REGULATORY EXPERIENCE FROM THE ROLLING REVIEW PROCESS AND THE CONDITIONAL MARKETING AUTHORIZATION PROCESS FOR COVID-19 VACCINES

CASSS-AT - 24 May 2022

Elisa Pedone, PhD
Pharmaceutical Quality Office, Quality and Safety, Human Medicines, EMA
Contents

- EU procedures for the crisis- flexibilities and EMA-company interactions
- CMC highlights from approved COVID-19 vaccines
- CMC learnings & Future direction
Regulatory standards will be maintained

- **Same legal requirements** for pharmaceutical quality, safety and efficacy as other medicines in the EU – subject to **scientific evaluation** demonstrating that their overall **benefits outweigh their risks**

- Due to the **public health emergency**
  - Development is **compressed in time**, applying the extensive knowledge on vaccine production gained with existing vaccines.
  - Simultaneous **mobilisation of human resources** – EMA Task Force - early, continuous dialogue between developers and companies
  - **Combining** clinical trial phases or conducting some **studies** in parallel, instead of carrying them out sequentially - where safe to do so.
  - Expanding **manufacturing** and production **capacity** to ensure efficient vaccine deployment
Regulatory Flexibilities

Questions And Answers On Regulatory Expectations For Medicinal Products For Human Use During The Covid-19 Pandemic

- Implementation of supply chain changes (ECMP*)
- GMP inspections & certificates - Validity of GMP cert. extended and DA**
- Which quality requirements can be waived?
- Postponing or waiving testing in the third country/
  Postponing certain testing in the EEA
- Adapting work of Qualified Person

*ECMP: Exceptional change management process
**DA: Distant Assessment
**Company-EMA interactions**

**Conditional Marketing Authorisation**
- Benefit-risk balance of the product must be positive;
- Manufactured/controlled in certified facilities
- Different from an Emergency Use Authorisation
Standard evaluation process compared with Rolling Review of COVID-19 vaccines

Rolling Review evaluation (days)
- Comirnaty: 56
- Spikevax: 30
- Vaxzevria: 101
- JCOVDEN: 85
- Nuvaxovid: 285

Cond Marketing Authorisation evaluation (days)
- AA MAA: 120
- Standard MAA: 210
- Comirnaty: 21
- Spikevax: 27
- Vaxzevria: 28
- JCOVDEN: 19
- Nuvaxovid: 26
40 COVID-19 vaccines in development have received Rapid Scientific Advice

COVID-19 medicines that have received EMA advice

Currently under rolling review
- Sputnik V, Gam-COVID-Vac (Gamaleya Institute)
- COVID-19 Vaccine HIPRA (PHH-1V) (HIPRA Human Health S.L.U.)
- COVID-19 Vaccine (Vero Cell) Inactivated (Sinovac)

Marketing authorisation application submitted
- Vidprevtyn (Sanofi Pasteur)
- COVID-19 Vaccine Valneva

Authorised for use in the European Union
- Comirnaty (BioNTech and Pfizer)
- Nuvaxovid (Novavax)
- Spikevax (Moderna)
- Vaxzevria (AstraZeneca)
- Jcovden (Janssen)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Developer</th>
<th>Key milestones</th>
<th>More information</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVnCoV</td>
<td>CureVac AG</td>
<td>Rolling review started: 12/02/2021</td>
<td>EMA ends rolling review of CVnCoV COVID-19 vaccine following withdrawal by CureVac AG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawn from rolling review: 12/10/2021</td>
<td>Paediatric investigation plan</td>
</tr>
</tbody>
</table>

*correct on 18 May 2022
Key CMC issues during COVID-19 vaccines MAA

- Risk-based approach to agreeing flexibilities
- Case by case depending on strength of supporting data: good product understanding
- Sufficient characterisation data and appropriate analytical technology needed
# Flexibilities used in COVID-19 vaccines

