ICMRA-Industry Virtual Workshop on Enabling Manufacturing Capacity in the COVID-19 Pandemic

Wednesday, July 7, 2021

ICMRA Chair Welcome

Emer Cooke, EMA and Chair ICMRA

Industry perspective

Greg Perry, IFPMA

Regulatory flexibilities to support the rapid increase in manufacturing capacity for COVID-19 therapeutics & vaccines

ICMRA-Industry Manufacturing Capacity Workshop
7 July 2021

Seán Barry (HPRA) and Evdokia Korakianiti (EMA)

- The current pandemic has necessitated significant acceleration to normal development timelines → companies have identified vaccine candidates, run clinical trials and received regulatory approval in under 12 months
- This accelerated development has been crucial to timely vaccination roll outs and significant efforts have been made by regulators to implement regulatory flexibilities and new ways of working
- A survey of regulators was carried out to determine which regulatory tools and flexibilities are being most commonly used

Mechanisms offered by Regulatory Authorities for expedited assessment

		Yes	No	Maybe
Organisational & regulatory flexibilities	Establishment of quick, frequent and continuous engagement with manufacturers	100%		
	Rolling submissions or other expedited regulatory actions	91%		9%
	Providing guidelines to clarify regulatory expectations on how assessment will be prioritized during the pandemic	100%		
	Dedicated resources to handle the extensive lifecycle management	73%	18%	9%
	Comparability protocols or post-approval change management	91%		9%
	Approval of post-approval changes in the absence of full data (with certain data provided at a later date)	100%		
Information sharing	Reliance on assessment carried out by other regulators or participation in joint assessment programmes	100%		
	Sharing of assessments between regulatory authorities from other regions	91%	9%	
	Full or partial reliance on assessment reports of regulatory authorities from other regions	64%	27%	9%
	Participation in joint assessment programmes	73%	27%	

Flexible approaches to CMC data requirements				
		Yes	**No**	**Maybe**
Method validation	Risk based approach (e.g., platform validation of methods for biologics	100%		
Process Qualification/ validation	For drugs, reduced data package based on risk	100%		
	For biologics & vaccines, leveraging of platform data and prior knowledge, concurrent validation, decoupling DS and DP validation, and/or continuous process verification	100%		
	Limited process qualification based on risk	100%		
Control Strategies	Interim specifications	100%		
	Alternative in process controls	100%		
Adventitious agents	Leveraging of platform knowledge to reduce viral clearance studies	91%	9%	
Stability	Alternatives to establishing a shelf life based only on real-time data	82%		18%

Regulatory tools for facility assessment in lieu of inspection			
	Yes	**No**	**Maybe**
Desk-based review of documents requested from the facility	100%		
Review of inspection reports by other agencies via a Mutual Recognition Agreement or Confidentiality Agreements	91%	9%	
Remote interactive assessment or Distant Assessments	100%		

Approaches to expedite CMC changes			
	Yes	**No**	**Maybe**
Concurrent Process Validation & Post approval commitment (additional information to be submitted after approval)	100%		
Grouped supplements	81%	9%	9%
Derogations to labelling requirements as a result of CMC changes	100%		

Take home message from the survey

- ✓ The majority of agencies have adopted the use of regulatory flexibilities for Covid-19 products
- ✓ Rolling submissions and frequent engagement with regulators are a common feature
- ✓ Multiple regulatory and scientific tools are being used
- ✓ In general, agencies can approve in the absence of certain data, with data provided post-approval
- ✓ There is already sharing of information between regulatory agencies, however reliance on assessment reports from other agencies or joint assessment is somewhat less common → this is an area for future exploration.

Regulatory flexibilities used to support approval of Covid products

Regulatory tools/work practices

- Rolling reviews
- Emergency authorisations
- Conditional authorisations
- Continuous communication
- Remote inspections
- Sharing of inspection reports
- PACMPs

Scientific tools

- Alternative process validation approaches
  - Concurrent validation
  - Decoupling DS & DP PPQ
- Prior knowledge/Platform
- Predicted shelf life
- Comparability protocols
- Interim specifications
- Submission of data post-approval

Post approval lifecycle management

Expected to be significant post-approval lifecycle activity for Covid-19 products

Example - number of post-approval changes (PACs) for Covid-19 vaccines approved in the EU

Product	Number of PACs (grouped)	Individual PACs
Comirnaty	35	108
Spikevax	18	68
Vaxzevria	18	26
COVID-19 Vaccine Janssen	8	14

Rapid assessment times for variations for Covid-19 products (EMA example)

	Standard variation	Covid variation
Type II variation	60 days	10 days
Type 1b e.g. to implement a PACMP	30 days	7 days

- One of the biggest challenges to increasing supply is the introduction of multiple new manufacturing sites post-approval
- The same change must be approved by multiple regulatory authorities
- Ensuring regulatory compliance in multiple regions while rapidly expanding the supply chain is a challenge that is recognised by regulators
- There is scope for further collaboration between regulators on the implementation of global post-approval changes

Example 1- COVID vaccine- PPQ/PV* comparability & stability approach

Scientific data

Manufacturing experience- > Submit extensive data

- Batch release and in process data, characterisation; range of sites (inc. commercial); PPQ /pre-PPQ lots (incl. GMP grade)

Good process evaluation & control strategy,

- Incl. extensive in-process controls/process parameters monitoring (even non-critical parameters until validation complete)

Extrapolation of stability data

- Based on comparability, accelerated condition, real-time stability data from similar process product

Benefit achieved

Accelerated approval of the initial authorisation

- Concurrent validation for commercial manufacturing process
- Extrapolated FP shelf-life

- **Rapid approval of new sites post approval**
  - 3 AS and 1 FP sites - 15 QC sites

