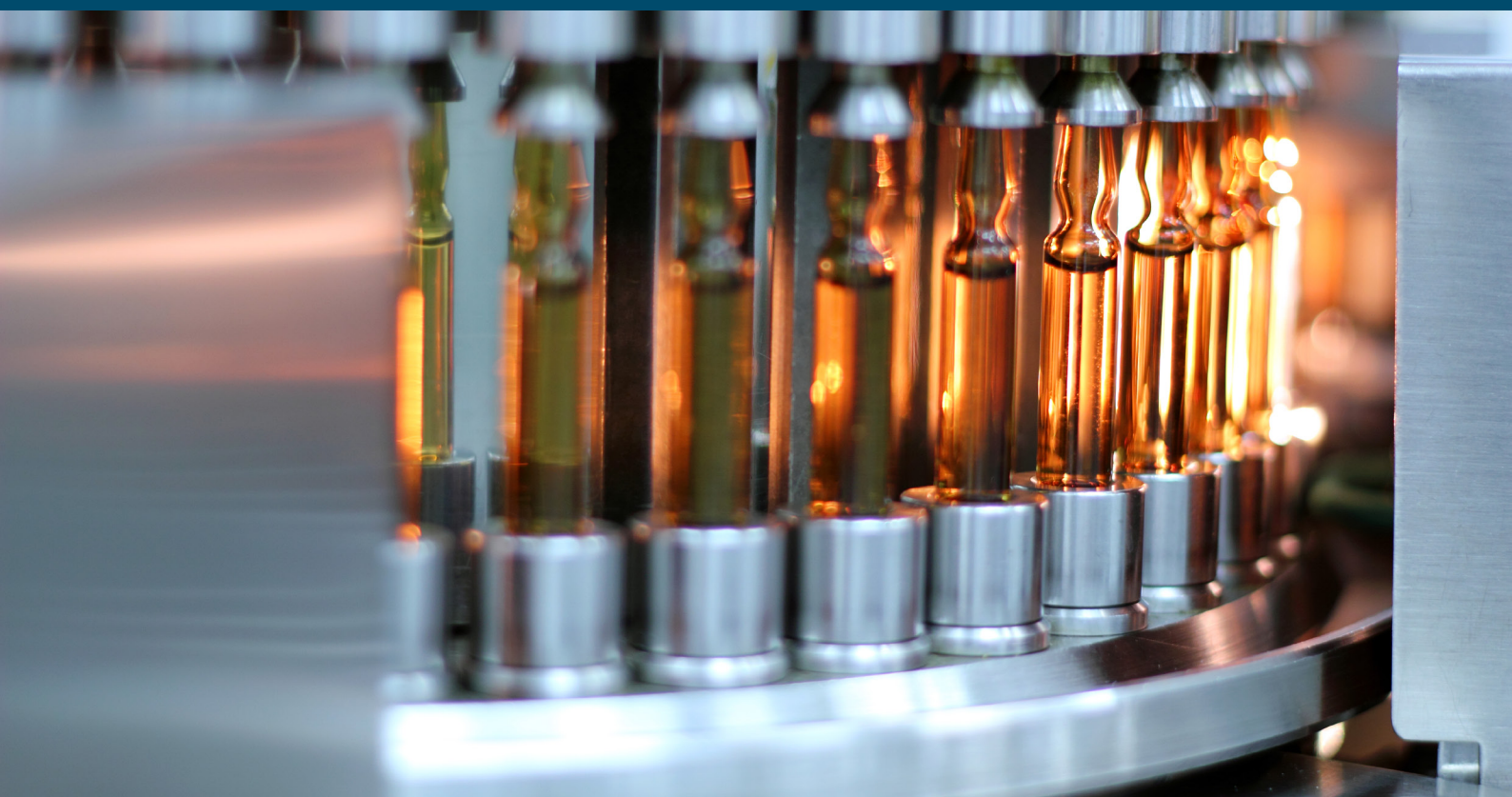




EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Meeting Report: Workshop with
stakeholders on support to quality
development in early access approaches
(i.e. PRIME, Breakthrough Therapies)



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Human Medicines Research and Development Support Division

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26 November 2018, European Medicines Agency, London

Introduction

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) launched the Priority Medicines (PRIME) and Breakthrough Therapy schemes to strengthen their support for the development of medicines that address unmet medical needs with the aim to help patients to benefit from these therapies as early as possible. Experience to date has shown that applicants face challenges to complete quality and manufacturing development and data requirements during development of products in early access approaches.

In order to address and overcome these challenges, EU and US regulators wish to support applicants with guidance and risk-based flexibility regarding their pharmaceutical development programme including, for example product characterisation, specification setting, validation and stability testing as well as early identification of quality issues / attributes that are critical to the clinical use of the medicinal product.

The aim of the workshop was to discuss between regulators and industry these quality challenges and possible scientific and regulatory approaches which could be used to facilitate development and preparation of robust quality data packages, to enable timely access to medicines for patients whilst providing assurance that patient safety, efficacy and product quality are not compromised.

These general discussions were further elaborated through a number of specific industry case studies [covering chemical molecules, biologicals and advanced therapy medicinal products (ATMPs)] and a discussion of experiences to date from early access approaches.

The workshop was a joint collaboration between EMA and its relevant working parties [Biologics Working Party (BWP), Quality Working Party (QWP) and Inspectors' Working Party (IWP)], and the US FDA.

This meeting report captures the discussions and main conclusions from the workshop.

This report constitutes a record of the presentations and discussions that took place at the workshop. It is not an action plan but it contains points for follow-up as identified by workshop participants to be further considered by EMA and FDA. This report should not be understood as an official position from EMA or its committees or working parties (i.e. BWP, QWP, IWG) or the US FDA.

The workshop was organised in the following sessions:

- Background & scope of early access approaches
- Process validation
- Control strategy
- GMP-compliance
- Breakout session on Biologicals process validation & control strategy, comparability and stability
- Breakout session on Chemicals control strategy and stability
- Regulatory tools to support early access
- General discussion, summing up and way forward

The workshop was attended in person by 56 regulators from the EU national competent authorities, EMA, FDA, PMDA and 64 industry representatives. The workshop was broadcast live on the EMA website and followed online by over 2400 individuals.

