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Regulatory approaches for accelerated development in Europe

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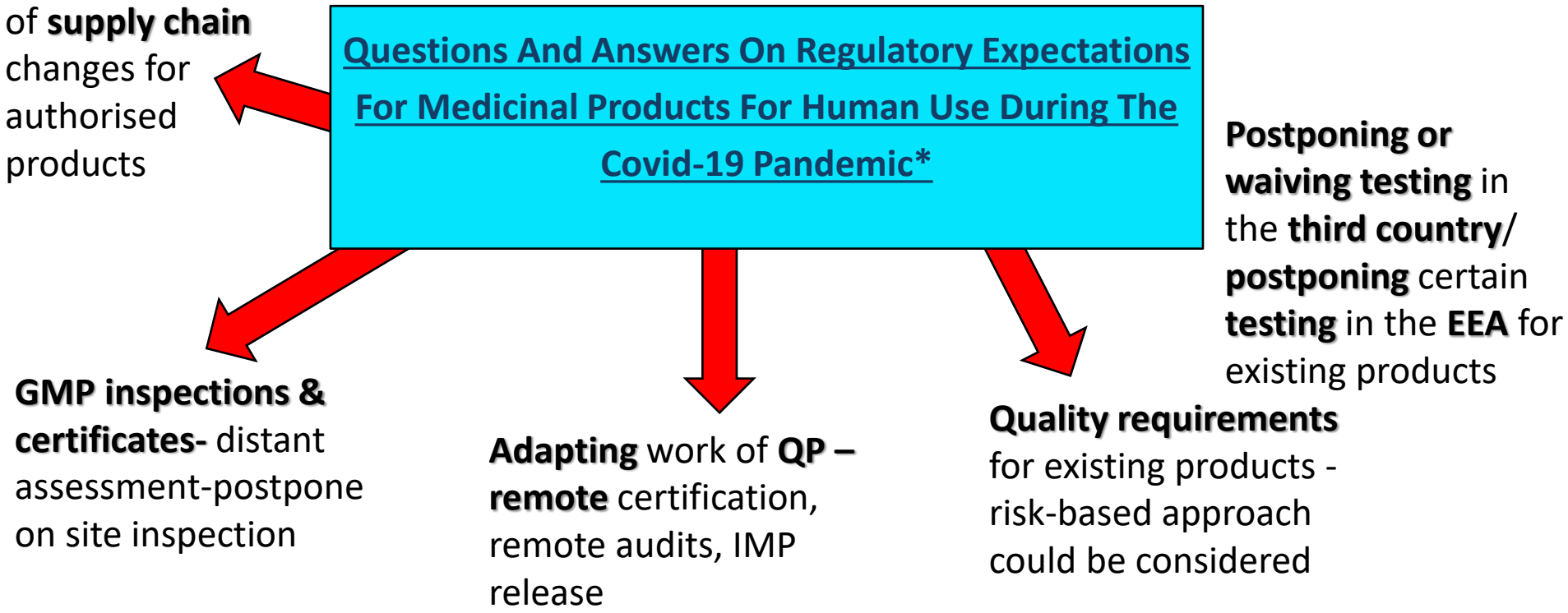
EU landscape in relation to accelerated procedures

- 27 Member states involved in decision making
- Several options for approval
  - Centralised procedure
  - Decentralised procedure/ Mutual recognition procedure
  - National applications
- Centralised procedure handled by EMA. Decisions on new applications taken by CHMP
- Multiple bodies involved
  - CHMP subgroups (Biologics WP, Vaccine WP etc)
  - European Commission
  - CMDh