Regulatory tools used

•**Rapid SA** sought on strategy/ follow-up meetings

•**Specific Obligations (SO)** : At CMA, accepted sites with reduced PPQ- with ongoing (monthly) PPQ/ PV data post approval

•**Post-Approval Change Management Protocols in MAA** to introduce new AS & FP sites

- **Accelerated Assessment Timelines**:

10 days or lower for Type II vs standard min 60 days usually longer up to several months is Insp is needed

7days or lower for Type IB vs standard min 30 days

•**Distant assessments** for assuring GMP compliance

•**EEA QC testing exemptions** acceptance of non EEA testing till method transfer

•**Weekly interactions** on supply plans

* PPQ- Process performance qualification/ PV- process validation

Learnings

- Alternative approaches and flexibilities in data submissions have been used extensively for all authorized COVD vaccines

- Extent of **regulatory flexibilities** subject to **product / process knowledge & site readiness.**

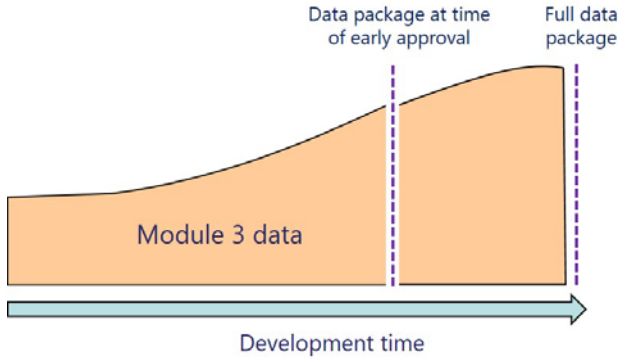
- **Early** and **transparent interaction** with Regulators highly recommended;

- **Distant assessments** useful alternative means of verifying GMP compliance

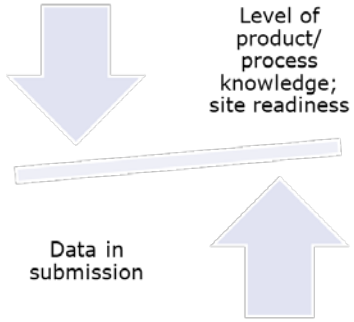
- **Expedited** reviews/ distant assessments exacerbate network **workload**

- **Clear prioritisation** of changes based on supply impact is needed

Regulatory flexibilities and early approval do not represent a reduction in standards → rather the **timing of data submission is changed**



The more process knowledge demonstrated → the higher the flexibility in data requirements



- Regulatory flexibility requires an appropriate supporting data package
- Uncertainties and risks due to incomplete data at time of approval need to be appropriately mitigated by e.g.:
  - Demonstrated manufacturing experience
  - Platform approaches
  - Prior knowledge
  - Sufficient characterisation
  - Demonstrated product understanding
  - Appropriate control strategy

What regulators would like to know from industry

- Of the changes introduced what has worked well?
- What tools do you consider to be the most useful?
- Which changes were less effective?
- What future changes should be prioritised?
- What are the major challenges foreseen over the next 12 months?
- Where are the regulatory bottlenecks?

Conclusion

- Regulators have responded rapidly to enable appropriate early access
- Risk-based regulatory agility has been a strong feature during the pandemic
- There are a suite of tools available to expedite the approval of CMC changes
- Future regulatory collaboration and harmonisation will allow for a more efficient and effective response to a global public health emergency

Industry Presentation: “Science and Risk-based Approaches to Enable the Rapid Increase of Manufacturing Capacity for COVID-19 Therapeutics and Vaccines”

Connie Langer, Pfizer (presenting on behalf of Industry)

Science- and Risk-based Approaches to Enable the Rapid Increase of Manufacturing Capacity for COVID-19 Therapeutics and Vaccines

Presentation by Connie Langer, Director, Global CMC, Pfizer

On behalf of: ABPI, BIO, DCVMN, EFPIA, IFPMA, IGBA, JPMA, Medicines Australia, PHRMA, Vaccines Europe

Introduction

- **Impact to Supply Chain** – COVID-19 created unprecedented strain on the global biopharmaceutical supply chain – raw materials suppliers, manufacturers, wholesalers, distributors

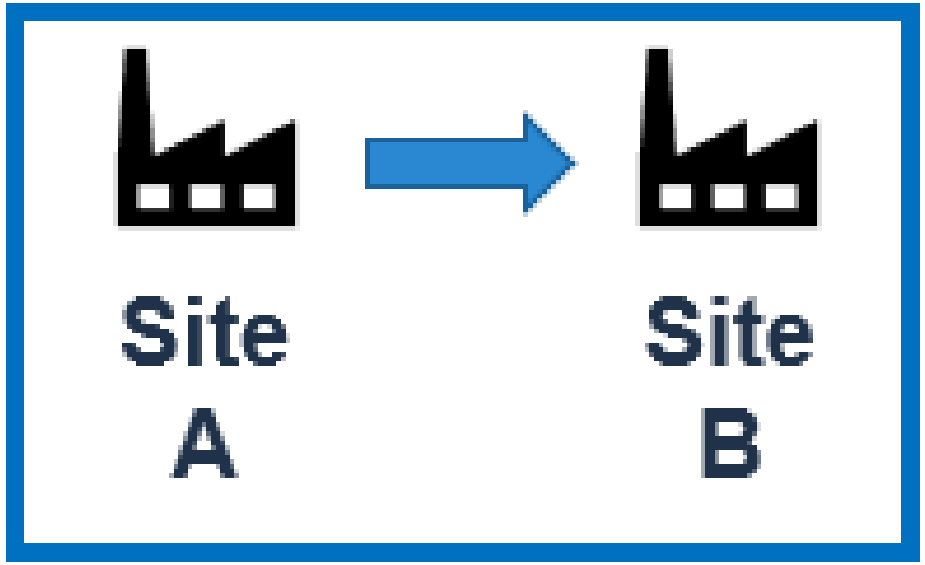
- **Need for Greater Regulatory Agility** – Greater regulatory agility is needed to allow manufacturers to make risk-appropriate changes to facilities and manufacturing processes to ensure that an adequate supply of quality medicines and vaccines can reach patients

- **Post-approval* Site Transfers** – One of the common strategies manufacturers will use to increase manufacturing capacity is the post-approval transfer of a product to additional manufacturing facilities, but the steps to execute a post-approval site transfer can present regulatory bottlenecks

*In this presentation, "post-approval" also refers to "post-authorization" such as in the context of therapeutics and vaccines that have been granted Emergency Use Authorization (EUA) or Conditional Market Authorization.

