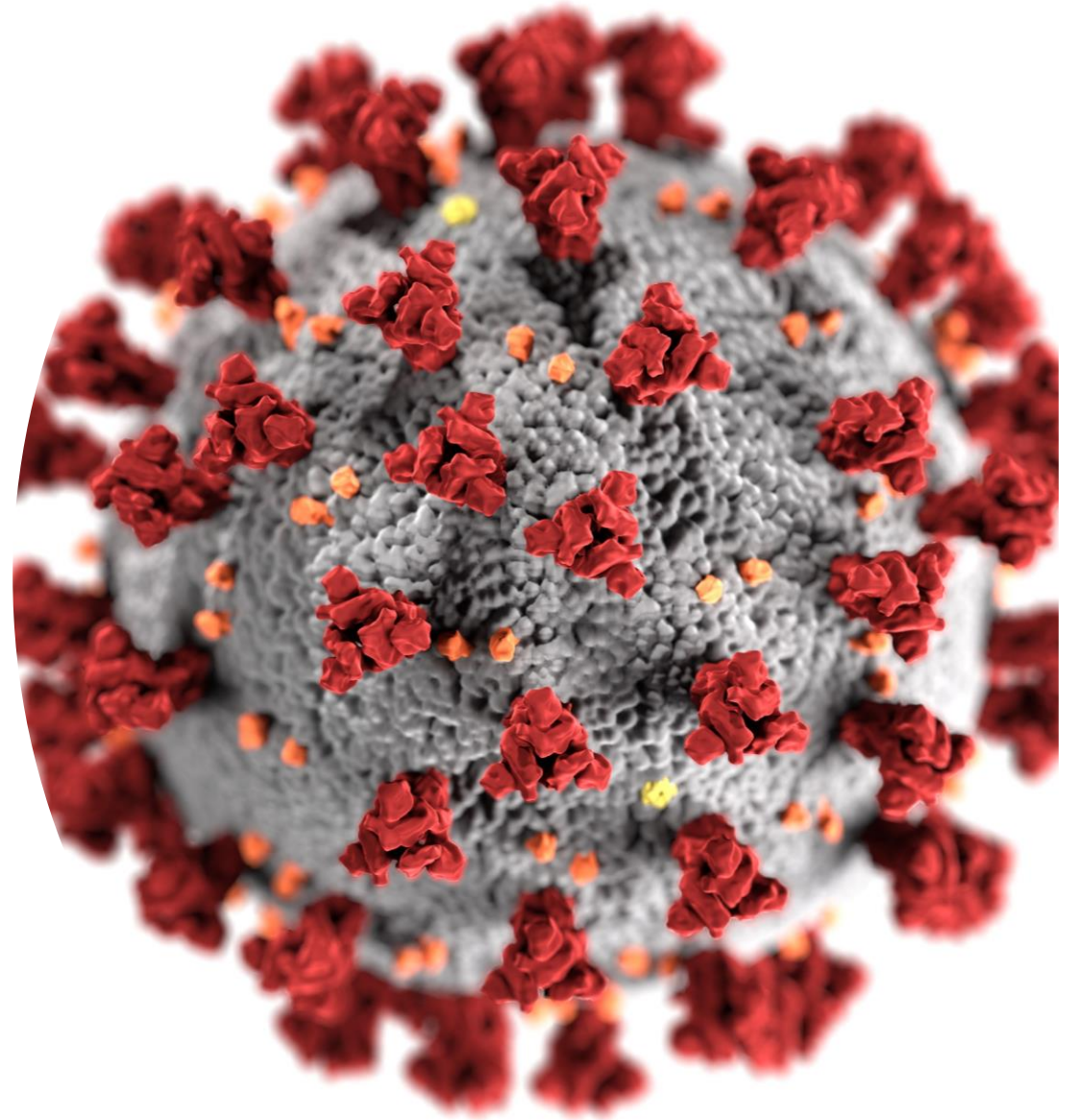


COVID Vaccine Development Strategies, Challenges and Lessons Learned Regulatory CMC Perspective

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AZ COVID-19 Vaccine Experience

- Unprecedented accelerated COVID-19 vaccine development in response to pandemic
- Extensive support required spanning pre- and post authorization, involving complex global supply chains
- Unprecedented collaboration and engagement with global health authorities and WHO:
 - Pre-approval CMC filing strategies
 - Rolling submissions, authorizations
 - Post approval change strategies
- AZ COVID vaccine global roll-out continues— currently approved in more than 170 countries; more than 2 billion doses released
- Through 2021, more than 200 CMC Post Approval Changes have been filed
- Development planning continues for boosters, variant vaccines



Acceleration strategies and challenges in a pandemic environment

The following strategies will be reviewed including AZ's experience in Japan/Southeast Asia:

- Early engagement with health authorities
- Rolling/emergency use submissions
- CMC acceleration strategies
- Use of reliance approaches
- Post approval acceleration strategies
- Lessons learned – future opportunities



Regulatory CMC Acceleration Strategies

Early and frequent engagement with Regulatory Agencies

- Some Regulatory Agencies engaged with AZ throughout development (e.g., rapid scientific advice)
- This allowed innovative and accelerated CMC approaches to be presented and discussed prior to initiating submissions including discussions on:
 - Use of platform knowledge
 - Use of rapid analytical methods
 - Concurrent validation
 - Analytical comparability strategy
 - Rolling submission
 - Stability strategy



Regulatory Agency Engagement – Japan/Southeast Asia Experience

- No interactions with regulators prior to submission
- May have been beneficial in order to explain:
 - Rolling submission strategy including CMC acceleration strategies
 - Use of CMC data specific to EU supply chain to support applications in other regions
- Lack of clarity led to many questions specific to EU supply chain
 - While some acceleration strategies were accepted (rolling submission) the lack of communication prior to submission reduced the overall efficiency of review and approval



