AstraZeneca

# Efficiency Toolbox - CMC Lessons Learned from COVID

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# Content

"Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need" EMA/CHMP/BWP/QWP/IWG/694114/2019

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# The Speed of the Operation

- WHO estimate 15 million people have died from COVID-19 (May 2022)
- Vaccines provided hope and successfully limited further deaths from COVID-19
  - 2020: development and initial registration activities for the vaccine
  - 2021:  additional initial registration activities and global distribution and administration
  - 2022:  continued distribution, life cycle management and post-approval changes

- Regulatory flexibility provided by some Agencies based on benefit:risk, but not universal

# The Scale of the Operation

## Licence Approvals

- Vaxzevria is approved in 92 markets (June 2022)
  - AZ MAH: 62 countries
  - Sub-licencing to four partners: 37 countries
- WHO managed supply via COVAX scheme: ~180 countries
  - Six WHO Emergency Use Listings (EUL) for supply chains for EU, CA, JP, SK, MX and AU
- Government donations totaling >250million doses
  - Often requiring new supply chain registration in the receiving country with very short turnaround times

## Complex supply chains

- Multiple manufacturing sites geographically dispersed
  - Challenges with logistics, customs, and international shipping.
  - Short product shelf life - initially 6 months at 2-8°C
- For EU:
  - Added 8 new manufacturing sites
  - Added 9 testing labs, as well as method updates
  - Inspections required for new sites (Virtual during pandemic)
- 200 plus active stability studies to support the supply chain

## Life Cycle Management

- Frequent updates to raw materials, reference standards, viral seeds, and cell banks
- New stopper and vials frequently needed as shortages were common also for single use ready to use components for filling and cell culture/purification
- Post approval changes, 2021
  - Submissions - 340
  - Approvals - 279
- Post approval changes, 2022 – June 2022
  - Submissions - 187
  - Approvals - 178

# Much Trade Association Activity Pre and During COVID Pandemic…and will continue

- EFPIA paper on potential acceleration CMC approaches, published 2022 https://pubmed.ncbi.nlm.nih.gov/36168002/
- EFPIA White Paper on CMC development, manufacture and supply of pandemic COVID-19 therapies and vaccines 2020
- WHO/VE/IFPMA positions established:
  - 9 Position papers issued and communicated to Manufacturing SWAT/COVAX RAG (status as of February 2022);
  - Note: see https://epi.tghn.org/covax-overview/manufacturing/ for the list of COVAX workshops (including minutes and presentations)
- EMA / FDA Stakeholder workshop 2018, in conjunction with EFPIA and PhRMA, on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough

# Risk Assessments: Commercialisation of Pre-Validation Batches

- *"…risk assessment is a systematic science-based process of organising information to support a risk decision to be made within a risk management process"*
- Pre-PPQ (pre-validation) batches were made immediately prior to the PPQ (validation) batches; Pre-PPQ vs PPQ
  - Same site
  - Same equipment
  - Same scale
  - Same testing
- Pre-PPQ batches not under a validation protocol, and were released after meeting set criteria

- Conclusion:
  - Every dose counts; Agencies accepted that Pre-PPQ batches could be commercialised

# Concurrent Process Validation

- *"Concurrent validation…carried out in exceptional circumstances, justified on the basis of a strong benefit-risk balance for the patient, where the validation protocol is executed concurrently with commercialisation of the validation batches"*
- Typically full validation studies are expected to be submitted for vaccine MAAs
  - Protocols were submitted
  - Partial data sets provided, e.g. full data for two out of three batches, and partial data for third.
  - Post-approval commitments to provide full data sets
  - Supported with the global manufacturing / validation experience from multiple sites

- Conclusion: This approach was successfully used for most MAA's.