Challenges with Post-Approval Site Transfers Conducted to Increase Manufacturing Capacity

- **Data generation** – Process validation, analytical method validation, real-time stability studies, and comparability testing are all resource intensive activities
  - Many NRAs currently require submission of all this data in the supplement/variation before the NRA can/will review the filing
  - The traditional model often results in significant delays as many NRAs are unfamiliar and uncomfortable with science- and risk-based approaches to streamline these activities



Transfer from Site A (Sending Site) to Site B (Receiving Site)

Challenges with Post-Approval Site Transfers Conducted to Increase Manufacturing Capacity, *continued*

- **Dossier preparation** – supplements/variations must be prepared for each market
  - Because of the different data requirements for each NRA, additional studies may have to be conducted for certain markets. Consequently, and due to resource limitations, manufacturers will prepare the supplements/variations on a rolling basis.
  - Divergent data requirements add substantial lead time to the post-approval site transfer process and significantly increase regulatory burden on manufacturers
- **Dossier submission** – Once supplements/variations are submitted, manufacturers receive and sometimes must respond to a number of queries from NRAs regarding each submission
  - There is no harmonized or streamlined process for submitting queries to manufacturers, so applicants must often respond to multiple requests per NRA. This adds significant regulatory burden and can delay the overall post-approval site transfer process.

Pfizer Data on Query Volume and Variability Across Regions

Board of Health Queries

QUERIES										
NCE 1	16	19/122	49	27	15	21	39	56	43	36
NCE 2	12	23/29	38	18	21	11	29	32	47	39
NCE 3	17	36/21	52	26	16	17	33	29	35	23
NCE 4	15	18/63	53	21	19	8	46	19	30	21
NCE 5	48	18/120		28	25	28			25	
NCE 6	9	12/164	37							
Combo 1		12/234								
Combo 2		23/157								
NBE 1	55	69/84	123	44	41	41	64	32	58	38
NBE 2	47	53/67	108	32	46	37	79	78	66	43
Vx	116	111/146	167	48	53	42	82	63	97	54

Rapporteur/Co-Rapporteur

Total Volume of Queries 2012 - 2018 for New Product Applications

Identical CMC content for all regional applications

- Accelerated Application
- New Application Accompanied by CPP w/Updated MAA
- Applications for Conventional Small Molecule Products
- Applications for Small Molecule Combination Products
- Applications for Antibody Drug Conjugates
- Applications for Vaccine Products

Less than ~20% of queries from individual regulatory authorities were the same

Challenges with Post-Approval Site Transfers Conducted to Increase Manufacturing Capacity, *continued*

- **Pre-approval Inspections** – For site changes or additions, many NRAs will require that the "receiving site" (i.e., Site B) undergo a pre-approval inspection (PAI) before the supplement/variation can be approved
  - COVID-19-related travel inspections have limited NRAs' abilities to conduct on-site inspections
  - NRAs have adopted varying approaches to remote/virtual facility assessments
    - NRAs' utilization of varying approaches with respect to "alternative tools" has impacted reliance practices leading to an inspection backlog
  - Alternative tools (e.g., document/records requests, virtual inspections) can be more resource intensive than on-site inspections

Additional Challenges that Impede the Rapid Increase of Manufacturing Capacity

- Equipment compatibility issues between sites may require manufacturing process modifications
- Transferring in-process and release testing, sample management, lab capacity
- Raw materials supply constraints (e.g., lipids for mRNA vaccines)
- Expedited raw materials supplier qualifications for new suppliers especially for critical items (e.g., product contact filters, resins, container closure materials)
- Workforce
  - Readiness – hiring, training, etc.
  - Experience in process and analytical procedures
- Updating Standard Operating Procedures (SOPs) as appropriate
- Import Testing
- Pandemic-related travel restrictions for employees (e.g., subject matter experts) as well as key vendors

Questionnaire Results – Industry's Top Priorities

The following **regulatory mechanisms** and **flexible CMC approaches** were identified as being **critical to success** to rapidly increase manufacturing capacity for COVID-19 therapeutics and vaccines and accelerate patient access to these products –

- Establishment of quick, frequent, and continuous communications/engagement with manufacturers to discuss their requests and provide regulatory recommendations and advice
  - Important for the NRA representatives communicating with manufacturers to have decision-making authority
- Full or partial reliance on assessment reports of regulatory authorities from other regions
  - This mechanism can and will enable rapid approval and implementation of post-approval changes (PACs), reduce the complexity and regulatory burden associated with lifecycle management, and promote convergence of regulatory requirements and expectations
- Acceptance of alternate process qualification/validation approaches, such as leveraging of platform data and prior knowledge, concurrent validation, decoupling DS and DP validation, and/or continuous process verification
  - In addition to the acceptance of alternate approaches, shifting regulatory evaluation of process validation data to inspections/facility assessments can further expedite post-approval site transfers and create resources efficiencies for regulators and manufacturers
- Approval of post-approval changes in the absence of full data (with certain data provided at a later date)
  - For activities with long lead times (e.g., stability testing, process validation), the ability to provide this data at a later date can result in substantially faster development timelines as well as enable expedited regulatory approvals