Guidance to the reader: *This report summarises the key aspects which were discussed during each session of the workshop. Abstracts and panel discussions are summarised in black boxes under each session. Conclusions from each topic session are displayed in a diagram outlining scientific elements and regulatory/procedural tools as introduced at the beginning of the meeting under 'Goals of the workshop & problem statement'.*

1. Background & Scope of early access approaches

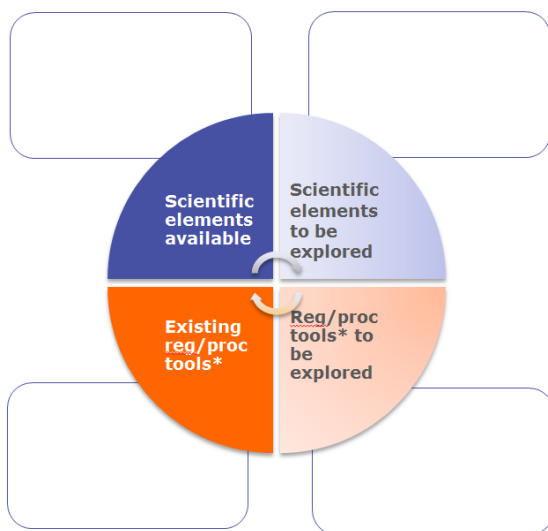
Session lead: V. Jekerle, EMA

E. Alteri, EMA's Head of Human Medicines Research & Development Support Division, opened the event by welcoming participants. The workshop was part of both Agencies' efforts to strengthen their support for the development of medicines that address unmet medical needs with the aim to help patients to benefit from these therapies as early as possible. Challenges to complete quality and manufacturing development and data requirements as part of early access programs are commonly encountered. This workshop aimed at identifying possible scientific and regulatory approaches which could be used to facilitate development and preparation of robust quality data packages, to enable timely access to medicines for patients whilst providing assurance that patient safety, efficacy and product quality are not compromised.

Presentations

Goals of Workshop & problem statement (S. Ruiz (BWP chair, EMA); K. Pugh (QWP chair, EMA); V. Jekerle (Quality Office, EMA))

This presentation defined the scope and deliverables of the workshop. The workshop aimed at identifying challenges faced by Applicants of PRIME and Breakthrough therapies to achieve robust and comprehensive quality and manufacturing data packages which often face time constraints, structural complexity & innovation and global development projects. The challenges were illustrated through Industry case studies and further reflected and discussed in Panel discussions with the aim to identify regulatory and scientific answers to these challenges. Regulators from FDA and EMA, together with industry identified key challenges and elaborated scientific elements and regulatory tools available in both regions to address the challenges and explored the flexibility within their current regulatory systems. FDA and EMA also reflected on areas that would benefit from further harmonization between both regions. Throughout the day scientific elements and/or regulatory/procedural tools that could help address the challenges were collected according to the below diagram.



Note: *within the existing regulatory framework.

Scientific elements are considered to be technologies and scientific concepts or principles for development, manufacture and quality risk management, which may or not be present or implied in existing guidelines. Examples include concurrent validation, new modelling methodologies, new analytical techniques, etc.

Regulatory/procedural tools are described in the legal, regulatory framework and can be specific to PRIME (or Breakthrough Therapies) (e.g. kick-off meetings) or generally applicable [e.g. Post-approval change management protocols (PACMPs), recommendations, scientific advice (SA)].

Perspective from US-FDA (R. Sood (CDER, FDA))

R. Sood presented FDA's Breakthrough Therapy (BT) program. The BT program was introduced in year 2012 as part of the Prescription Drugs User Fee reauthorization. An additional program, Regenerative Medicines Advanced Therapy (RMAT), was also established as part of 21st Century Cures Act (2016) to advance regenerative medicines therapies in the Center for Biological Evaluation and Research (CBER). Both programs provide expedited development and review of a drug for serious or life-threatening disease or conditions where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies. The candidate drugs given BT or RMAT designation enjoy several benefits including, timely advice and interactive communication with the sponsor regarding development of the drug, collaborative cross disciplinary review utilizing senior managers and experienced review staff and mostly an expedited review clock. The success of the BT program was demonstrated by 126 approvals through BT program alone between 2012-2018.

The drugs approved under BT program typically have an accelerated clinical and manufacturing development program. This results in less than optimum amount of manufacturing information available at the time of submission and during the review. The talk focused on the challenges faced by the applicants in collecting all the manufacturing data needed and providing an adequate manufacturing control strategy, and for the Agency in reviewing this information. It becomes important for the Agency reviewers to do a risk-benefit assessment regarding risk of less manufacturing information versus patient benefit. This requires innovative risk-mitigation strategies to ensure product quality and reduce the quality related product risk to an acceptable level. The talk emphasized how industry and Agency share the responsibility of meeting patient expectations and ensuring that the patients get a quality product.

Perspective from EU-EMA (V. Jekerle (Quality Office, EMA))

V. Jekerle introduced EMA's PRIME scheme with a specific focus on product features and quality aspects. PRIME eligibility is evaluated according to the medicine's potential to offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. Features of the PRIME scheme include the potential for accelerated assessment; early Rapporteur appointment; kick-off meeting with multidisciplinary expertise from the EU network; enhanced SA; EMA dedicated contact point and fee incentives. An overview of PRIME eligibility recommendations (up to October 2018) was provided in relation to success rate, type of applicant, product class and therapeutic area.

The talk also illustrated the scientific challenges common to PRIME candidates including shortened timelines, which put constraints on the ability to complete commercial manufacturing sites set-up & description, compilation of validation and stability data and determination of the appropriate control strategy including specification setting. Product characterization, in particular, determination of biological activity and demonstration of comparability, is particularly challenging for many PRIME candidate products due to their highly innovative and complex features (i.e. genetically modified cells and viral vector-based products). Finally, global developments require applicants to put extra efforts into demonstrating comparability, where manufacturing processes are being changed or moved across geographic regions and suitable batch-release testing arrangements need to be identified in line with the applicable legal framework. An analysis examining scientific issues most commonly identified by PRIME applicants (as indicated by SA requests) revealed the following areas as the most critical: starting materials, comparability, process validation, analytical control strategy, specifications and stability.

In conclusion EU regulators view PRIME as a support scheme for development, whereby the product quality should not be compromised but considered in the context of the benefit/risk assessment.

