EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Communications, Regulatory Flexibilities and Quality Challenges for Biologics in the COVID-19 Pandemic: An EMA Perspective

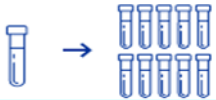
2020 CASSS CMC Strategy Forum Japan 09 December 2020

Ragini Shivji

Contents

Communications

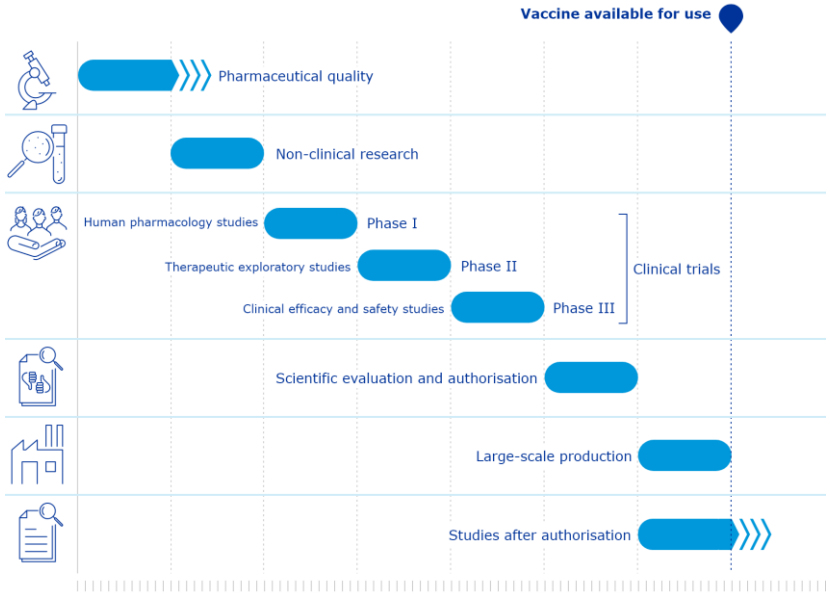
Regulatory processes



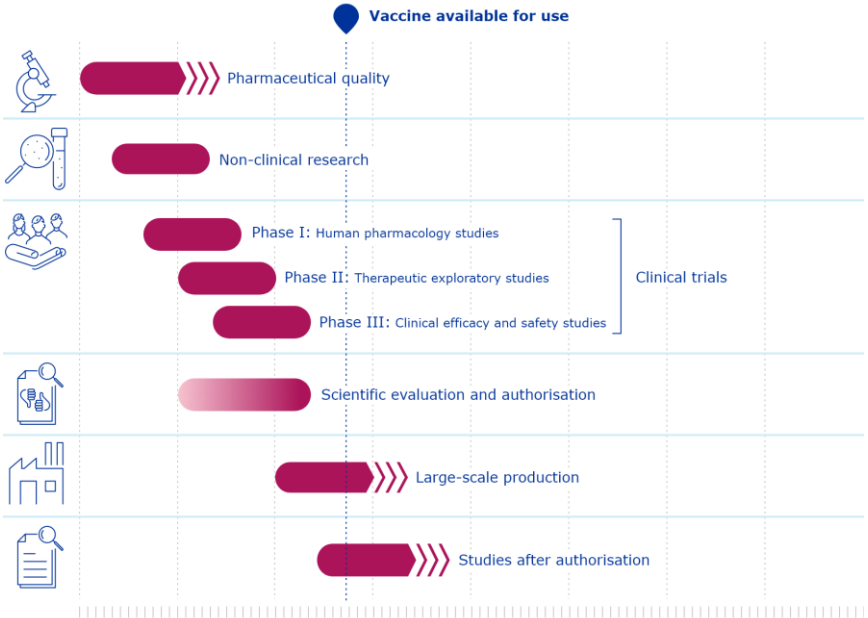
Quality and Manufacturing

- **Transparency and company interactions**
- **EU regulatory flexibilities and EMA procedures for the crisis**
- **Quality challenges**