Priority Recommendations to NRAs – Science- and Risk-based Approaches to Enable the Rapid Increase of Manufacturing Capacity for COVID-19 Therapeutics and Vaccines

- **Streamline Stability Testing Requirements** –
  - Reduce the timelines for real-time stability testing; focus testing on stability-related quality attributes (or, if well understood, shelf-life limiting attributes), allow for the submission of non-site-specific data, and increase the acceptance of both accelerated stability testing and predictive stability modeling for biopharmaceutical products
- **Embrace Alternate Process Validation Approaches** –
  - More consistently allow manufacturers to utilize alternate process validation approaches for biopharmaceutical products, such as decoupling DS and DP validation activities, concurrent validation, and appropriately leveraging prior knowledge to defer the submission of certain process validation data to post-approval

Priority Recommendations to NRAs – Science- and Risk-based Approaches to Enable the Rapid Increase of Manufacturing Capacity for COVID-19 Therapeutics and Vaccines, *continued*

- **Increase Utilization of and Harmonize Approaches to Inspection Alternatives**
  - Begin conducting voluntary "virtual inspections" with the consent of the inspected manufacturer
  - Streamline processes, share lessons learned with other NRAs as well as industry, and align with other NRAs on best practices
- **Enhance Collaborative Review & Reliance Practices**
  - Develop and/or expand existing reliance practices for inspections of facilities manufacturing COVID-19 therapeutics and vaccines
  - Expand reliance practices to include on-site inspection alternatives (e.g., virtual inspections)
  - Adopt reliance practices for NRA-issued queries and associated manufacturer responses for supplements/variations
  - Establish collaborative review arrangements, similar to ACCESS and Project Orbis, for the review of supplements/variations for PACs of COVID-19 therapeutics and vaccines, as well as for non-COVID-19 products impacted by the pandemic
  - Reduce the need for duplicative import and release testing

ICMRA
International Coalition of Medicines Regulatory Authorities

Thank You

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Discussion

Moderated by Emer Cooke, EMA
and Theresa Mullin, FDA

Panelists:

- Sean Barry, HPRA, and Evdokia Korakianiti, EMA
- Connie Langer, Pfizer

ICMRA-Industry Workshop: Enabling Manufacturing Capacity in the COVID-19 Pandemic

Regulatory Case Studies

07 July 2021

Case Study # 1 - FDA

Technical Transfer Request for Commercial Products

Stelios C. Tsinontides, Ph.D.

Description

- Request for site changes for commercial product to create capacity for COVID Therapeutics
- Request for type C meeting covering multiple products with rapid turn around

Challenges & Accomplishments

- Expedited assessment timeline
- Level of engagement & effort was very resource intensive
- Concurrent validation; In some cases, narrowing requests to allow for downgrading of a supplement
- Use of 704(a)(4) for multiple manufacturing suites
- Approved 6 PAS supplements with 14 to 35-day timelines
- A later follow up inspection verified the 704(a)(4) conclusions

Engagement with Sponsor

- Within a week of request held meeting w/ Sponsor
- During the key timeframe, there were standing weekly meetings with sponsor with updates on multiple related submissions
- The sponsor provided a timeline for planned submissions and requested assessment dates based on demonstrated supply needs
- Ensured scope of submission focused on immediate supply needs

Learnings/Recommendations

- Clarity on detail and format of supply chain needs
- Clarity on the level of detail necessary for expedited assessments
- Approaches to prioritize requests based on public health impact as this level of effort would not be sustainable across a large number of products
- Approach to verify expedited capacity was actually used for COVID 19 Therapeutics

Case Study # 2 - ANVISA

Change in Primary Packaging

Dr. Raphael Sanches Pereira

ANVISA
Brazilian Health Regulatory Agency

ANVISA
Brazilian Health Regulatory Agency

Description

- Change from Amber glass to Transparent glass Vial
- Amber glass shortage (Oct/2020)
- OTI-related product
- 10x increase in demand in 5 months
- Necessary to avoid product shortage

Challenges & Accomplishments

- Product relatively photolabile
- Previous data showed dubious photostability with secondary packing protection
- Difficult to trust photostability in secondary packaging because there are boxes with too many vials (50 to 100 vials in a box)
- Approval was achieved after risk mitigation measures (special alert, less vials in box)

Engagement with Sponsor

- Understanding mechanism of photodegradation (zero-order? First order?) - ASAP
- “Scalated” photostability study (different intensity of light)
- Labelling alert
- Shelf life reduction (limited stability data)
- Limitation to specific site

Learnings/Recommendations

- Supporting data and previous knowledge leverages flexibility on post-approval changes
- Dependence of one supplier (API, excipients, packaging material) represents an important risk
- PAC’s should be considered as opportunities rather than demand.
- Flexibility on PAC’s is an important sanitary measure

Case Study # 3 - Health Canada

Vaccine, new manufacturing DS facility

Dr. Maria Baca-Estrada

Health Canada

Description

- Vaccine, new manufacturing DS facility
- Amendment, to address Canadian supply chain and vaccine delivery
- Limited DS facility information available; decision deadlines and manufacturing concerns arose contemporaneously; expedited review required

Challenges & Accomplishments

- Extremely tight timelines & very resource intensive
- Intersection of regulatory decisions vs perceived risk by the public
- Different countries had different benefit/risk context due to vaccine supply and disease prevalence
- Lack of harmonization of product specifications across jurisdictions, additional evaluation had to be conducted