Flexibility can be explored in terms of the time point of completion of quality data however Module 3 data requirements must be in line with scientific guidelines and technical requirements according to the EU legislation (Annex I of Dir. 2001/83/EC). In case of ATMPs, the content of the application can be adapted under a risk-based approach. Alternative data sources (e.g. platform/pilot scale data) can be considered provided the relevance is established.

Industry case study: In-licensed small molecule oncology drug: complexity of accelerated development with multi-Health Authority interactions. F. Schwarb (Roche)

A case study of an accelerated development product (synthetic molecule) that was acquired from a SME sponsor less than 12 months before the planned New Drug Application (NDA)/Marketing Authorisation Application (MAA) submission date was presented. As the project was granted PRIME, BTM and SAKIGAKE designation, early and simultaneous submission of the NDA/MAA in the EU, US, and Japan is expected by regulatory authorities.

By nature, for accelerated Quality/Characterisation-Manufacturing & Control (CMC) development products that were in-licensed or acquired in the pivotal clinical phase, a lot of substantial Quality/CMC

development activities are ongoing in parallel to, or even beyond, the generation/submission of the initial NDA/MAA. Contract Manufacturing Organisations (CMOs) selected by the previous sponsor need to be integrated into the CMC network of the new sponsor.

Enhancement of process robustness and addition of manufacturing, testing or packaging sites may be needed to ensure a robust supply chain. Rapid and predictable PACMP procedures are vital in case these adaptations cannot be completed prior to submission.

In this case study, the strategy for process performance qualification had to be changed tardily due to different views of the regulatory authorities on the use of a matrix design (for multiple strengths) versus a concurrent validation approach.

PRIME, BTD, SAKIGAKE foster early and enhanced dialogue with regulators, and the presenter shared positive experiences with a shortened/truncated EMA SA Procedure (including a pre-submission meeting with the presence of the Rapporteur's Quality Assessor) facilitated by the PRIME coordinator, as well as the enhanced dialogue with FDA to discuss CMC topics in Type B meetings, teleconferences and written responses. Establishment of a rapid combined multi-agency feed-back pathway (EMA, FDA, PMDA), and ability to contact regulators to inform about emerging topics and get informal insight might help sponsors to advance these accelerated development programs.

In conclusion, the regulators opening perspectives and the industry case study illustrated many of the consistent themes (i.e. scientific and regulatory/procedural challenges) which were addressed during the workshop through the subsequent case studies and panel discussions.

2. Process

validation

Session lead:

S. Barry (BWP member, EMA)

Presentations

Regulator's perspective S. Barry (BWP member, EMA)

S. Barry described an integrated holistic approach for the approval of the CMC process validation package of products in accelerated pathways. This involves the coordinated use of Prior Knowledge, innovative control strategies, PACMPs and tailored process validation packages. He emphasised that a more targeted use of ongoing (continued) process verification protocols could facilitate deferral of certain process validation data to the post-approval phase. Such protocols can provide assurance to regulators that the appropriate data will be gathered and evaluated post-approval. Concurrent validation can also be a valuable approach in certain cases. This could include a combination of standard PPQ batches and some batches validated concurrently post-approval. Such an approach may allow applicants to defer submission of some validation data to post-approval phase, which ultimately depends on the benefit/risk profile. It was highlighted that the level of process validation data required pre-approval could be linked to the risk associated with the manufacturing step. Furthermore, many aspects of the process validation data package can be supplemented with data from Prior Knowledge. It was concluded that there is no one-size-fits-all solution and that a combination of process validation approaches may be necessary to avoid delayed submission/ approval for products on an accelerated path.

Industry case studies:

Innovative validation. S. Finnie (Astra Zeneca)

AstraZeneca acquired a small molecule product that showed great promise in a niche indication. The firm approached FDA and was advised to apply for Breakthrough Designation at the time of filing. Following these negotiations, it was clear that Astra Zeneca was looking at significantly shortened review clock. Although this was positive, it presented an issue with the company's standard process validation. It was anticipated that with a standard sequential validation campaign, it would be a further 4 months following approval before they could supply patients. AstraZeneca approached the Agency and discussed decoupling the validation of drug substance and drug product. To facilitate this approach, Astra Zeneca proposed to use drug substance manufactured in the clinical facility to supply drug product validation. Furthermore, the one batch from this campaign would be used to support launch.

Three key elements lead to the success of this proposal. Firstly, the applicant provided the Agency with significant evidence of similarity in terms of quality, manufacturing process and quality system between the clinical campaigns and the proposed commercial campaign. Secondly, during the site inspection there was open and close engagement between the inspectors, reviewers, subject matter experts & quality departments ensuring that questions raised were answered swiftly leading to a balanced and aligned view on risk assessment. Finally, and most importantly, it was clear that throughout the interactions all parties were focused on ensuring supply to the patient.

Process Validation Approaches for Accelerated Programs. L. de Cardenas (Genentech)

A case study of the validation strategy for an accelerated development antibody-drug conjugate (ADC) was presented. This ADC was granted both PRIME and BTM based on very promising results from a Phase Ib/II clinical study.

Given acceleration, several process validation approaches were considered that could potentially enable a faster path to submission. A non-linear approach to process performance qualification (PPQ) was taken whereby drug substance and drug product PPQ campaigns used existing clinical antibody intermediate; this was a viable option as the antibody intermediate was manufactured using the intended commercial process. Additionally, while maintaining focus on the patient and continued development of product knowledge, the need for conducting some process design studies during development was challenged.

Deferral of non-critical process design studies was possible, while still delivering a validated process and complete data package in the initial MAA/BLA. However, the outcome of deferral of these studies resulted in a constrained manufacturing process due to an increased number of Critical Process Parameters (CPPs) and narrow process ranges. Although a constrained manufacturing process was registered, the intent was to conduct additional process design studies to increase understanding of sources of variability and robustness of the process, and provide this information post-approval to potentially downgrade CPPs and widen acceptable ranges.

While this approach provides a faster-to-patient timeline and ensures consistent product quality, safety and efficacy, there is an opportunity to explore other types of information that may be suitable for establishing parameter ranges when some process knowledge is lacking.

Panel discussion

Regulators: S. Barry (BWP member, EMA), J. Limberg (QWP member, EMA), E. Lacana and M. Ramanadham (CDER, FDA); Industry: S. Finnie (Astra Zeneca) and L. de Cardenas (Genentech)

During the panel discussion, the benefits of **decoupling drug substance and drug product process validation activities** were discussed. Regulators agreed that it is possible to use clinical drug substance material to manufacture drug product PPQ batches. This allows drug substance and drug product PPQ activities to be de-coupled.