Standard vaccine development



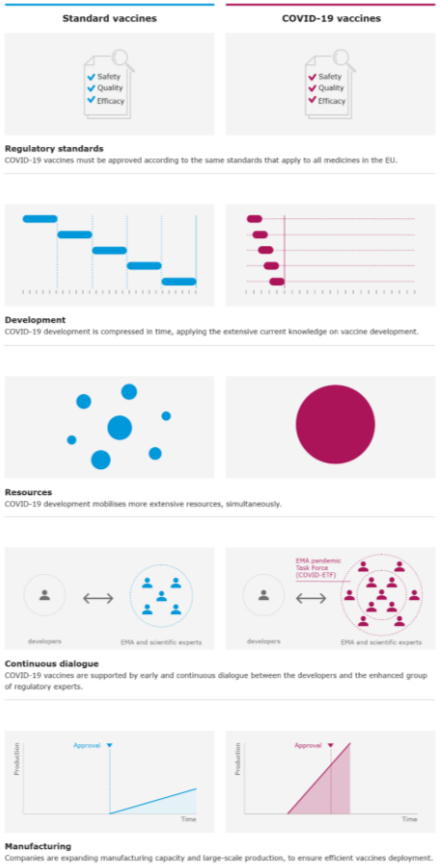
Fast-track development in a public health emergency context



Regulatory standards will be maintained

- **Same legal requirements** for pharmaceutical quality, safety and efficacy as other medicines in the EU
  - subject to **scientific evaluation**

- Speed of development and approval is **much faster** 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
  - **combinin**g clinical trial phases or conducting some **studies** in parallel, instead of carrying them out sequentially - where safe to do so.



See EMA website for details

Transparency for COVID-19 medicines vs standard practice

Comparison with standard transparency

Regulatory procedure	Standard practice	COVID-19 medicines
Scientific advice (new)	No information published	List of medicines that have received scientific advice or guidance from COVID-ETF published
Compassionate use opinion	Published in Compassionate use after CHMP opinion	News announcement published within 1 day of CHMP opinion
Start of rolling review	Not applicable	News announcement published within 1 day of start of review
Marketing authorisation application	Active substance and therapeutic area listed in Medicines under evaluation	News announcement published within 1 day of application
Product information	Published in all EU languages with EPAR	Published (in English) within 1 day of positive CHMP opinion; published in other EU languages with EPAR
Publication of European public assessment report (EPAR)	Published at least 2 weeks after marketing authorisation	Published within 3 days of marketing authorisation
Risk management plan (RMP)	Summary of RMP published	Full RMP published
Clinical trial data	Publication suspended until further notice	Published on Clinical data website after marketing authorisation
Application for extension of indication	Not announced	News announcement published within 1 day of application

See EMA website for details

Company-authority interactions prior to MAA submission

EMA Pandemic Task Force (ETF) requests data from & pro-actively engages developers in preliminary discussions

ETF considers rapid Scientific Advice (SA) requests, supported by relevant working parties e.g. BWP for biologics quality

Once evidence of proof of concept is agreed by ETF, rapporteurs can be nominated for a potential Rolling Review (RR)

Rapporteur engagement–presubmission/ ETF agrees on level of evidence sufficient to start RR

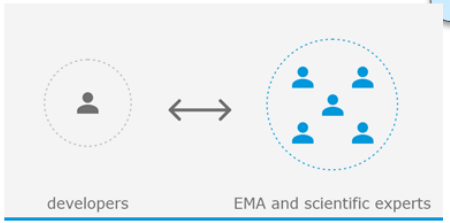
Rapporteurs review RR submissions, to be reviewed and ultimately agreed by ETF and CHMP

At certain point, ETF/CHMP agrees on readiness of package for MAA

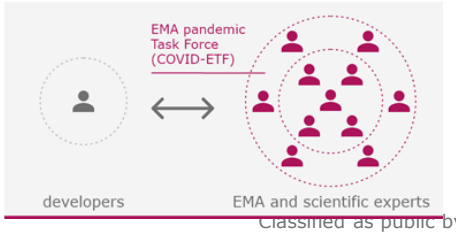
Continuous dialogue

COVID-19 vaccine development is supported by early, continuous dialogue between developers and a dedicated group of regulatory experts (ETF).