Engagement with the Sponsor

- Lack of transparency regarding critical manufacturing deviations (e.g. contamination)
- Deviations noted as an asterisk without explanation
- Learned of other major manufacturing concerns via third party
- Requested information and a meeting post-authorization

Learnings/Recommendations

- Timely communication & transparency with sponsor
- Importance of communication and support among regulatory authorities
  - Harmonization of specifications
- Regulatory decisions based on national benefit/risk context
- Clearly defined supply chains can aid in focused utilization of resources

Case Study # 4 – EMA

Adding manufacturing and testing sites
&
introducing manufacturing changes and new equipment

Evdokia Korakianiti, PhD

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Description

- **Prior knowledge from other products using same platform** [incl Ebola vaccine] : e.g.Process design, and control strategy, Formulation development, Shelf -life
- **Process validation and comparability strategy evaluated** with well-defined and controlled CPPs and CQAs
- **Site readiness:** prior manufacturing experience with the same or similar products; GMP compliance considered; OMCLs timely identified
- Initial MAA: included prior knowledge data, full PV and PPQ from 3 batches; **3 PACMPs**

Challenges & Accomplishments

- **Rapid addition of 3 FP sites within less than 1 week from submission** compared to a minimum standard > 60 days
  - Site approval with CoA from 1st PPQ lot based on prior knowledge and PACMP; PPQ and PV completed post approval
- 1 site required GMP inspection; normal turn around time > 3 m, but completed in <1 wk using **distant assessment** prior to variation submission
- Sites for **WHO COVAX program** were also included to allow 3rd countries reliance on EU GMP certificates

Engagement with Sponsor

- **Sci. advice on PV and comparability** strategy
- **Rolling review of CMC data for the MA. Submission of data as they become available**
- **Regular interactions on supply chain plans** pre- and post approval
- Use of Exceptional Change Management Protocols (ECMPs) to transfer QC tests rapidly

Learnings/Recommendations

- Use and extent of regulatory flexibilities is subject to the product/process knowledge and site readiness.
- Use of platform technologies and sites with manufacturing experience on the same type of products
- Early and transparent interaction with Regulators
- Expedited reviews and distant assessments put a strain on Network workload; clear prioritization of changes is needed

Industry Case Studies

Matt Popkin, GSK, Boris Zimmermann, Genentech/Roche, and Graham Cook, Pfizer

Industry Presentation #2 – Case Studies

Case Study 1 – ***Comparability Approaches for a Monoclonal Antibody Treatment for Mild-to-Moderate COVID-19 in High-risk Adults***

Case Study 2 – ***Stability and Shelf-life Modeling for a COVID-19 Monoclonal Antibody "Cocktail"***

Case Study 3 – ***COVID-19 Vaccine Development & Commercialization***

Case Study 1 –

Comparability Approaches for a Monoclonal Antibody Treatment for Mild-to-Moderate COVID-19 in High-risk Adults

Matt Popkin, Sr. Director, CMC Excellence, GSK

Comparability is on the critical path – multiple changes (post-pivotal clinical trial and post-approval) to drug substance manufacture are required to secure supply.

There is a clear need for **science- and risk-based approaches** to rapidly enable changes to cell lines, introduce new manufacturing sites and scales, and execute the requisite analytical testing to satisfy regulatory expectations.

For example –

- Changes could be implemented following protocols, commitments.
- Batch analysis at the drug substance level would form the basis of establishing comparability.
- Supporting stability testing (if required, on the basis of risk assessment) could be conducted on drug substance instead of drug product.

	Clinical and EUA Supply	BLA and Early Commercial Supply	Long-term Commercial Supply
Cell Source	Non clonal	Monoclonal MCB	New WCB
Manufacturer	CMO 1	CMO 1	CMO 2
Scale	2000L	12000L	15000L
Equipment	Single Use System	Single Use System	Stainless Steel
Country	3rd country A	3rd country A	3rd country B
Potency Testing	Binding ELISA for potency	Cell-based bioassay	Cell-based bioassay

Analytical testing is also a significant concern –

- Wasteful importation testing sites in both EU and US, due to limits of EU/US MRA.
- Significant time and resource to conduct tech transfer/validate multiple methods at multiple sites.
    - Amplified where methods are new and additional testing has been put into place for EUA pre-marketing application.
- Implementation of a cell-based bioassay for potency could be deferred to a post- approval commitment.

Case Study 2 –

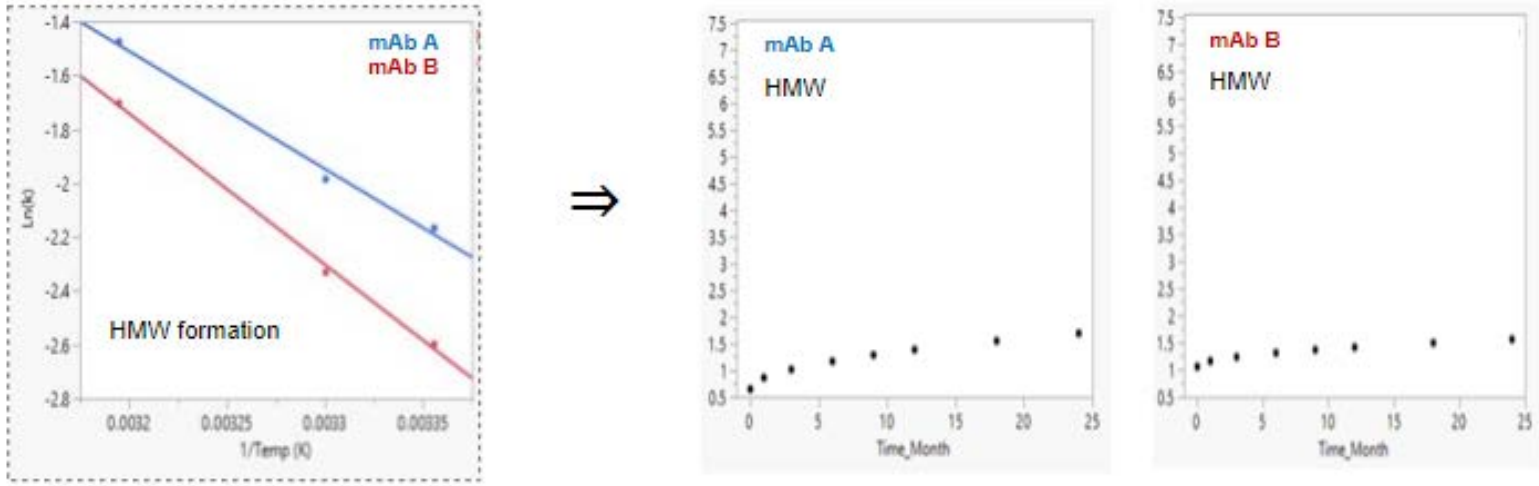
Stability and Shelf-life Modeling for a COVID-19 Monoclonal Antibody "Cocktail"