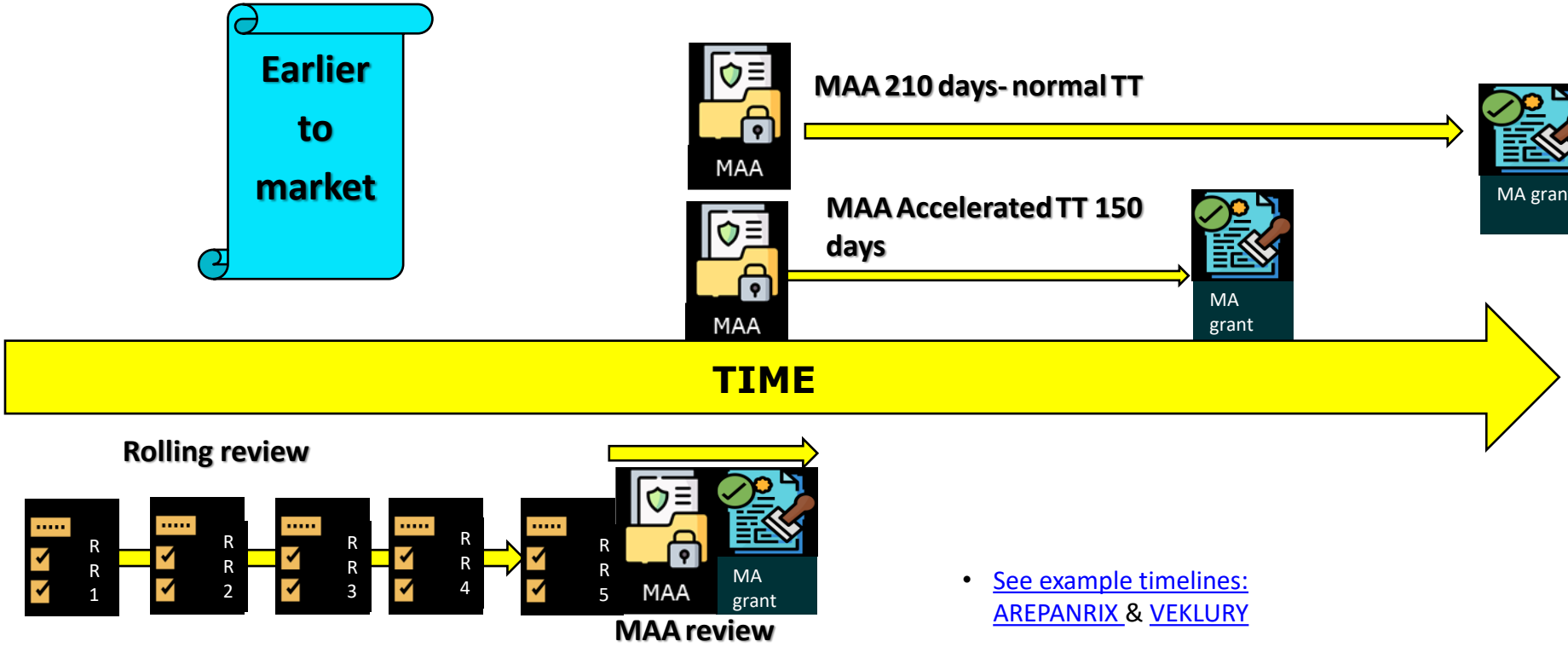
PRIME: Priority medicines

- A sceme launched by EMA to enhance support for the development of mediciens that target an unmet medical need
- Enhanced interaction
- Scientific advice
  - Early dialogue and scientific advice to speed up the approval
- Approval through accelerated assessment
  - Covid 19 medicinal products Ultra accelerated.



* See document for restrictions for all scenarios.

Rolling review for COVID-19 MAAs



- See example timelines: AREPANRIX & VEKLURY

Conditional Marketing Authorisation (CMA)

- 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

Basics

- **Devolopment time significantly shortened compared to standard products**
  - Less validation data available
  - Less product understanding (criticality/ acceptable ranges etc)
  - Few batches produced in total
  - Even fewer batches in clinical trials
- **New concepts (e.g. mRNA/ DNA vaccines)**
  - Relevant tests?

- **More uncertainties but products are still expected to be safe and efficacious (and to have a positive benefit/ risk ratio). Control strategy will differ to assure this.**