# Exceptional Change Management Process (ECMP's)

- Process was specific to EU/EMA, and not applied by other Agencies
- Available for the following changes:
  - Changes in the manufacturing and/or control sites.
  - Changes in suppliers of starting materials, reagents, intermediates or active substances.
- Process
  - Notify EMA in advance
  - Two working day Assessment of the change within 2 working days
  - Notify Agency within 48 hrs of implementation
  - Submit variation within 6 months


- Conclusion:  Process not used by AZ
  - No real advantage seen over PACMP's which received accelerated reviews for data review/implementation
  - International Agencies "rely" on approval letter for implementation

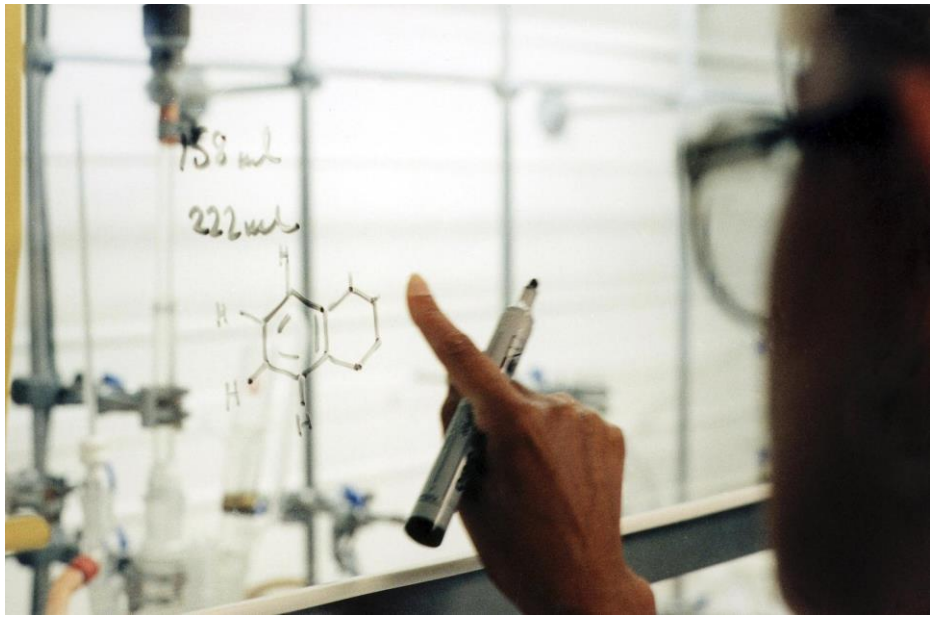
# Scientific Advice Meetings

- *"EMA seeks to support the medicine development process from an early stage and to offer regulatory mechanisms to help promising new medicines reach patients as early as possible, without compromising their quality, safety and efficacy. In this context, procedures are already available to establish an early dialogue with regulators and support prospective planning"*
- During the peak of regulatory activity, AstraZeneca had regular meetings with the EMA to help with planned submissions (rolling reviews) for the MAA and post-approval changes; questions were answered and alignment was sought for adopted strategies.

- Conclusion:
  - An invaluable meeting to ensure expedited review and approval of the Quality component of the registration. Without these meetings, there would have been a delay to approval.
  - Ensured that CMC registrations aspects kept in pace with the anticipated approval.

# Prior Knowledge - Stability

- *"Based on scientific justification, which may include prior knowledge and/or data from development/pilot scale batches of the same formulation, it may be possible to submit less data than described in ICH guidelines"*
- Requested six months shelf life at time of approval
  - Real time data normally used to help support the shelf life for biologicals
  - Waiting for real time data is not compatible with the global need to register and distribute the vaccines
  - Development data (including Pre-PPQ stability data) / data from other sites used to help support the shelf life proposal