Boris Zimmermann, Head of Product Analytical Science, Global Quality Control, Genentech/Roche

Accelerating CMC stability for COVID-19 monoclonal antibody 'cocktail' through the use of prior knowledge and risk-based modeling – *Motivation*

- COVID-19 emergency highlighted the need for new/different stability and shelf-life approaches for biotherapeutics (e.g., monoclonal antibodies) beyond ICH Q1 series and Q5C
- Pre-pandemic situation:
  - (Prior) Knowledge- and risk-based approaches are commonly used to establish the control system of biotherapeutics
  - Stability and shelf-life for biologics expected to be based on long-term data at storage temperature (real-time data)
  - Statistical tools and well characterized stability behavior for MAbs established
- Pandemic situation: (very) limited R&D & representative stability data for specific project, real-time data just about to be started

Accelerating CMC stability for COVID-19 monoclonal antibody ‘cocktail’ through the use of prior knowledge and risk-based modeling – *Approach*



- Predicted shelf-life of 2 MAbs through modeling based on accelerated/stress stability data, extended characterization, and Arrhenius-Theory
- Stability data compared to similar MAbs (IgG1) and formulations
- Based on prior knowledge, significant progress has been made towards understanding temperature-dependence of MAb degradation for predicting stability/ shelf-life, including limitations
- Above: MAb A/B-High Molecular Weight (% HMW) aggregate formation modeling, 2-8ºC, 24 months (verification by real-time, long-term data ongoing)

Accelerating CMC stability for COVID-19 monoclonal antibody 'cocktail' through the use of prior knowledge and risk-based modeling – *Summary*

- Pandemic experience highlighted significant potential to accelerate CMC stability using predictive modeling for biologics (e.g., mAbs), noting that models used could differ based on knowledge:
  - Pre-Market
    - Formulation changes
    - Configuration/presentation changes
    - Accelerated launch; setting initial shelf-life
  - Post-Market
    - Shelf-life of post change material
    - Stability lifecycle management
- Several health authorities have accepted predictive shelf-life setting/modeling for COVID-19 mAb "cocktail" Emergency Use Authorizations (EUAs)
  - This has enabled faster patient access to this critical therapeutic

Case Study 3 –

COVID-19 Vaccine Development & Commercialization

Graham Cook, Sr. Director, Pfizer Global Supply – Quality Operations, Pfizer

COVID-19 Vaccine Development & Commercialization

Description of the Case

- In response to the recent COVID-19 pandemic, the urgency for rapid development, authorization/approval & sustainable launch of a vaccine required an adjustment of conventional paradigms.
  - Novel mRNA platform (first commercial product)
- The pharmaceutical industry & regulatory authorities globally, engaged in close & frequent interactions to ensure that a safe, effective & consistently reliable vaccine could be distributed & administered widely.
  - Weekly, sometime daily, conversations with regulators
  - Independent interactions with each agency not resource sustainable

Regulatory Challenges and Accomplishments

- Challenged by multiple global regulatory pathways (e.g., EUA and Conditional Market Authorization)
  - EUA pathway flexible (different regulatory expectations)
  - Some markets constrained by legal framework; industry challenged by rolling submission while still in development
  - Confirmation of manufacturing consistency and quality through post-authorization obligations and commitments
- The delivery of COVID-19 vaccines effectively achieved with the following paradigm shifts:
  - Single dossier for all markets – additional market-specific studies not conducted due to time limitations
  - Full transparency and a balance of flexibility in regulatory expectations and processes
  - Mutual, risk-based reliance among regulatory authorities globally

COVID-19 Vaccine Development & Commercialization

TECHNICAL CHALLENGES & ACCOMPLISHMENTS

- Parallel commercial process development while supplying product under EUA
  - Provisional specification criteria w/subsequent post-approval/authorization commitments
  - Develop and optimize manufacturing & analytics as process evolves
- Scale-up/adding manufacturing sites very challenging
  - Adding new raw material suppliers (e.g., from single supplier to 5 suppliers for one critical raw material)
  - Demonstrating consistent quality across multiple supplier sites while developing the process
  - Significant post-authorization/approval commitments
- Process validation approach
  - No validation or alternate validation approach
  - Only validate when the process is ready – decouple marketing application and validation

Learnings/Recommendations

- Learnings
  - Dialogue with the regulators is key to success
  - Single dossier for global markets appropriate for pandemic situation
- Recommendations
  - More consistently allow manufacturers to utilize alternate process validation approaches for biopharmaceutical products
  - Decoupling DS and DP validation activities, concurrent validation, appropriately leveraging prior knowledge to defer the submission of certain process validation data to post-approval
  - Harmonized global pathway for emergency use/conditional marketing authorization with a similar set of rules
  - Enhance collaborative review & reliance practices