Standard vaccines



COVID-19 vaccines



Company/ Authority Interactions during MAA

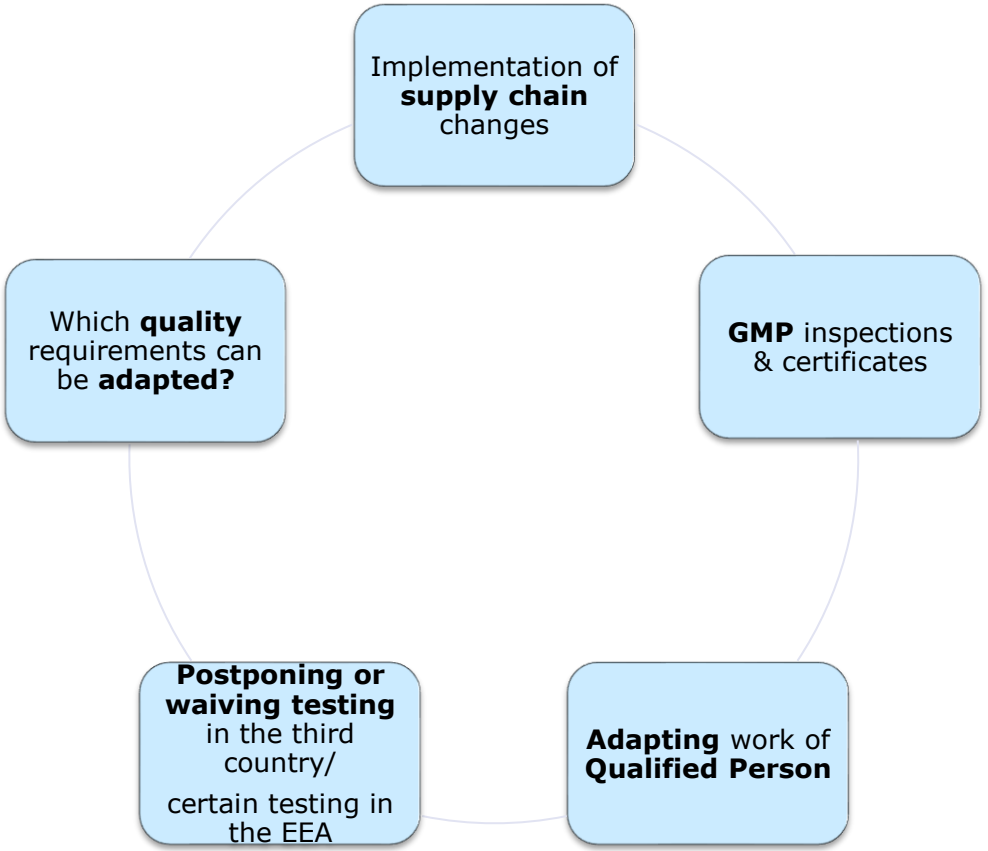
Continuous dialogue
Expect continuous dialogue, enhanced (EMA/ETF/CHMP) from usual interactions throughout MAA

EU regulatory flexibilities and EMA procedures for the crisis

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

EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines

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



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

2.1 Changes in the manufacturing/supply chain

Exceptional change management process (ECMP)- crucial medicines for COVID-19 patients-

√ Swift changes to suppliers and/or manufacturing/control sites necessary to reduce risks of shortages under certain conditions, while deferring the full assessment of the variation.

X line extensions/ deviations from the Marketing Authorisation (MA)/other GMP changes/other changes to the dossier

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

2.2. GMP certificates, authorisations, inspections

✓ GMP authorisation validity (all products) (manufacture/importation) can be extended

EEA & non-EEA sites- Automatic extension, Distant inspection/ postpone on-site inspection

2.5 Adaptations to the work of the QP

✓ Remote batch certification/ Remote audits etc.