Some of the benefits and pitfalls of **launching from a clinical site** were discussed. In general regulators had no objection to launching from clinical sites. However, launching from clinical sites does also need to consider licenses in the EU. In addition, consideration must be given to the need for ongoing patient supply and the technical requirements to establish comparability for product subsequently manufactured at a new commercial site.

There was general agreement that for products of high unmet clinical need, it would be acceptable to **defer the submission of certain process validation data to the post-approval phase**. The extent and type of process validation data which can be deferred remains to be further agreed. Industry requested clarity on the mechanism for submission of such deferred process validation data. Several possibilities were discussed, among them using a **process validation scheme** as described in the EMA guideline on process validation guideline for finished products and a **commitment** to provide the validation data post-authorisation. The precise details of the mechanism for receiving this data remain to be fully elaborated by regulators. The need for certainty in this regard was highlighted by industry, as there can be several parties in the supply chain, e.g. contract manufacturers, responsible for gathering the data.

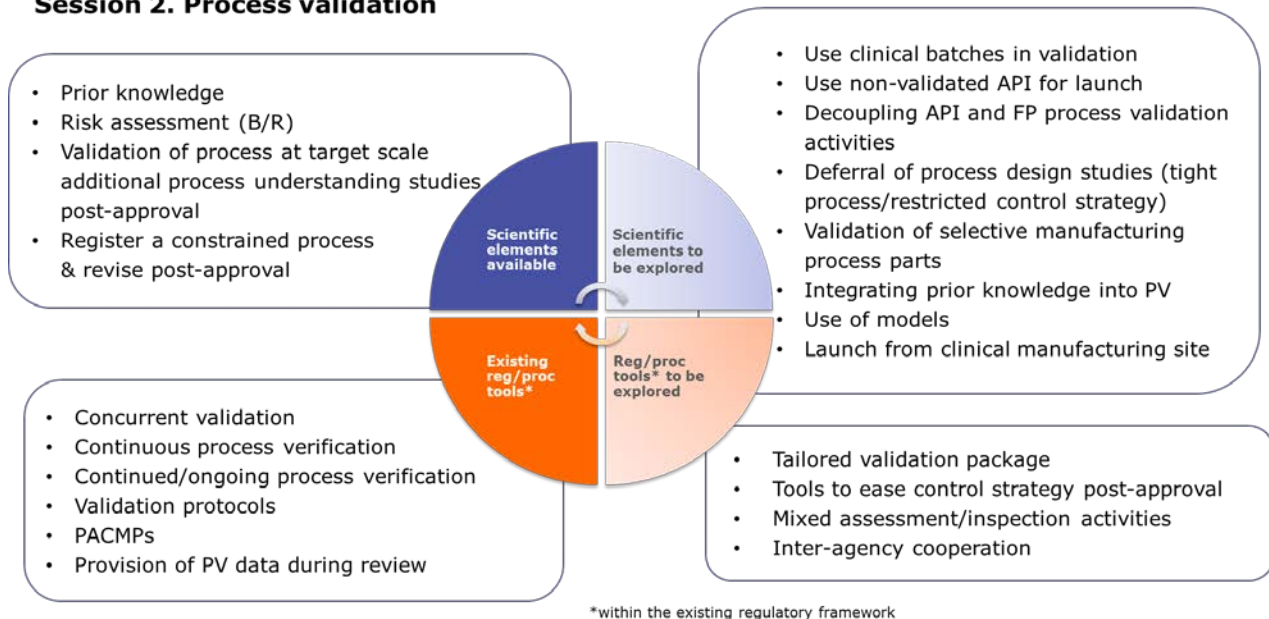
The benefits of **concurrent validation** were highlighted, and regulators expressed their openness to the use of concurrent validation data when appropriate. Industry emphasized that companies are currently researching the area of concurrent validation but are generally hesitant to use this approach in submissions due to the perceived high regulatory bar for acceptance. Another challenge is that for products undergoing accelerated development, there can be a short timeframe between the gathering of pivotal clinical data and the submission date. Preparing a concurrent validation protocol in a short timeframe can be challenging. In such cases, industry often favours strategies that can be implemented quickly and have a recognized path to success. Industry was encouraged to present their proposals to regulators during early meetings and scientific advice procedures in order to get agreement in principle during development.

The benefits of filing with a **more comprehensive control strategy** were discussed specifically for biotechnologically derived proteins. Some of the approaches considered were the registering of additional CPPs, IPCs or specifications, and/or filing with tighter process parameter ranges. The **stringency** of such a control strategy could then **be eased post-approval**, once additional data is gathered. Industry questioned whether regulators would allow widening of ranges, downgrading of CPPs and removal of specifications and IPCs in the post-approval phase. Regulators assured that if data was available to support the approach, then it would be acceptable in principle. It was highlighted that the approach could be agreed upfront as part of a PACMP.

It was emphasised by regulators that process validation is a lifecycle activity. If there is a clear lifecycle validation plan in place and there is assurance that manufacturers know how to appropriately control their process, then regulators are open to exploring new avenues for the submission of confirmatory validation data. Regulators recognise that when there is a significant patient benefit, completion of PPQ activities should not represent a barrier to patient access.

The patient should always remain the focus during the discussions on tailored validation packages. It was strongly emphasised that the earlier that discussions take place between industry and regulators, the greater the chance for a successful outcome. This was a consistent theme throughout the discussion.

Session 2. Process validation



Several tools which can facilitate flexibility in the extent and type of process validation data required prior to approval exist. Process validation is a lifecycle activity; process validation knowledge and understanding is a continuum from early clinical development through to a fully mature commercial process. For products under an accelerated program, the main question is when, during the validation lifecycle, has sufficient data been generated to support approval. Use of continued/ongoing process verification plans or concurrent validation (e.g. 10.43 and 10.44 of the GMP for ATMPs guideline) can allow for a flexible approach in this regard. A departure from the traditional requirement of data from 3 PPQ batches can be accepted by regulators where there is a strong benefit/risk. Such approaches need to be accompanied by clear plans which outline how process validation data will continue to be gathered in the post-approval phase. The plan agreed between industry and regulators can be clearly laid out in a PACMP.