ICMRA
International Coalition of Medicines Regulatory Authorities

Thank You

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Break

PANEL DISCUSSIONS

Panel 1 – Priority Regulatory Mechanisms and Flexible CMC Approaches Lessons Learned

Moderated by Sau "Larry" Lee, FDA

Panelists: Regulators	Panelists: Industry
Stelios Tsinontides, FDA	*Matt Popkin, GSK*
Karl Cogan, HPRA	*Boris Zimmermann, Genentech/Roche*
Raphael Sanches Pereira, ANVISA	*Graham Cook, Pfizer*
Maria Baca-Estrada, HC	*Connie Langer, Pfizer*

Panel 2 – Lifecycle Management – Tools, Challenges, and Key Learnings During the COVID-19 Pandemic

Moderated by Markus Goese, Roche (EFPIA)

Panelists: Regulators	Panelists: Industry
Evdokia Korakianiti, EMA	*Thierry Gastineau, Sanofi Pasteur (Vaccines Europe)*
*Patricia Aprea, ANMAT**	*Diane Wilkinson, Astra Zeneca (Vaccines Europe)*
Raphael Sanches Pereira, ANVISA	*Suresh Jadhav, Serum Institute of India Pvt. Ltd. (DCVMN)*
Maria Baca-Estrada, HC	
Mohammed A. AlMuteri, SFDA	

Panel 3 – Inspections, Alternative Tools, and Reliance Practices During the COVID-19 Pandemic

Moderated by Lorraine Nolan, HPRA

Panelists: Regulators	Panelists: Industry
Derek Smith, FDA	*Rajiv Desai, Lupin Ltd. (IGBA)*
Brendan Cuddy, EMA	*Steve Mendivil,* Amgen (*PhRMA)*
Mohammed Alaqeel, SFDA	*Caroline Bell, Kindeva Drug Delivery (PBOA)*
Paula Walker, MHRA	

Industry Concluding Remarks

David Jefferys, IFPMA

ICMRA Chair Concluding Remarks

Emer Cooke, EMA and Chair, ICMRA

THANK YOU FOR PARTICIPATING IN TODAY'S WORKSHOP

Additional Materials

Case Study # 5 - SwissMedic

To introduce a new fill & finish site for a Vaccine to increase Production Capacity

Panelist – TBC

Contacts: Name of Regulatory Expert(s)

- **Description of the Case:**
  - Request: The applicant informs the authorities on the planned submissions and provides information on the criticality of the timing (supply)
    - A post-approval Change Management Protocol (PACMP) is submitted as Type II Variation a couple of weeks in advance
    - Implementation of the New Manufacturing Site can then usually be accepted based on the PACMP and the data of PPQ batches within much shorter timelines
    - Extended characterization of the PPQ Batches can be performed at a later stage and data can be submitted as post-approval commitment

- **Challenges & Accomplishments**
  - Such kind of expedited assessment is acceptable only because of the urgency of the supply / high need in the current pandemic situation
  - This flexible approach is only possible in the current extraordinary pandemic situation, as the daily business and less urgent applications have to be postponed, which is a disadvantage for other companies (and possibly also for other patients)
  - Accomplishments: The time-critical CMC Changes of Covid Vaccines were all assessed and accepted very fast and supply for the Swiss population was not slowed down by Swissmedic despite the extensive amount of variations

- **Description of Engagement Between Regulatory Agency and Industry**
  - Actions/approaches adopted to address the request: Instead of sending a List of Questions, a less formal way interaction with the applicant has been encouraged. Regular information on planned submissions and their criticality; missing documents are asked for and received by email, and only integrated in a later eCTD Sequence
  - Missing information that is judged to be less critical for the quality can be submitted as post-approval commitments
  - As the variations are accepted based on less data than would usually be demanded, more post-approval commitments are made, and companies have consented to extensive comparability/characterization and stability studies

- **Learnings/Recommendations**
  - Recommendation for Industry: Inform the Agency in advance about the most important and time-critical post-approval Changes ahead, but inform also, when a CMC change is less important

Case Study # 6 - TGA

Priority review of post-approval changes to prescription medicines (chemical entities)

Panelist – TBC

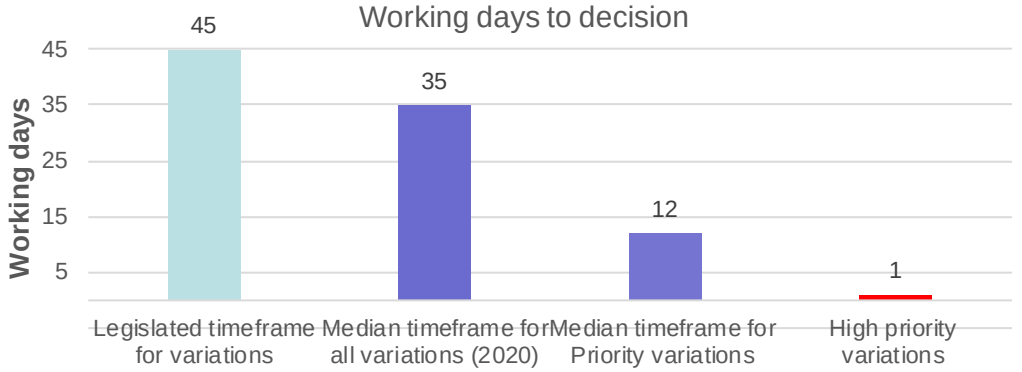
TGA - Priority review of post-approval changes to prescription medicines (chemical entities)

Contacts: Dr Jeremy Shonberg (Jeremy.Shonberg@health.gov.au)