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

3.1. Adapting quality requirements for medicines intended for treatment of COVID-19 patients

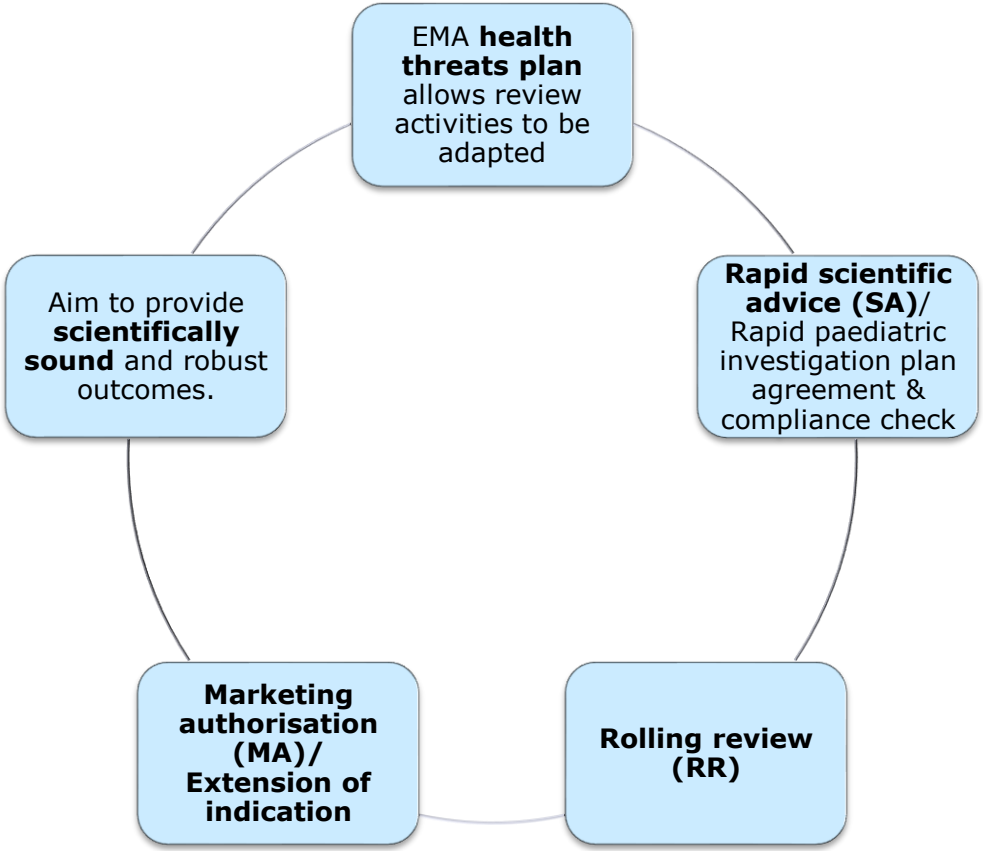
✓ …present an adapted control scheme based on a risk-based approach. This request should be submitted as a variation.

6. Temporary flexibilities to address imminent market shortage of imported medicines, crucial for treatment of COVID-19 patients.

✓ Postponing or waiving the testing in the third country

✓ Postponing certain testing in the EEA?

EMA initiatives for acceleration of development support & evaluation procedures for COVID-19 treatments & vaccines