Control Strategy Expectations

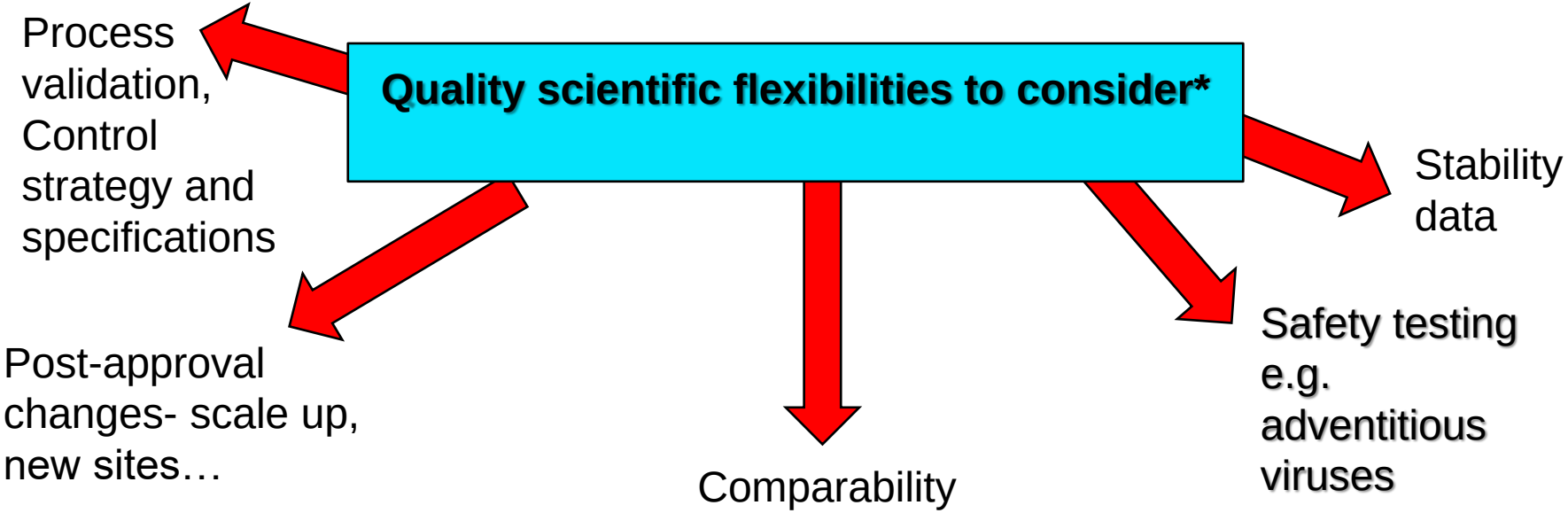
- **Applicant should address residual risks of control strategy and can include consideration for in-process testing, lot release, stability, comparability, monitoring, control of raw and starting materials, etc**
- **Potentially more attributes, process parameters, and assays in the application control strategy. The control strategy can be revised when more knowledge is gained.**
    - **e.g. capacity of purification process to remove impurities as shown in validations or batch testing, updated criticality assessment showing less criticality for certain attributes**

Use of prior knowledge

- Prior knowledge of quality attributes and processes can be used to support control strategy flexibility, including acceptance criteria and process parameter ranges outside of manufacturing and clinical experience.
  - ✓ Need to be shown applicable for product in question.
  - ✓ Include data in file where it replaces product specific data
  - ✓ Could allow postponement of certain studies post approval or replace product specific data.

Risk assessment considerations

- Difference in intended patient categories between vaccines (healthy people, many) and biotherapeutics (often severely ill people with unmet medical needs, fewer) → difference in risk assessment.
- Differences in posology- single/ few injections vs life long treatment.
- Novel concepts and techniques → limited experience
  - No DNA or RNA vaccines yet approved
  - New delivery systems
  - Certain new analytical concepts to be introduced for the 1st time



*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

Tools

Area & need for flexibility	Available tools/ scientific principles to consider
Cell banking	• Stably transfected non-clonal cells may be acceptable for early clinical trials. Change as soon as possible to clonal MCB. Comparability in line with Q5E expected. • OK to start production from a MCB but early development of a 2-tier system is recommended due to expected high demand
Adjuvants	• General guideline apply. Flexibility on the data package to be provided should be possible based on the excipients used. SA with authorities to agree on data to be submitted recommended.

Tools

Area & need for flexibility	Available tools/ scientific principles to consider
Process validation	• Concurrent validation? • Prior knowledge • Acceptance: relevance of supporting data, interim data. • Well-defined protocol (tests and AC) • Early inspections dialogue

Tools

Area & need for flexibility	Available tools/ scientific principles to consider
Flexible use of PACMPs	• To accept post-approval PV data • To introduce new sites/scale-up • Allow protocol adaptation within existing reg. framework
Comparability	• Risk-based approach for data requirements-based on prior knowledge/process understanding • Specific Obligations for CMA possible (See Ervebo) / RECs depending on situation

Tools

Area & need for flexibility	Available tools/ scientific principles to consider
Multi dose / “ In use stability”	• Multi dose without preservative can be accepted if in-use time is sufficiently short to avoid risk of contamination. • In use stability studies important in particular for vaccines which contain an adjuvant after extemporaneous dispensing. Stability indicating attributes + reconstitution conditions, homogeneity of the vaccine, potential adsorption to the container, particle formation, antigen-adjuvant chemical/physical interaction, multiple withdrawal of doses in case of multi-dose preparations within a vaccination session (several hours/days), and preservative efficacy in case a preservative is used.

