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

CASSS-AT - 24 May 2022

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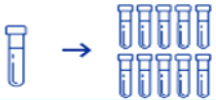
Contents

Regulatory processes

- **EU procedures for the crisis- flexibilities and EMA-company interactions**



Quality and Manufacturing

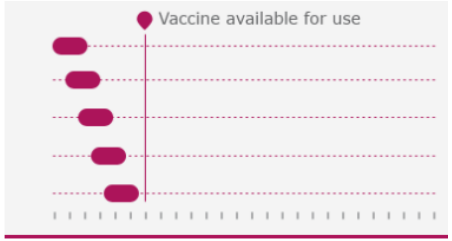
- **CMC highlights from approved COVID-19 vaccines**

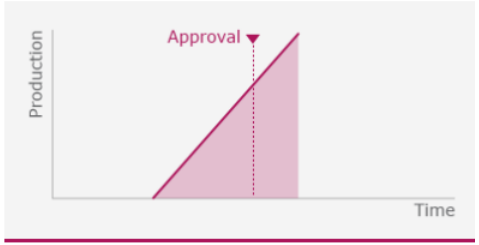
Opportunities

- **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 a 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


EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

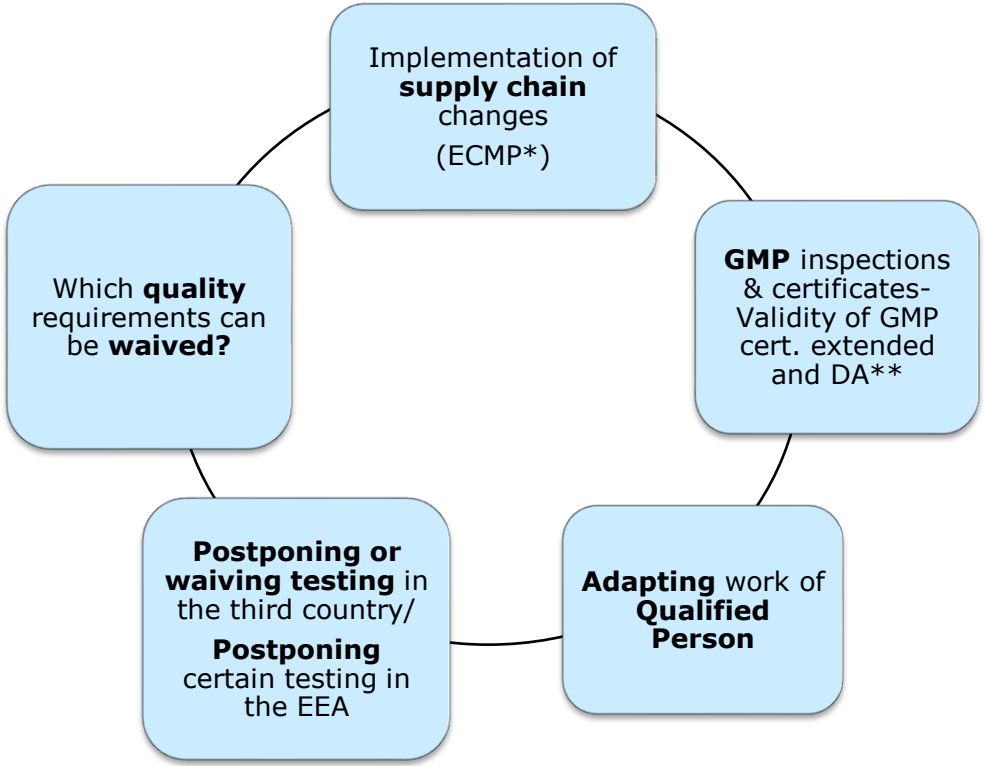
HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Brussels, 30 September 2021
(Revision 4 – July 2021)

NOTICE TO STAKEHOLDERS

QUESTIONS AND ANSWERS ON REGULATORY EXPECTATIONS FOR MEDICINAL PRODUCTS FOR HUMAN USE DURING THE COVID-19 PANDEMIC



*ECMP: Exceptional change management process
**DA: Distant Assessment

Company-EMA interactions

EMA Pandemic Task Force (ETF) requests data, pro-actively engages developer discussions