- **Company can request CMC changes for chemical entities (API and drug products), including changes to manufacturing process and sites**
  - **Changes to COVID-19 related therapeutics, e.g. Remdesivir, Atracurium, Fluticasone, Hydroxychloroquine**
  - **Company uses online system to make application and provide relevant CMC data in eCTD format**

- **Informal mechanism for prioritising variation applications**
  - **Company can request priority review of application by phone, email and/or application cover letter**
  - **Priority due to COVID-19 requested for approximately 10% of variation applications**
  - **CMC area works closely with relevant post-market areas, including Medicine Shortages team, to prioritise applications based on clinical need**
  - **Minimal changes to data requirements provided by company, ensuring continued safety, quality and efficacy of goods**

- **Challenges & Accomplishments**



- **Learnings/Recommendations**
  - **Informal prioritisation of applications can be highly effective**
  - **Adaptability of regulatory personnel is critical to achieve rapid evaluation and decision**
  - **Safety, quality and efficacy of goods not compromised to achieve prioritised decisions**
  - **Prioritisation delays all other applications**

Case Study # 7 - SFDA

Addition of manufacturing site

Panelist – TBC

Saudi Food and Drug Authority / SFDA experiences related to post approval CMC changes to address manufacturing capability for COVID-19 therapeutics or vaccines

Contacts: Manal M. Turkistani mmturkistani@sfda.gov.sa and Abdulaziz A. Alsayyari AASayyari@sfda.gov.sa

- **Post-approval variation: Addition of manufacturing site**
  - **Expansion of Covid-19 vaccine production capacity**
  - **Sponsor will apply for variation (as part of rolling submission) through e-mail notification on the application of the post-approval change.**
  - **Data must be completed and submitted within 2-5 Months.**

- **Challenges**
  - **Delays or insufficient submission of essential CMC requirements such as process validation and comparability studies for the new manufacturing site.**
  - **Limited stability data for the batches manufactured at the new site.**
  - **Limited available information requires a Risk-based decision.**

- **Description of Engagement Between Regulatory Agency and Industry**
  - **Risk-based assessment of the proposed change.**
  - **Written inquires are sent to the sponsor.**
  - **Virtual meeting are held (if needed) between SFDA's quality and regulatory departments and the sponsor.**
  - **The assessment decision is sent by E-mail.**

- **Learnings/Recommendations**
  - **It is recommended to follow the ICH Q12 guidance to facilitate the approval process.**
  - **The high number of post approval variations calls for the need of a standardized regulatory guidance to accelerate the approval process and meet the expansion of Covid-19 therapeutics and vaccines production.**

Case Study # 8 - ANVISA

Inclusion of different manufacturing sites with manufacturing process changes

ANVISA
Brazilian Health Regulatory Agency

Anvisa/Post-Approval CMC Changes during COVID-19 – Multiple changes for vaccines

Contacts: Maria Fernanda Thees – Fernanda.thees@anvisa.gov.br

- **Description of the Case (the Ask by the Industry)**
  - **Inclusion of different manufacturing sites with manufacturing process changes for a vaccine critical component to increase the production and improve logistics.**
  - **Presentation in a meeting and formal submission of change**
  - **The changes needed to be approved in a 2 weeks deadline so there wouldn't be shortage of the vaccine.**

- **Challenges & Accomplishments**
  - **To review the applications in a timely manner so that the vaccine could be sent to Brazil.**

- **Description of Engagement Between Regulatory Agency and Industry**
  - **Pre-submission meeting for discussion and orientation on how to present the data and documentation**
  - **Actions/approaches adopted to address the request: sharing of documents before the submission, prioritization of the review, reliance and post-approval commitments.**

- **Learnings/Recommendations**
  - **Reliance in other authorities' assessments/decision is being key to a fast approval.**
  - **Some kind of guidance or rule should be in place to allow flexibility of the data to be presented.**

Case Study # 9 - FDA

Expedited Pre-marketing Manufacturing/Facility Assessment during COVID-19

Ying Zhang, Derek Smith, Mahesh Ramanadham, and Stelios Tsinontides

Description

- Request of expedited approval for COVID-19 therapeutic via a rolling submission of data including addition of commercial manufacturing sites post-submission
- Fast track request granted, informal communications with Agency regarding submission plans and requests for flexibility in data requirements for a rolling submission
- Written advice on submission contents to active application in 2 weeks; EUA request evaluated and authorized prior to full application; 4 months between initial submission and complete application; active CMC assessment for all 4 months; approval within 2.5 months of complete application

Challenges & Accomplishments

- Dedicated extensive resources to assessment
- Sponsor intended 12 facility/line combinations and were successful in generating data to support 11 facility/line approvals
- Inspection challenges early in the pandemic required unique application of inspection alternatives (both distant assessment and reliance on MRA partner inspection reports) to assess facility capability
- Agency made unique use of publicly available information to inform sponsor of potential concerns to facilitate agreement on final facilities to include in the application

Engagement with Sponsor

- Biweekly meetings to discuss assessment issues; additional ad hoc meetings as issues identified
- Ensured clear communication of required data to support manufacturing facilities and intended timing of action to allow sponsor to determine which facilities could be supported with required data
- Communications included requested updates on anticipated drug substance and drug products supplies versus demand under the EUA to determine which facilities were most critical to ensuring drug supply

Learnings/Recommendations

- Helpful to provide early guidance on required data to multiple facility/manufacturing lines for expedited assessment/action (i.e. emergencies)
- Agency should not assume sponsor is aware of all guidances and regulations that impact application data and assessment
  - Reminders on approvability requirements and publicly available data on CGMP status of facilities was helpful information/advice provided
- Resource allocation was key to supporting early therapeutics, but unsustainable at level used for this case
  - Efficient dedication of resources from both industry and regulators; be mindful of time and resources