A greater level of process understanding (e.g. from platform or small scale studies) can help facilitate the use of tailored validation packages. However, where process understanding is at an early stage, Applicants could register a constrained control strategy with tighter control of the process in the initial period post-approval. As additional knowledge is gained, such a constrained control strategy can be eased post-approval. This can reduce the time needed to perform a traditional formal process validation programme prior to approval. Prior Knowledge can also be leveraged to complement product-specific validation data.

In order to accelerate the time to market, launching from a clinical manufacturing site may be an acceptable strategy as long as continued commercial supply can be guaranteed. In this case the provision of comparability data could be deferred to the post-authorisation phase when the registration of the commercial site is planned through a variation procedure. The strategy for moving to the final commercial site post-approval can be agreed during the initial review period and documented in a PACMP.

Continuous process verification as described in the CHMP Process Validation guideline on finished products & EU guidelines (e.g. GMP Annex 15) were highlighted as already existing regulatory concepts to be considered.

Main points identified for further follow-up:

In this session a considerable number of scientific elements and regulatory tools were highlighted.

Further agreement is needed among regulators on the type of validation data which could be deferred to the post-approval setting. A mechanism for how this data would be submitted (e.g. regulatory commitment, PACMP, handled by the PQS and examined on inspection) needs to be agreed so that industry can have certainty regarding how to use this approach.

There is still relatively little experience with the use of concurrent validation. Further agreement is needed on how protocols for concurrent validation can be most efficiently presented in regulatory submissions and how they will be assessed.

Industry expressed some hesitation regarding making an initial filing with a more comprehensive control strategy because of the perceived difficulties in changing this post-approval when more knowledge and experience has been gained. In order to allay this concern, it should be made clear by regulators that this is a viable option and that an easing of the control strategy (e.g. downgrading of CPPs, widening of ranges) is possible post-approval when supported by appropriate data.

Specifically the following points are identified:

- **Commercial supply of clinical batches post-approval**
- **Decoupling of AS and FP process validation activities**
- **Deferral of process validation studies / restricted control strategy**
- **Reinforce value of concurrent validation**
- **Mechanisms to submit delayed validation data**
- **Tailoring validation packages**
- **Widening control strategy post-approval through PACMPs (i.e. agreement on the principle of “relaxing” control strategy post-approval when supportive data is available)**
- **The extent that Prior Knowledge can compensate for a deferral of certain process validation data**

3. Control strategy

Session

lead: M. Welin (BWP member, EMA)

Presentations

Regulator's perspective from EMA & FDA: M. Welin (BWP member, EMA), L. Graham (CDER, FDA)

M. Welin and L. Graham presented a joint EMA/FDA regulators view on control strategy. It was recognized that expedited development programs have a number of challenges: e.g. limited manufacturing and clinical experience, too few batches to assess consistency, process and method validation studies not finalized, and understanding of criticality and interactions may still not be mature. Despite this, these products are still expected to be safe and efficacious with a positive benefit risk ratio. Flexibility in what CMC information will be required for marketing approval will depend on

factors such as the strength of: product and process knowledge, analytical capability and the quality system. Increased knowledge of quality attributes and process can be used to support control strategy flexibility. Expedited development programs can, at the time of approval, lead to a broader control strategy to mitigate the risks associated with uncertainty due to limited product and process knowledge (e.g., uncertainty on the criticality of attributes, their control by the manufacturing process, and analytical capability) which will need to be addressed, potentially including more attributes, process parameters, and assays in the control strategy at the time of application approval. The control strategy can be revised when more knowledge is gained.

Industry case studies

Use of Prior Knowledge to Establish Flexible Enhanced Model-based Control Strategies. D. Wilkinson (Biogen)

The case study illustrated the use of prior knowledge to set-up flexible enhanced model-based control strategies. As acknowledged in ICH Q10, control strategies should evolve and be based on current understanding; a concept that allows in the case of accelerated filings, to start at an earlier stage to define a control strategy for a MAA and commercial use, recognizing that it will need to be reviewed and refreshed as learning and control evolves, similar to the build of Investigational Medicinal Product Dossier (IMPD) strategies. Control strategies are multi-faceted and specifications, stability and shelf life, manufacturing process and controls, analytical methods and controls could all need to be re-evaluated. For accelerated assessments, aspects of control strategy may be based primarily on prior knowledge with limited historical batch data. Post-approval commitment to re-evaluate control strategies may be needed and could be assisted for major changes using flexible PACMPs. Where prior knowledge does not exist then use of predictive tools and modelling may also help provide earlier reassurance that a control strategy is fit for control of quality product for patients.

The use of performance-based adaptive process control (e.g. advanced process control (APC)) could also be used to focus control on the final output for high risk attributes through set-point adaptation, rather via more traditional fixed parameter limits and use of these will be important to help build early confidence in an accelerated development control strategy.

Intelligent process control strategies (like those used in other advanced industries) could be used to increase product and process capability. To develop models for APC, significant amounts of data and intricate process knowledge/ experience (experience with the overarching control strategy) is required and again this would need to evolve through development and post-submission and approval.

This could include review of the approach for technologies where little platform knowledge exists, for example non – monoclonal antibodies, recombinant proteins, even non-proteins for example non-platform oligonucleotides or ATMPs.

The goal is always to ensure consistent product quality and supply chain predictability and reliability, while providing for lifecycle flexibility to account for patient and supply chain needs and will be facilitated by early on on-going dialogue with assessors, through development, approval and post-approval phases.

CMC information to support Vaccine Early Access designation- Composite Case Study from Vaccine Manufacturers (GSK, Janssen, MSD, Pfizer, Takeda). C. Campa (GSK)

A combined case study from several vaccine manufacturers (GSK, Janssen, MSD, Pfizer, Takeda) was presented. Vaccines are very complex and diverse products, requiring continued product and process understanding throughout development and lifecycle. Therefore, risk-based product understanding strategies are needed to assess the potential for prevention of the targeted disease, and, ultimately, support early access designation. For instance, safety demonstration combined with physicochemical characterization/ in vitro potency testing could be important supportive information for early access in

accelerated scenarios. Early focus on product characterization is critical, with phase- appropriate expectations for specifications, considering attributes selection, acceptance criteria and test methods. The use of innovative analytical approaches is considered of outstanding importance in accelerated scenarios, due to the need of best- in- class tools for fast and reliable product and process testing. For vaccines with limited information on structure- function relationship, clinical dose selection strategy is a possible pathway to support evolving product understanding in accelerated scenarios. The control strategy extent, the complexity of the process, and the level of prior knowledge are proposed to drive the decision on validation state for pivotal trials and on process validation data required at different stages of development, including registration versus post-approval. Robust strategy for product characterization sets the grounds for smart planning of process evaluation and prioritization of process validation activities, in function of acceleration of the program, based on unmet medical need. For all the above- mentioned aspects, it is critical to have open and early discussion with Regulatory Agencies for feedback and alignment on product-specific expectations.