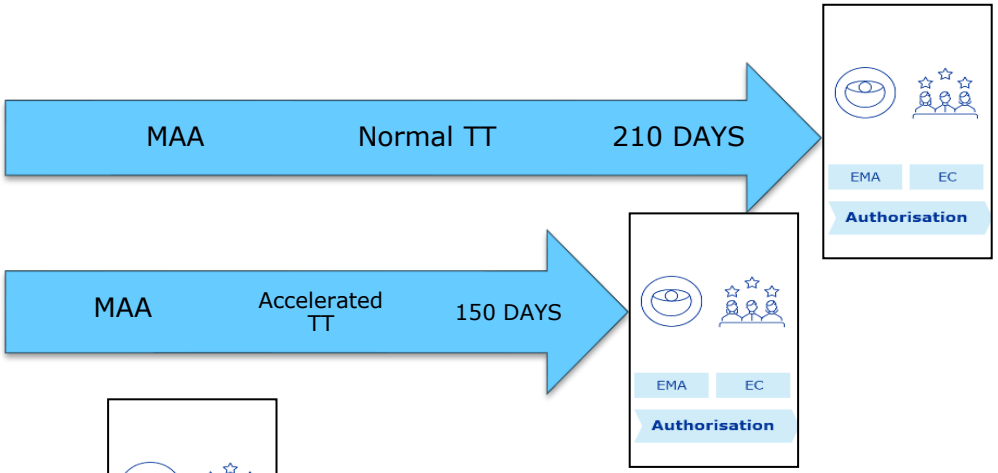
Rapid Scientific Advice

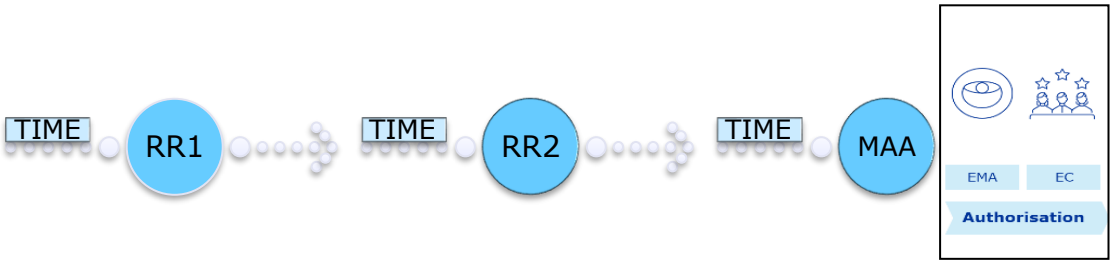
- **Ad hoc procedure** follows general principles SA, adapted to allow acceleration. Regular SA also available.
- **Flexibility** on **type & extent of briefing dossier** & **submission deadlines**
- This scientific advice is **free of charge** (EMA Decision (EMA/134143/2020).
- Total **review time** from start to final letter reduced to **20 days (could be shorter)**, compared to usual 40/70 days (acceleration of all milestones).
- Advice involves **ETF** - still adopted by **CHMP**

Rolling Review

- **Ad hoc crisis** procedure prior to MAA/ LE (indication)
- Discrete data sets, usually **2 week cycle,** involves **ETF,** still **CHMP adopted**
- **MAA review** within RR → RR **pre-agrees** on **all** dossier parts
- Each RR: **eCTD data** + **Application form** + **M2** + **responses to cumulative LoQ** from previous rounds
- Each RR will have **AR** and interim **opinion**
- Approx. **half MAA fee payable upon first RR** submission (amount **deductible from** the **future MAA** from same applicant)