Rapid Scientific Advice (SA) ETF supported by relevant working parties

Threshold to start Rolling Review (RR)- proof of concept + mature dossier/ manufacturing plans + if MAA expected no later than 4 months

RR starts = Pre-agreed content - eCTD, M2 and responses to cumulative LoQ in each cycle

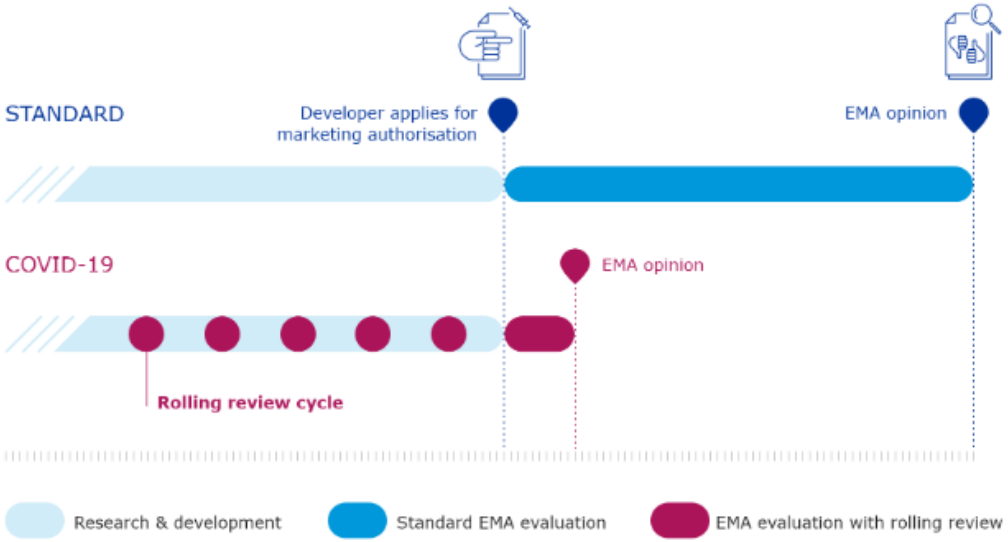
Can be several RR cycles- TT and questions agreed by Rapp/EMA for each cycle

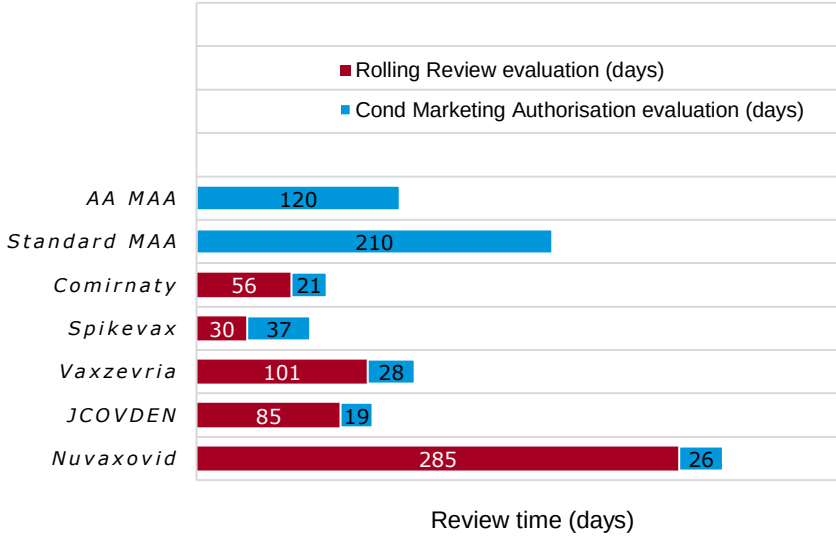
Readiness for MAA – agreed by ETF/CHMP (for rapid review)