- Conclusion:  Proposals were widely accepted

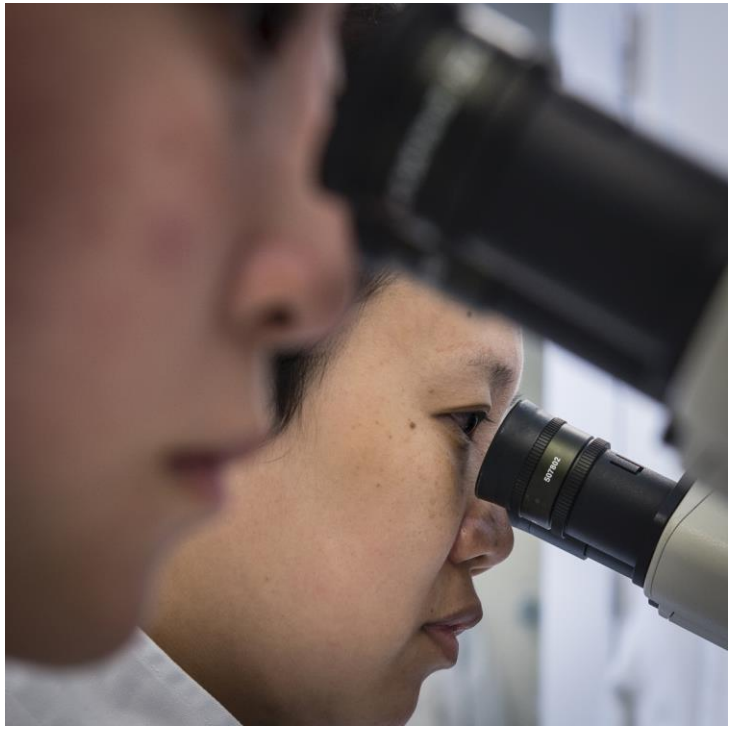
# DS and DP Manufacturing Sites – PACMP's

- *"…early assessment of the strategy to be pursued, thereby lowering the reporting category of the implementing variation, which in turn reduces the regulatory review and implementation time."*
- Needed to meet manufacturing capacity for 3 billion people globally and as soon as safely possible.
- Manufacturing Sites
  - Approx 30 DS and DP sites used to manufacture the vaccine globally
  - Essentially same process / test methods applied across all drug substance and drug product manufacturing sites with differences in scale and availability of equipment
  - All coming online at different times
- PACMP's
  - Included in MAA's / EUA's; used to help accelerate approvals
  - Only accepted in a number of countries, however requested approval of site additions within 30 days

- Conclusion:
  - Although not globally accepted, extensive use of PACMP's where allowed which facilitated approval of multiple sites
  - Continue to advocate for global acceptability of harmonised approach to PACMP's

# Global Post-Approval Measures

- *"…in certain cases, some data generation to support approval may be on-going at the time of MA assessment (e.g. stability, process validation studies)…"*
- While the pandemic enabled speed to patient, all requirements must be met resulting in a large number of post approval measures generated from both initial marketing applications as well as post approval variations:
  - Post approval quality measures were made in almost every market.
  - Resulting in 137 submissions for global quality post approval measures in 2021 and 2022 (through June)



- Conclusion: A useful approach that was pre-agreed with Agencies which allows regulators to provide reassurance on public health

# Reliance - WHO Registrations

- Regulatory Authority of Record (RAR), e.g. EMA, identified and agreed between RAR and WHO
- One Emergency Use Listing (EUL) for each RAR
  - Six EUL's managed for Vaxzevria to support registration of different supply chains
- Submitted dossier to RAR first
  - Submissions to WHO were made in parallel or sequentially to the RAR
  - All post-approval changes submitted sequentially
- Full reliance from WHO for the RAR approvals
  - No questions received from WHO pre-approval (mostly reviewed and approved within weeks)
  - Sometimes questions received at time of approval (post-approval commitments or points of clarification); it did not delay distribution

- WHO managed reliance with ~180 countries; supply managed under COVAX
- Conclusion:  Excellent collaboration and partnership with WHO to enable patient access to the vaccine in low to middle income countries.

# Conclusions – Toolbox for Expedited Regulatory Activity

- ✔ Risk Assessments - Commercialisation of Pre-Validation Batches
- ✔ Concurrent Process Validation
- ✔ Exceptional Change Management Process (ECMP)
- ✔ Scientific Advice Meetings
- ✔ Prior Knowledge - Stability
- ✔ DS and DP Manufacturing Site Additions - Post-Approval Change Management Protocols (PACMP's)
- ✔ Global Post-Approval Measures
- ✔ Reliance / Collaborative Assessments
- ✔ Trade Associations

- ✖ Exceptional Change Management Process (ECMP)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