Rolling Review Path- earlier to market





- See example timelines: AREPANRIX & VEKLURY

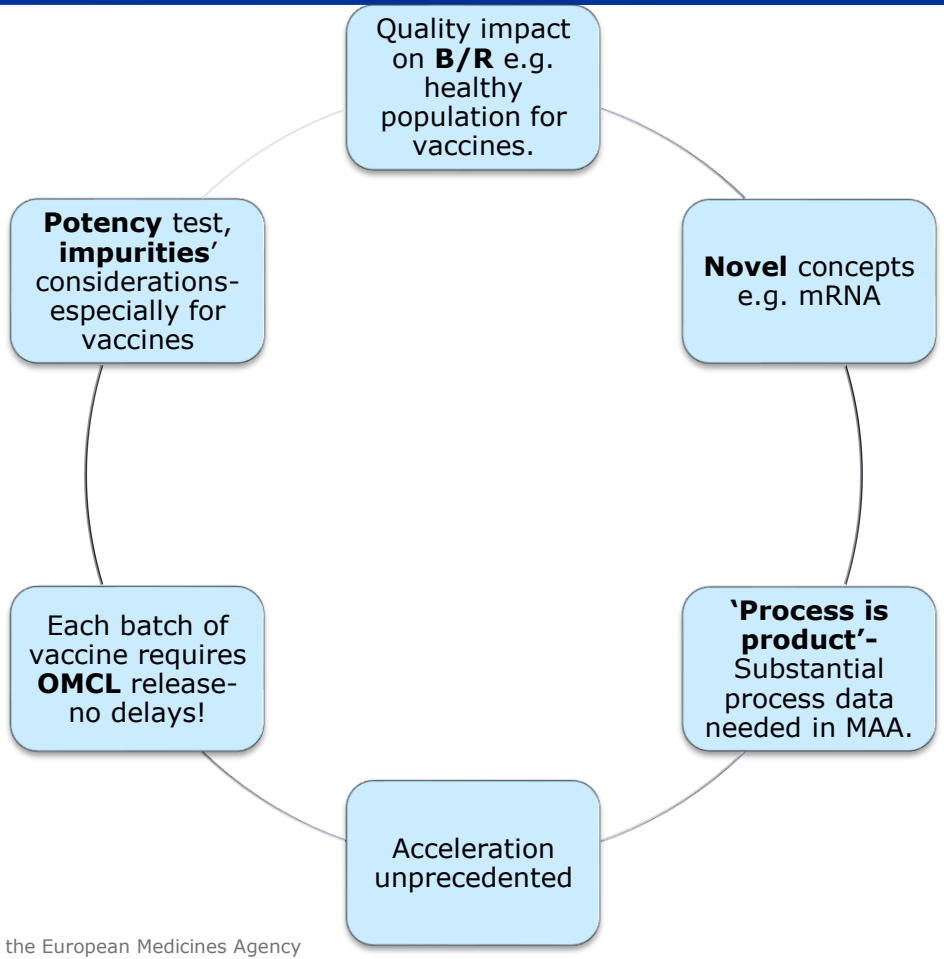
Other Regulatory approaches for COVID-19 medicinal products

- EMA is ready to apply **further flexibility** as needed
- EMA will substantially **accelerate linguistic review** processes. Labelling flexibilities being discussed now for vaccines.
- EMA will keep the EC informed → help **speed up authorisation** decisions
- **PRIME** scheme (predominantly suitable for treatments and vaccines in **earlier stages of development**) available
- **Conditional marketing authorisation** procedure
- **Compassionate use** programmes.

Conditional MA

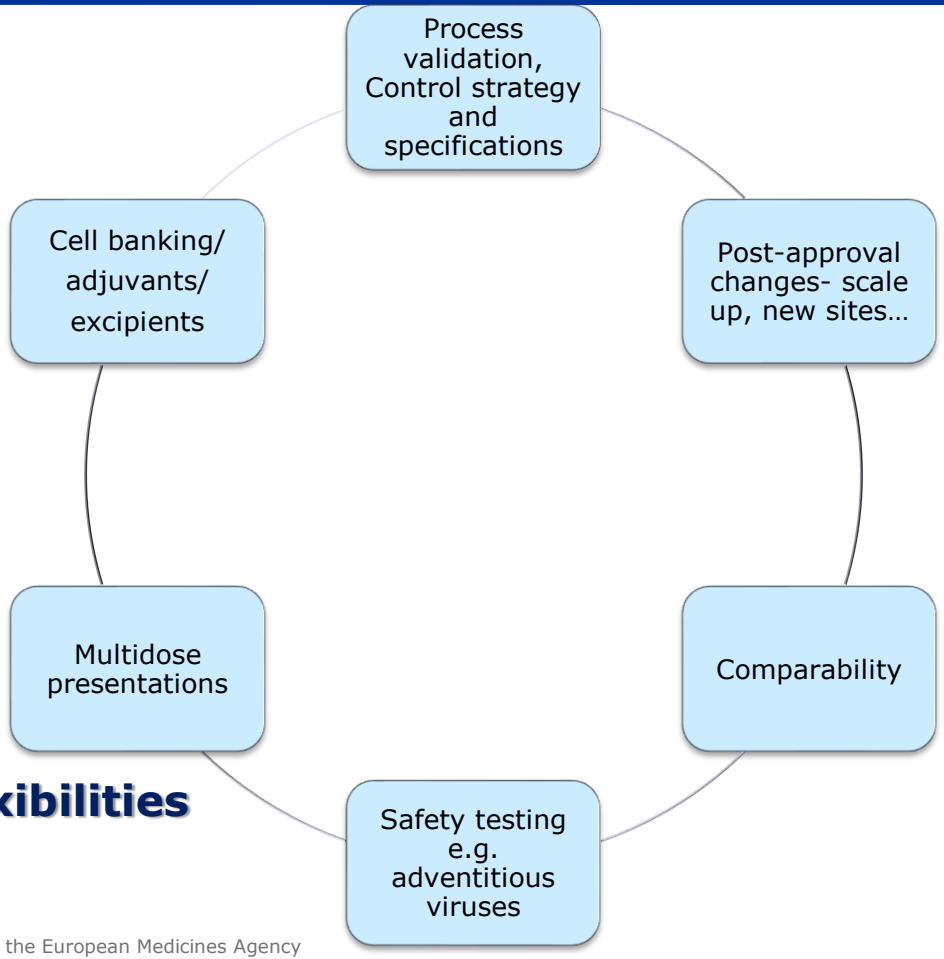
- May be granted if CHMP finds all the following are met:
  - the **benefit-risk balance** of the product is **positive**;
  - it is **likely** that the applicant will be able to **provide comprehensive data**;
  - **unmet medical needs** will be fulfilled;
  - the **benefit to public health** of the medicinal product's immediate availability on the market **outweighs the risks** due to need for further data.
- Can be **granted** on **quality grounds** in an emergency