Tools

Area & need for flexibility	Available tools/ scientific principles to consider
Stability	• Shorter initial shelf-lives - product to be used rapidly? • Predictive stability models • Stressed data to support claims? • Extrapolation of data from different presentations? • Post-approval commitments to continuously update RT results
Safety testing (Adv. Agents)	• PCR tests or NGS methods to be used? Consider equivalence & validation • Virus to be tested based on risk assessment

Aspects of specification setting

Reality:

- Few batches produced in total, even fewer in clinical trials ⟹ results not representing normal variability
- Transfer to new sites including upscale for commercialization
- Risk for OOS if these ranges are used for setting of acceptance criteria
- More attributes tested

Key Question

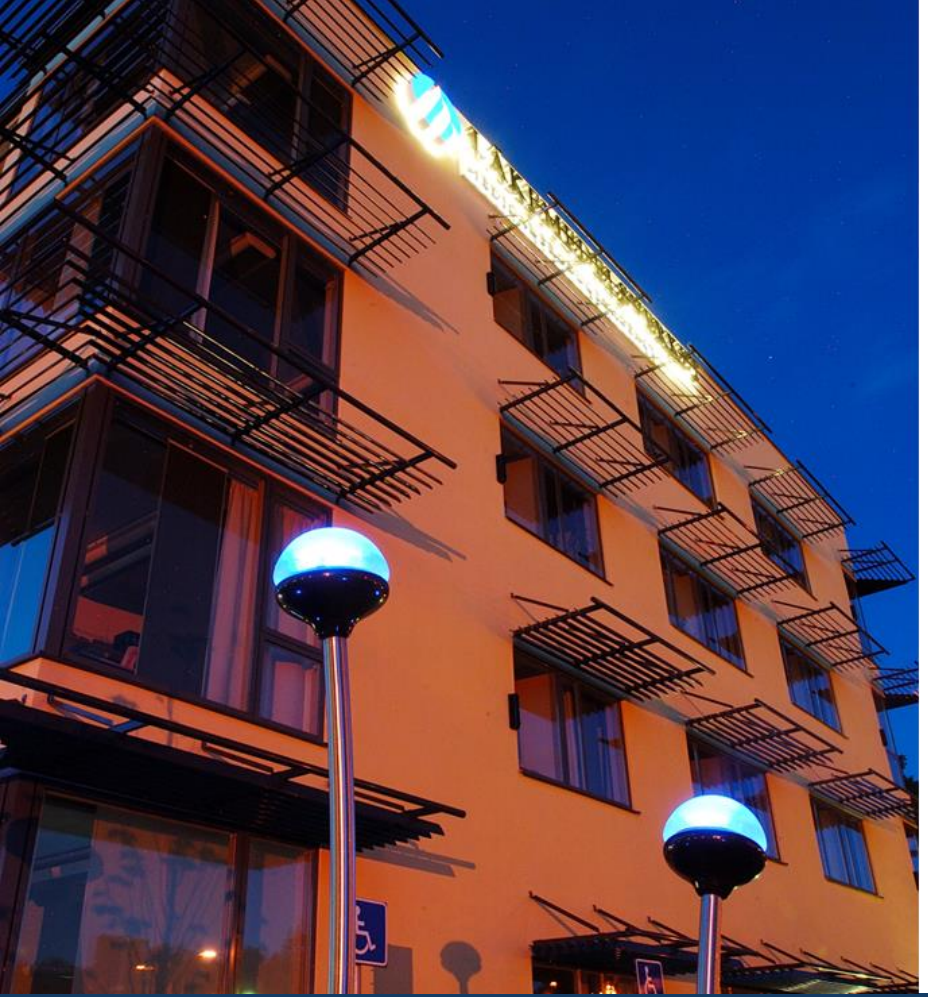
- Wider acceptance criteria than seen in production would need to be proposed but how to justify these as the products should consistently be safe and efficacious and the limits are beyond what has been seen in clinical studies?

Possible way out

- Prior knowledge and the ability to link it to the product in question will be fundamental.
- Small scale & QbD to establish criticality of attributes. May impact set of tests included and limits
- *In vitro* data & Dose finding studies can help
- Safety justification?
- Agreement needed on how the limits will be revised over time (e.g. PACMPs at prespecified timepoints)
- Stability models based on platform understanding may be used to assign release requirements to assure acceptable levels at the end of shelf life.

Conclusions- Quality flexibilities- how might they be agreed?

- CHMP will decide if **full MA/ Conditioned MA**
- Quality flexibilities will be considered 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
- Data submission can be delayed - **quality data** still deemed **outstanding** must be fulfilled **post-approval**



Thank you!