Panel discussion

Regulators: M. Welin and N. Kruse (BWP members, EMA), T. Agasoster (QWP member, EMA), L. Graham (CDER, FDA); Industry: D. Wilkinson (Biogen) and C. Campa (GSK)

The question on which **control strategy activities** can be **front loaded** for expedited development programs vs. standard development programs was discussed. Industry argued that **risk assessment** to inform uncertainty should be used and risk between constrained control strategies and risk of supply should be balanced.

Regulators pointed out that a less constrained (e.g. more flexible) control strategy may however question the consistent quality of the products. It is acknowledged that these products are intended for an unmet clinical need and any incomplete data packages on quality, including on the control strategy, will be placed into the context of the benefit/ risk consideration.

There are many things that can be done early in development but others which cannot, and these issues need further discussions between regulators and industry to find an acceptable balance. In short, 'not one size fits all'. During standard development companies optimize the manufacturing process to ensure adequate manufacturing opportunities and process capability over time. When development is accelerated, this lifecycle balance is changed and an agreement needs to be found with regulators globally on what would still be acceptable time points by when the studies are conducted.

It was further discussed that **qualification in line with ICH Q3A/B and ICH Q6** presents a challenge. It was noted that the aspects of justification of acceptance criteria in IPC's and specifications differed between small and biological molecules. For small molecules, the limits can be clinically qualified through animal studies and specifications are commonly set based on process capability. The situation is different for biological molecules where product related forms may have higher or less biological activity or give rise to immunogenicity for example; effects which will not be able to be elucidated in preclinical models. Relevant **prior knowledge** can be used to justify the acceptance criteria for certain attributes and attributes to monitor/ not monitor in the control strategy. Depending on the benefit/risk it could still be acceptable to have wider limits than the levels exposed to patients in clinical trials. Understanding how the Pharmaceutical Quality System (PQS) handles out of trend or out of specification (OOS) results will be an important factor in the assessment of the overall control strategy.

Another question for discussion was how a **PACMP for control strategy changes** (e.g. in-process (IPC), attributes tested, limits applied, etc.) would look like. In the current setting, PACMPs are used to enable an implementation of the proposed change through a Type 1b variation (for Biologicals), however the submission of the implementing 1b variation is not bound by time. For the discussion of expedited approvals there will be very limited data at the time of approval leading to a situation where these commitments should be fulfilled as soon as possible. It might therefore be necessary to

distinguish between those PACMPs which are time bound and those which are not. It was pointed out that the philosophy of protocols can nevertheless be used.

As already mentioned for small molecules, safety and efficacy is easier to verify in animal models and levels proposed may be considered clinically qualified even if much wider than what is given by product consistency. **Specification limits** based on process capability on 10 batches increases risk of failures in the long term. In this case PACMPs for tightening specifications, IPC etc. can be used when more experience is gained. For biological products, however, this is not the case as the limits are mainly qualified by levels used in clinical trials and PACMPs will not allow for inclusion of more clinical data to justify new wider limits or deletion of tests when more experience is gained.

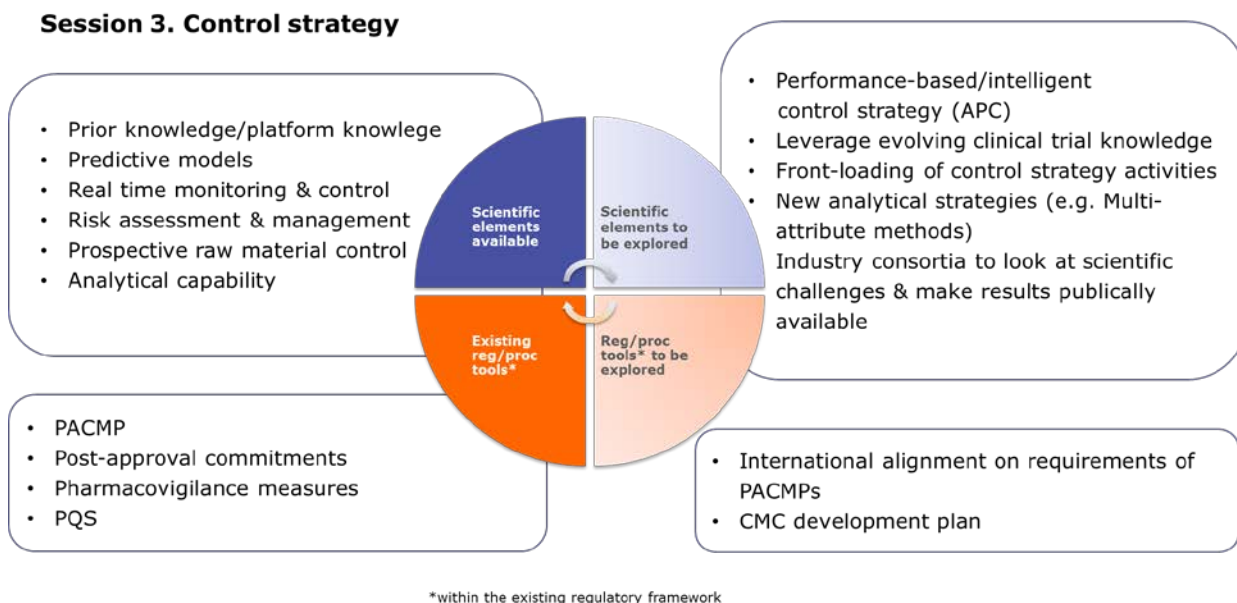
A third question was raised on whether certain **performance-based and intelligent control strategies** should be introduced for standard CMC development programs before introducing them into expedited development programs. Regulators were of the opinion that it would be a risk if totally new analytical concepts were introduced in expedited developments as the product knowledge is limited and would make the justification of their applicability difficult. It was therefore recommended to initially introduce such techniques for standard products where there is more prior knowledge, to verify the feasibility of those new methods. If put in the application dossier the importance of making their descriptions clear and understandable was highlighted, acknowledging that these methods/ approaches may also be novel to the assessors. Industry responded that they wished regulators to be open to introduce innovation even in accelerated processes. Regulators were asked to consider whatever characterisation approaches industry had, even if these were unconventional approaches, as it may not be possible to wait for a 'standard' characterisation program. It can then be decided if the testing strategy should be with orthogonal methods considering the information companies may have from different strengths, different assessment approaches and general specification testing.