COVID-19 biologicals - quality challenges



We must be able to ensure that quality standards are not compromised

Quality scientific flexibilities to consider? *



*Build on outcomes from previous workshops –

- Workshop with stakeholders on support to quality development in early access approaches
- Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications

…fine balance in granting flexibilities in view of urgency without compromising quality

Quality scientific flexibilities to consider on a case by case basis

Cell banking

- Stably transfected **non-clonal cells** acceptable for early CT? Change to clonal MCB.
- **Comparability** in line with Q5E expected.
- Use **MCB for production** in early development ? Then 2-tier system

Adjuvants/ Excipients

- General guidelines apply
  Flexibility on data package based on excipients (nature, manufacturing process & function).
- **SA** with authorities to agree on **data** to be submitted recommended.
- **No cross-reference** to existing MA

Quality scientific flexibilities to consider on a case by case basis

Process Validation

Concurrent validation?

Prior knowledge

Acceptance: relevance of supporting data, interim data

Well-defined protocol (tests and AC)

Early inspections dialogue

Safety testing (Adv agents)

PCR tests / NGS methods to be used?

Consider **equivalence** & **validation**

Consider drawing up list of relevant viruses.

Post Approval Change Management Protocols (PACMP)

Quality scientific flexibilities to consider on a case by case basis

- **Scale up-** Where sufficient process evaluation/ prior knowledge- use of PACMPs?
- **New QC testing site-** For non-bio methods already accepted- use for bio/immunochemical method?
- **Process Validation data-** To accept post-approval PV data/ de-constrain comprehensive strategy for limited process data?

Quality scientific flexibilities to consider on a case by case basis

Comparability

- **Risk-based** approach for data requirements-based on prior knowledge/process understanding
- **Specific Obligations** for CMA possible (See Ervebo) / RECs depending on situation

Stability

Quality scientific flexibilities to consider on a case by case basis

- Shorter initial **shelf-lives**? Product to be used rapidly?
- **Predictive stability models** (prior knowledge of structurally similar molecules) in absence of RT data?
- **Post-approval commitments** to continuously update RT results
- **Stressed data** to support claims-showing trends