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





Current status of COVID-19 vaccines approvals*

*correct on 18 May 2022

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**

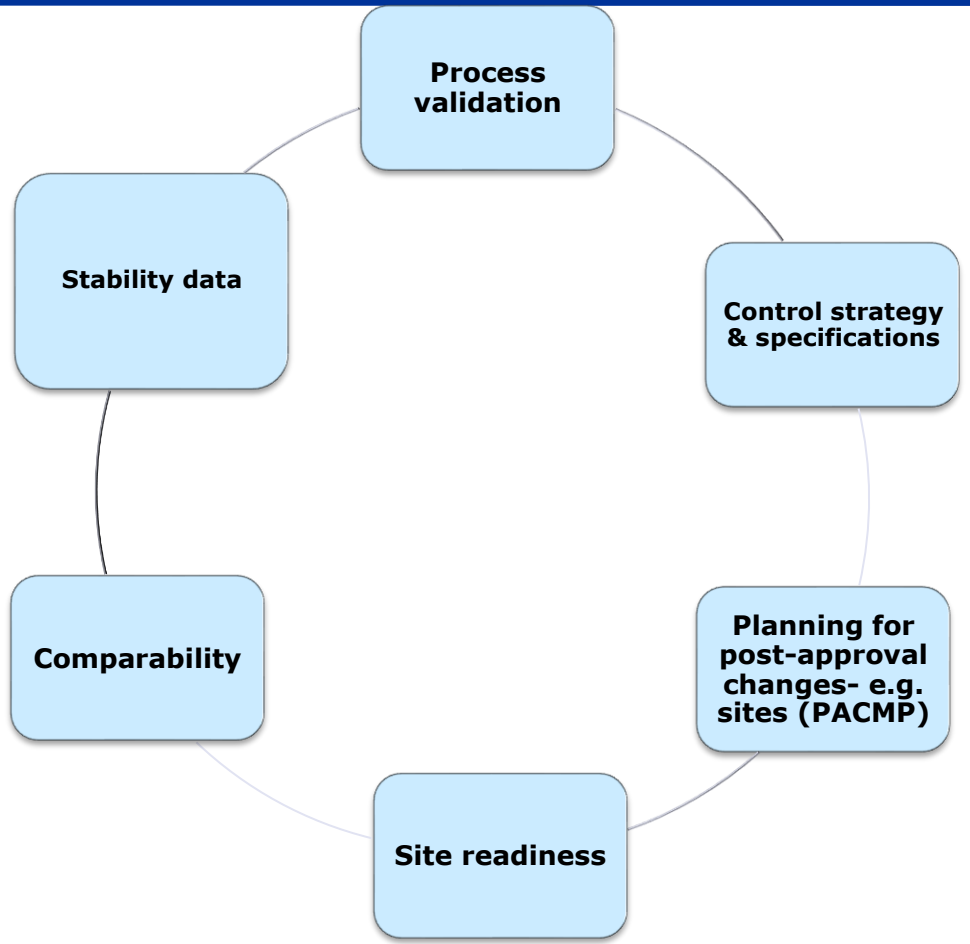
Authorised for use in the European Union

- **Comirnaty** (BioNTech and Pfizer)
- **Nuvaxovid** (Novavax)
- **Spikevax** (Moderna)
- **Vaxzevria** (AstraZeneca)
- **Jcovden** (Janssen)

Vaccine	Vaccine developer	Key milestones	More information
CVnCoV	CureVac AG	Rolling review started: 12/02/2021 Withdrawn from rolling review: 12/10/2021	EMA ends rolling review of CVnCoV COVID-19 vaccine following withdrawal by CureVac AG Paediatric investigation plan