Dose selection plans for vaccine clinical trials and MAA were discussed. An innovative approach was pointed out by Industry as follows: as a prerequisite and where no impact on safety is seen, the aim for somewhat higher doses for the commercial product compared to what has been used in clinical trial will add a safety margin to compensate for residual risks and can be considered. It was proposed that companies seek SA and/or discuss with the responsible agencies during development such innovative approaches.

Building reassurance on the acceptance of Company's strategies was raised as an important issue. Industry argued that the current **SA procedure** is quite formal and takes time from the submission of questions until the formal answer. Alternative channels for communication were discussed and examples about **assessor-inspector interaction and rapid communication** of findings affecting development strategies were mentioned. It was also reminded that in the US there are programs allowing companies to come during development and BLA to discuss specific scientific aspects. This is not only helpful for the company but also for the assessor to understand the scientific rationale of the company which make the regulatory review easier.

It was stressed that the files should clearly discuss the control strategy as a whole in a summary document to justify the proposed strategy, in particular any potential differences from the level of information requested for a standard product. This will be a very important part of the file to help the assessor understand the control strategy and how this will assure the quality of the product.

Scientific elements or regulatory/procedural tools collected from Session 3 Control Strategy.



Several tools exist which can be used in establishing the control strategy.

Prior knowledge/ predictive models from similar products (platforms) or different products can be used to justify the design of the control strategy. In this context Industry consortia could help share their findings on a particular scientific issue and information affecting certain product classes (e.g. prior knowledge) through general publications or white papers etc. and thus make the information available for consideration by Regulators and Industry.

QbD studies will help the understanding of what is important and what is less so and can be useful in deciding what needs control, but to do so they need to have reached a certain level of maturity.

For this category of products, aimed for an unmet clinical need, the benefit/ risk ratio may be different from standard products and certain uncertainties may be acceptable taking the intended use into account. Initially it is still expected that more attributes than normal are tested due to this uncertainty. In particular for small molecules appropriate analytical testing may balance lack of initial process understanding. PACMPs may be useful to update the control strategy when more experience is gained. To make their use universal the principles of PACMPs as a tool for future variations needs to be introduced globally. Currently PACMPs are not linked to a specific timetable. This should be further discussed.

It is noted that several proposals are raised on PACMP (e.g. international alignment of PACMPs) which are considered to be subject to ICHQ12 guidance and implementation. Therefore it is proposed to refer to and await implementation of ICH Q12 to avoid potential overlapping activities on this topic.

New analytical technology/ strategies may add important information to verify the quality of the product. It should be taken into account that the novelty of these methods and strategies may in themselves add uncertainty which may delay the approval and companies are encouraged to seek scientific advice in these matters.

In addition, **CMC development plans** (or 'quality lifecycle plans') were discussed as a tool to describe the Quality development and product life-cycle planning (e.g. front-loading of control strategy activities).

Main points identified for further follow-up:

A number of scientific elements and regulatory tools were identified and highlighted. Like in the previous session, several aspects identified and included in the diagram are suggested for follow-up by Regulators in a Q&A/guidance document. The two points below are specifically identified for joint EMA-FDA follow-up.

- **Performance-based / intelligent control strategy / New analytical strategies (e.g. multi attribute method)**

These elements are not unique for accelerated access products but more of a general issue allowing for more tailor-made controls. Nevertheless, it is important that the regulatory approaches are harmonized as far as possible between different regions and it is therefore suggested to develop further guidance.

- **Front-loading of control strategy activities / CMC development plan**

With expedited procedures, the development will in certain areas not be as thorough as what would normally be seen. Taking the specificities of these products into account, it should be discussed which areas may be less developed and how the possible remaining non-mitigated risks will be compensated by other means, also taking the benefit/risk ratio of the product into account.

4. GMP-compliance

Session

lead: G. Lorenti (IWG, EMA)

Presentations

Regulator's perspective. G. Lorenti (IWG member, EMA)

A presentation was provided on the main Good Manufacturing Practice (GMP) difficulties encountered by regulators and industry during the accelerated assessment of PRIME applications.

The presentation focused on the relation between GMP and PRIME. The GMP is that part of the PQS ensuring that the medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization (MA), Clinical Trial Authorization, and that the medicinal products do not place patients at risk due to inadequate safety, quality or efficacy. The GMP compliance is an important part of PRIME approach, to enable faster development and approval in areas of unmet medical need/major public health need without compromising quality, safety and efficacy.

The presentation provided an overview of GMP topics raised during the evaluation of PRIME applications. The first topic was related to the use of a conditional marketing authorization application based on clinical trial data generated with products manufactured in a facility, like academic laboratory, that did not meet full GMP requirements, focusing, in particular, on the use of the Comparability Assessment Plan for the evaluation of GMP gaps to support the (conditional) marketing authorization application. Another point was the use of concurrent validation that could be acceptable

only in exceptional circumstances, and the documentation to be used to support the choice to apply a concurrent validation approach. For ATMPs the use of concurrent approaches is possible in cases of limited availability of the starting materials and/or where there is a strong benefit-risk ratio for the patient (see EC guideline on GMP for ATMPs).

An important aspect that was further discussed was the out-of-specification (OOS) topic, in particular how to deal with an OOS, the importance of the quality risk management, and the OOS in case of ATMPs, exploring the specific EU GMP requirements and the possible administration of cells/tissues that are contained in a cell/tissue based ATMP that is OOS.

The last two GMP items discussed were the possible use of Master Cell Bank (MCB) and/or Working Cell Bank (WCB) not manufactured under GMP, where the importance of extensive characterisation and testing and the interaction with the Competent Authorities; and the batch release from a laboratory based in a third country, where the requirements of the European Legislation and EU GMP, with particular focusing on the testing on importation, were illustrated.