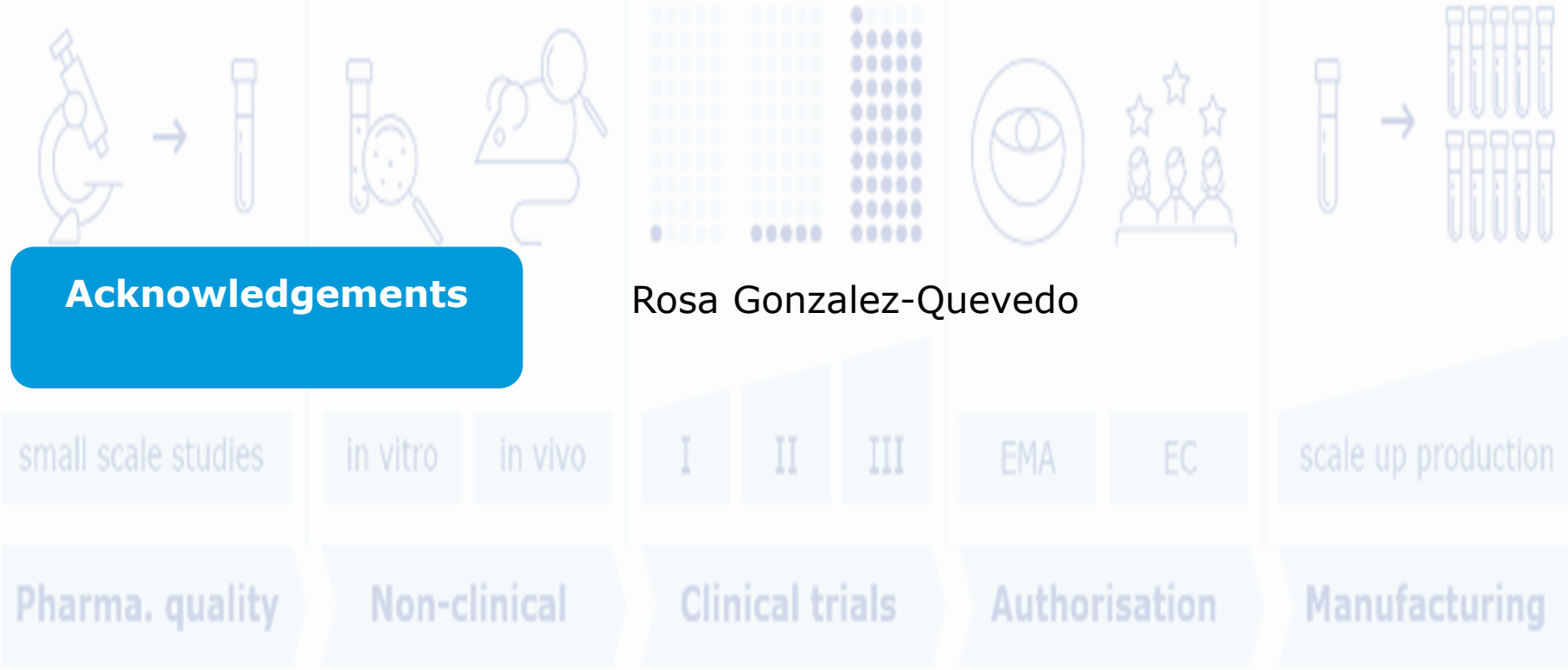
Multi-dose presentation

Quality scientific flexibilities to consider on a case by case basis

- **Preservative not required** if in-use time short.
- **In-use stability studies-** stability-indicating attributes, homogeneity, adsorption?, particle formation, multiple withdrawals etc.
- 10 doses max usually approved- **special considerations for much larger** unit presentations: filling validation, homogeneity, compatibility, stability, risks of microbial contamination?

Conclusions

- Quality flexibilities may be granted in context of **benefit/risk** & the **strength of supporting information**
- **Prior knowledge/ platform data** could be used
- A **risk assessment** can ensure whether additional measures are required to mitigate potential risks in the interim
- Based on the assessment, CHMP will conclude on whether **full MA/ CMA** is appropriate
- Data submission can be delayed - **quality data** still deemed **outstanding** must be fulfilled **post-approval**



Acknowledgements

Rosa Gonzalez-Quevedo

Any questions?

Further information: ragini.shivji@ema.europa.eu

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**