<table>
<thead>
<tr>
<th>Pre-requisite</th>
<th>Scientific tools used</th>
<th>Regulatory tools used</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Development data from non-commercial sites</td>
<td>• <strong>Protocol</strong> to complete process validation &amp; comparability post-approval</td>
<td>• <strong>Specific Obligations</strong> (completing validation/comparability/novel excipient datasets) with interim timepoints</td>
</tr>
<tr>
<td>• Platform data</td>
<td>• <strong>Concurrent validation</strong> of commercial manufacturing process</td>
<td>• <strong>Recommendations</strong></td>
</tr>
<tr>
<td>• Strategy agreed in rapid scientific advices</td>
<td>• <strong>Extrapolation</strong> of stability data (comparability, accelerated conditions + supportive stability data)</td>
<td>• Post-Approval Change Management Protocols (<strong>PACMPs</strong>)</td>
</tr>
<tr>
<td>• Close dialogue</td>
<td>• <strong>2-tiered comparability</strong> of AS / FP (1: comparison of release and IPC results; 2: additional characterisation test results post-approval)</td>
<td>• Exceptional change management process (<strong>ECMP</strong>) to transfer analytical methods to already approved QC sites</td>
</tr>
<tr>
<td>• Comparability to clinical development batches shown</td>
<td>• Initial batch data + supplier information for excipient from clinical development and <strong>risk-based considerations</strong> (safety/quality)</td>
<td>• <strong>Temporary derogations</strong> (batch release testing in EU)</td>
</tr>
</tbody>
</table>

- Knowledge and dialogue
- Validation, comparability, stability, excipients
- PACMPs, SOB and Recs, Derogations, *COVID scope only*
## Key CMC flexibilities + manufacturing experience /GMP during COVID-19 vaccine MAA

<table>
<thead>
<tr>
<th></th>
<th>Vaccine A</th>
<th>Vaccine B</th>
<th>Vaccine C</th>
<th>Vaccine D</th>
<th>Vaccine E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sufficient manufacturing experience for MA in view of B/R</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ Prior Knowledge, platform data</td>
<td>✓</td>
</tr>
<tr>
<td><strong>GMP issues during rolling review</strong></td>
<td>✓ GMP (sites)</td>
<td>✓ GMP (sites)</td>
<td>✓ GMP (sites)</td>
<td>✓ GMP (sites)</td>
<td>✓ GMP (sites)</td>
</tr>
<tr>
<td><strong>Control strategy/specifications flexibilities</strong></td>
<td>✓ some outstanding data, incl. for excipients, impurities. Additional characterisation data required –SO</td>
<td>✓ some outstanding data incl. characterisation data required –SO</td>
<td>✓ additional output parameters agreed- for review after PV completion- REC. Spec to update-SO</td>
<td>✓ limited outstanding data-confirm criticality of assigned CPPs-&gt; REC</td>
<td>✓ some outstanding data, incl. for excipients, impurities, characterisation data, specs required –RECs</td>
</tr>
<tr>
<td><strong>Comparability flexibilities</strong></td>
<td>✓ limited commercial data &amp; characterisation issues- SO</td>
<td>✓ limited commercial data-&gt; complete package-SO</td>
<td>✓ complete the package-&gt; review comparability ranges post-auth -SO</td>
<td>✓ complete the finished product package- SO</td>
<td>✓ complete the finished product package- SO+RECs</td>
</tr>
<tr>
<td><strong>Process validation flexibilities</strong></td>
<td>✓ concurrent-SO</td>
<td>✓ concurrent-SO</td>
<td>✓ concurrent-SO</td>
<td>✓ concurrent-SO</td>
<td>✓ concurrent, REC</td>
</tr>
<tr>
<td><strong>Stability flexibilities</strong></td>
<td>✓ limited real-time &amp; commercial-SO</td>
<td>✓ limited real-time &amp; commercial-SO</td>
<td>✓ limited real-time &amp; commercial, review spec-SO</td>
<td>✓ limited real-time &amp; commercial-but platform data- REC</td>
<td>✓ limited real-time &amp; commercial, review spec-SO</td>
</tr>
</tbody>
</table>