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

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

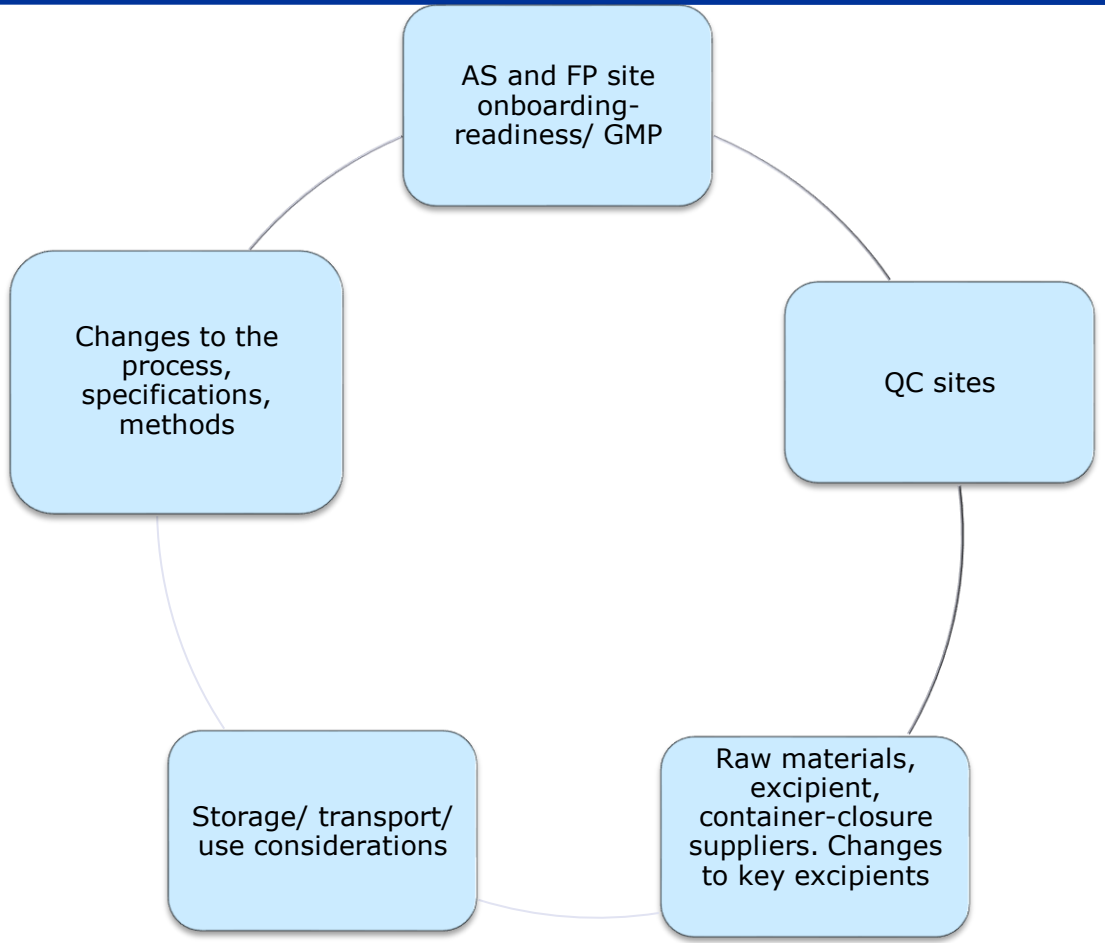
* COVID scope only

Key CMC flexibilities + manufacturing experience /GMP during COVID-19 vaccine MAA	Vaccine A	Vaccine B	Vaccine C	Vaccine D	Vaccine E
Sufficient manufacturing experience for MA in view of B/R	√	√	√	√ Prior Knowledge, platform data	√
GMP issues during rolling review	√ GMP (sites)	√ GMP (sites)	√ GMP (sites)	√ GMP (sites)	√ GMP (sites)
Control strategy/specifications flexibilities	√ some outstanding data, incl. for excipients, impurities. Additional characterisation data required –SO	√ some outstanding data incl. characterisation data required –SO	√ additional output parameters agreed- for review after PV completion- REC. Spec to update-SO	√ limited outstanding data-confirm criticality of assigned CPPs-> REC	√ some outstanding data, incl. for excipients, impurities, characterisation data, specs required –RECs
Comparability flexibilities	√ limited commercial data & characterisation issues- SO	√ limited commercial data-> complete package-SO	√ complete the package-> review comparability ranges post-auth -SO	√ complete the finished product package- SO	√ complete the finished product package- SO+RECs
Process validation flexibilities	√ concurrent-SO	√ concurrent-SO	√ concurrent-SO	√ concurrent-SO	√ concurrent, REC
Stability flexibilities SO= specific obligation REC= recommendation	√ limited real-time & commercial-SO	√ limited real-time & commercial-SO	√ limited real-time & commercial, review spec-SO	√ limited real-time & commercial-but platform data- REC	√ limited real-time & commercial, review spec-SO

Regulatory Tools for accelerated review for COVID-19 vaccines	Vaccine A	Vaccine B	Vaccine C	Vaccine D	Vaccine E
Rapid Scientific Advice (CMC)	x	√	√	√	√
Meetings	√	√	√	√	√
Included PACMP at MA grant	X	X	√	√	√
Accelerated assessment of MA	√	√	√	√	√
CMC Specific obligations /CMA	√	√	√	√	√
Recommendations	√	√	√	√	√
Time-limited batch control testing in 3rd country at MA	√	√	X	√	√