Regulatory CMC Acceleration Strategies (continued)

Rolling submissions supporting accelerated approvals with unprecedented level of EU post-approval activities, many requiring global roll-out:

- Detailed plans for submission packages
 - Content
 - Timelines – for submission packages and supplemental data
- Follow-up submissions/post approval measures

Accelerated CMC approaches key to enable rolling submissions and post approval changes:

- Submission of CMC data including validation data on a rolling basis
- Analytical comparability - key to support introduction of new supply chains
- Stability – clinical data for stability forecasting; extrapolation; use of platform data



Rolling submission – Japan/Southeast Asia Experience

Japan:

- Rolling submission was accepted starting in Sept 2020 with nearly complete quality dossier in Dec 2020; CMC queries began immediately after submission of clinical data
- Rolling submission generally successful – review time shortened, data submitted during review
- Rolling submission strategy not fully accepted; completed process validation reports required prior to authorization, for example (no reliance applied)

Southeast Asia:

- Rolling submissions provided; Agency interaction at later stage
- Elements of rolling submission were helpful but also resulted in some confusion and questions related to EU supply chain
 - Available CMC data from supply chain not relevant to SEA



Regulatory CMC Acceleration Strategies (continued)

Acceptance of reliance approach is variable:

- Some independent markets practiced reliance type acceptance of EMA dossier
- WHO Emergency Use Listing (EUL) process worked very well: many markets relying on EMA then WHO approval
- Others asked high number of questions – some over 200 for original MAAs



Reliance – Japan and Southeast Asia Experience

Japan

- Reliance was not applied to the JNDA for the COVID vaccine
- There was no reliance applied regarding virtual inspections to confirm GMP status; PMDA performed a virtual inspection following the EMA virtual inspection which was not leveraged

Southeast Asia:

- Number of questions received initially indicated lack of reliance but recently we have seen a shift towards more reliance approaches in many countries



Post approval burden following acceleration

Accelerated and innovative CMC approaches led to significant post approval submission burden:

- More than 100 EU Post Approval Measures following EMA authorization
- More than 200 Post Approval Changes submitted globally by the end of 2021
 - Addition of manufacturing sites, testing sites, analytical method updates, etc.
- To support multiple additional manufacturing sites, Post Approval Change Management Plans (PACMP) were developed. These PACMPs have increased efficiency of submission and review of site additions, many of which were rolled out globally.
- Acceptance of PACMP approach has resulted in greatly reduced review/approval timelines by EMA and other global regulatory agencies



Use of Regulatory Tools for post approval changes

Post Approval Change Management Plans developed for addition of New Drug Substance and Drug Product manufacturing sites criteria; no/minimal change to the following:

- Manufacturing process, batch size, container closure, control strategy
- Validated release and stability testing procedures and specifications
- Transfer of analytical methods for in-process controls validated
- Shelf-life strategy; storage conditions
- All sites meet all cGMP requirements; provide evidence of GMP compliance at the time of submission



Use of Regulatory Tools for post approval changes

- PACMP data requirements:
 - The manufacturing process for the additional Drug Substance/Drug Product site/s will be validated in accordance with proposed validation protocol.
 - The quality of the material is assessed in accordance with a comparability protocol.
 - The following studies to qualify equipment and product specific procedures used in the Drug Product manufacturing process will be provided:
 - Validation of Sterilization Methods
 - Media Fills
 - Cleaning Validation
 - Container Closure Integrity Qualification



Acceptance of PACMP for post approval changes

- Post approval Change Management protocols (PACMPs) for addition of manufacturing DS and DP sites approved in UK and EU: type II reduced to ‘accelerated’ type IB: approval seen in up to 10 days
- PACMPs are not recognized by all regulatory agencies (not part of legislation), therefore other mechanisms for acceleration were agreed in many cases:
 - Many Agencies are approving through reliance or their own review within 30 days
- Acceleration of the review and approval of multiple variations to add Drug Substance and Drug Product manufacturing sites either by PACMP or other mechanism have had a major positive impact on AZ’s ability to supply vaccine globally



Post approval acceleration strategies in Japan/Southeast Asia

Japan

- JNDA special approval for emergency use - highly accelerated approvals for PCAs (within 30 days)

Southeast Asia

- Experience varied but variations (especially for introduction of new supply nodes) reviewed and approved relatively quickly
- Several countries were not able to follow reliance for variations due to local regulations, but accelerated reviews to the extent possible
- As mentioned, more recently we have observed a shift towards more reliance approaches



Flexibilities and further opportunities for vaccines and other therapies

What is working well:

- **Good engagement** on science-based strategies with many Agencies
- Agreed use of **platform or prior knowledge** data
- Consideration of **agile CMC approaches**, based on data, e.g. process validation approaches
- Ability to apply **PACMP approach and accelerated PAC approvals** for supply changes
- Agreement to use **rolling reviews** and submit proposals and draft M3 documents
- General willingness to support accelerated and innovative strategies to expedite life saving medicines to patients

Further opportunities:

- Adoption of the **flexibilities globally**: further engagement with Global Agencies on CMC principles
- Gain agreement to apply **same dossier for many markets**: development strategies, control strategies, specifications, documentation etc.
- Harmonize GMO requirements
- **Apply reliance** for initial licence and apply this to **post approval changes as well**
- **Expand the use of PACMP to other categories of changes (risk based approach)**
- **Mutual recognition of inspections**
- Need for **on-going dialogue** to continue to apply these strategies outside of pandemic