SO= specific obligation
REC= recommendation
<table>
<thead>
<tr>
<th>Regulatory Tools for accelerated review for COVID-19 vaccines</th>
<th>Vaccine A</th>
<th>Vaccine B</th>
<th>Vaccine C</th>
<th>Vaccine D</th>
<th>Vaccine E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid Scientific Advice (CMC)</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Meetings</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Included PACMP at MA grant</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Accelerated assessment of MA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CMC Specific obligations /CMA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Recommendations</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Time-limited batch control testing in 3rd country at MA</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Key CMC issues during COVID-19 vaccines Post-authorisation

- Post-authorisation weekly EMA-MAH meetings/interactions
- Many public health-prioritised CMC variations changes reviewed quickly
- GMP –initial verification prior to submission for site changes
- CMC PACs changes approx. x10 higher than other vaccine MAs
- Where PLANS anticipated in MA- more successful!

AS and FP site onboarding-readiness/GMP

Changes to the process, specifications, methods

QC sites

Storage/transport/use considerations

Raw materials, excipient, container-closure suppliers. Changes to key excipients
Regulatory planning for MAA
• COVID-19 vaccine applications are **resource intensive**, requiring well-planned, timely data packages of good quality

Engagement
• Early & continuous engagement with regulators from development through post-authorisation required using the right regulatory tools.

Manufacturing readiness
• ‘At-risk’ investment
• Intensity of regulatory engagement from early stage
• Need for distant inspections, MRA, trusted partners’ inspections

CMC dossier
• Understand major CMC issues to build dossier
• Understand that the extent of regulatory flexibilities subject to product/process knowledge & site readiness- tailored to each product
• Key confirmatory data expected to be filed post-approval

Post-approval planning
• Should be incorporated during MAA (PACMP, plan GMP)
• **Resource intensive** (prioritisation), requires regular interaction, acceleration when impacted supply
Future directions

- Variants
- Applicability of CMC flexibilities
- Revision of pharma legislation?
- Support to global alignment
Classified as public by the European Medicines Agency

Variants - scientific reflection paper

CMC considerations are technology dependent

+ Procedural guidance for variation for variant update to coronavirus vaccines

Active substance

- Starting materials update
- Parent control strategy reliance - with needed strain-specific adaptations
- Testing of critical quality attributes (e.g. purity, content) to demonstrate compliance to specifications (or justify)
- Demonstrate manufacturing consistency
- Registered shelf-life applicable, but confirmation needed (could be post-approval)

Finished Product

- Similar considerations to AS for specifications, stability & control
- Possible additional considerations if intended for multivalent use:
  - Total impurity control
  - Test method validity
  - Adaptation of specifications
  - New Pharm. Dev. studies
  - New formulation?
  - Batch analysis and PV data requirements higher
Future applicability

Products for unmet medical need

Pro-active planning (MAA and post-authorisation), & enhanced engagement to facilitate accelerated MAA review

Utilise flexible ‘risk-based’ approach for CMC (case by case)

Promote regulatory tools* to manage flexibilities

Review of the Pharma Legislation for wider applicability?

* Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications (europa.eu)
Key Messages

- Health treats preparedness plan, mobilisation of network of EU vaccine experts, collaboration with international regulators
- Early interaction, Pro-active planning
- Rapid SA, RR and CMA have been extremely resource intensive
- Regulatory, CMC flexibility and risk-based thinking in the context of public health
- Openness for change (by the legislator)
- Global alignment

Acknowledgements

Veronika Jekerle, Ragini Shivji, Dolores Hernan, Klara Tiitso, Evdokia Korakianiti, Brian Dooley
Thank you for your attention

Further information

Dr Elisa Pedone, Pharmaceutical Quality, Quality and Safety of Human Medicines, European Medicines Agency

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Send us a question Go to www.ema.europa.eu/contact

Telephone +31 (0)88 781 6000

Follow us on @EMA_News