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!**



CMC Learnings

Learning

Regulatory planning for MAA

- COVID-19 vaccine applications are **resource intensive**, requiring well-planned, timely data packages of good quality

Learning

Engagement

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

Learning

Manufacturing readiness

- 'At-risk' investment
- Intensity of regulatory engagement from early stage
- Need for distant inspections, MRA, trusted partners' inspections

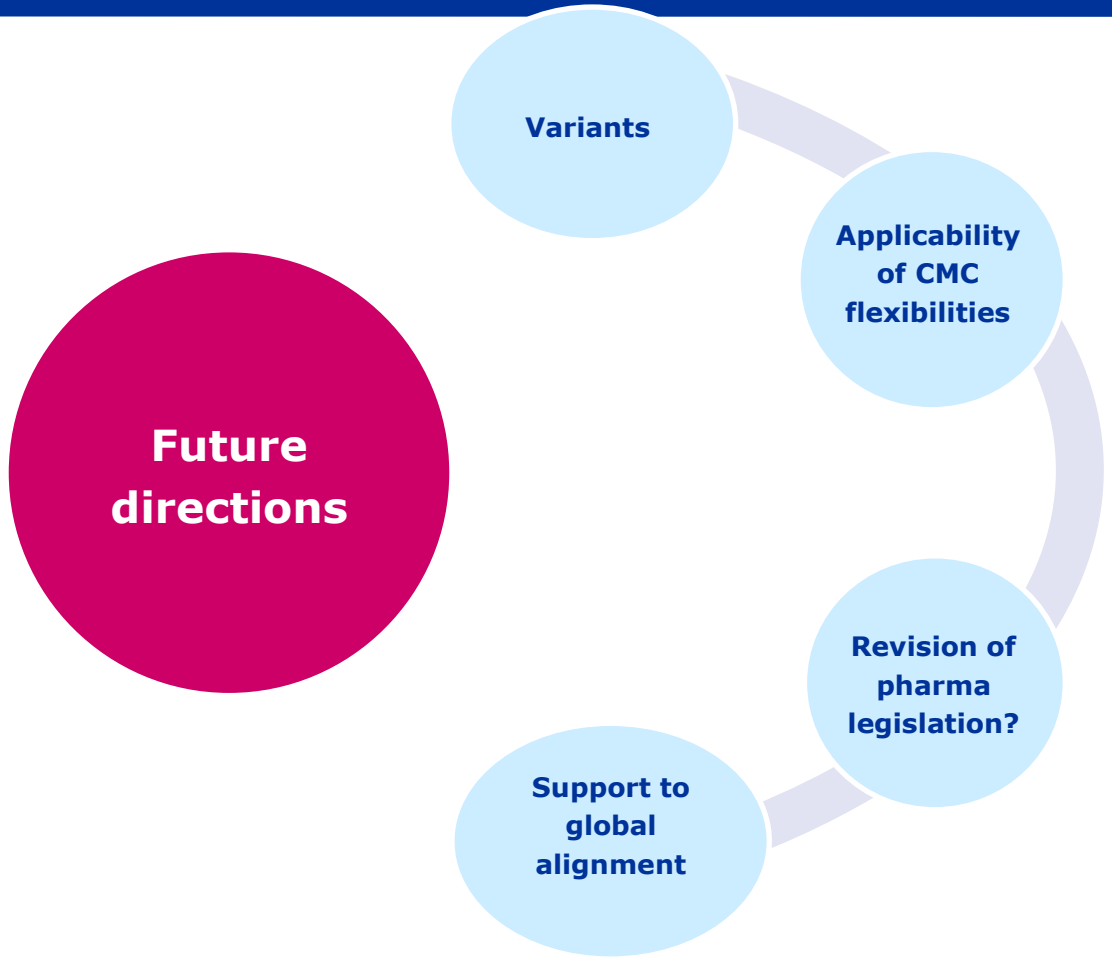
Learning

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

Learning

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



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

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

Products for unmet medical need

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

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