Industry's case study: [Perspective on GMP Considerations for Accelerated Access](#). M. Popkin (GSK)

The founding principles of GMP apply to all supplies of medicines to patients. In accelerated access scenarios, where time to develop the long-term supply chain and complete commercial GMP activities is limited, alternative approaches to GMP may be appropriate, in particular where manufacturing sites only supply limited numbers of products to small number of critically ill patients for a limited period of time.

The workshop reviewed a scenario where the critical path for supply of an oncology drug is limited by the time taken to transfer the manufacturing process from a development facility manufacturing clinical supplies without a commercial GMP license to a similar, commercial manufacturing facility. Elements of GMP that may differ between clinical and commercial supply include labelling (e.g. tamper evident devices and unique identifiers), cleaning verification approaches, processes for data trending and periodic product review and validation/PPQ for processes and methods. Development sites supplying clinical studies are well suited to rapid scale-up and manufacture. They are used to rapid turnover of products and processes to support multiple clinical programs and are used to running processes where knowledge is more limited and where unforeseen events and deviations can occur more frequently. Companies use this as part of building process knowledge during development.

Overall, the case study highlighted a series of GMP considerations which could facilitate accelerated access early in the commercial lifecycle, including greater clarity on how clinical GMP considerations can be applied, the benefit of enabling commercial supply from clinical manufacturing sites, the need to ensure GMP consideration is viewed in a harmonized way in inspections by different authorities and the need for SA procedures to address GMP matters in a meaningful way.

Panel discussion

Regulators: G. Lorenti (IWG member, EMA), M. Ramanadham and L. Graham, (CDER, FDA); **Industry:** M. Popkin(GSK), M. Ganapathy (MSD), A. Lodge (Kite Pharma)

During the panel discussion, the issues illustrated in the presentations were discussed in more detail.

In particular, the OOS management, with special reference to ATMPs, and the supply of products where the risk from GMP limitations must be carefully balanced against the benefit to patients were discussed (Reference is made to the Guideline on GMP for ATMPs). The importance to always remain on the side of caution and strongly justify any decision taken was highlighted. The need to comply with the GMP requirements and the benefits of establishing an early dialogue with the Regulatory Authorities was stressed.

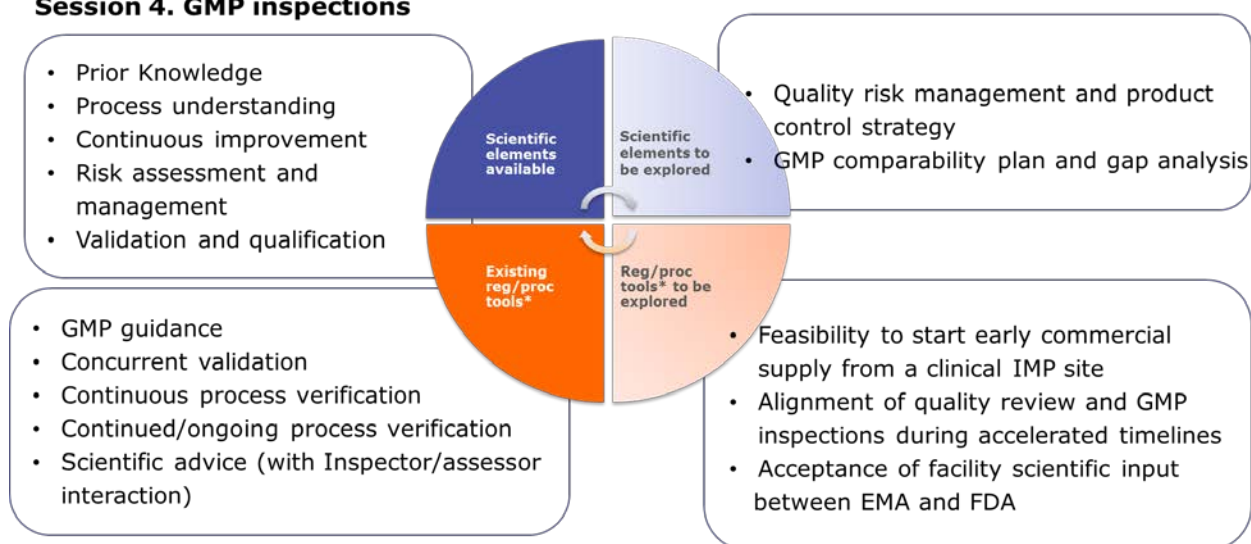
Another aspect discussed was the problem regarding the marketing of medicinal products manufactured at a site that produces medicinal products for clinical investigation but no commercial products. The discussion highlighted that the problem could be more of regulatory nature rather than technical, considering that, in order to manufacture medicinal products for clinical investigation, the manufacturer should have implemented an adequate PQS and that manufacturing should be carried out in accordance with regional GMP requirements, even if focusing on the IMP manufacturing. The need to further discuss how to facilitate early access to the market of medicinal products, in particular innovative medicines, was highlighted.

The discussions also addressed the need to avoid, where possible, a dis- harmonized approach between Regulatory Authorities.

Examples of the use of IMP sites and clinical materials to support validation and early commercial supply were also discussed. See section 2 Process validation

Scientific elements or regulatory/procedural tools collected from Session 4 GMP Compliance.

Session 4. GMP inspections



*within the existing regulatory framework

Discussion and main points identified for further follow-up:

Existing regulatory tools which are helpful to address challenges with GMP compliance are summarized above. In addition, some tools for further exploration have been identified. These topics were further discussed and highlighted for in-depth follow-up (see points below).

Increased harmonisation between Regulatory Authorities (e.g. EU-US MRA agreement for recognition of GMP inspections, scientific advice on GMP matters) is already underway and these efforts were supported by stakeholders.

Furthermore, the importance of establishing a constructive and interactive dialogue between Industry and Regulatory Agencies was highlighted as it was considered fundamental for timely release of medicinal products to the market, with particular reference to the innovative medicines in areas of an unmet medical need.

Specific points identified for follow-up are highlighted below:

1. **Using comparability as the basis for accepting clinical trial data which has been generated with product manufactured in a facility not fully compliant with GMP requirements (e.g. academic laboratory / research hospital) (see session 6a. on comparability)**
2. **Guidance on requirements to use of IMP manufacturing sites for early commercial supply of innovative medicines**
3. **Concurrent validation as a suitable tool to deal with assurance of manufacturing consistency post-authorisation. It is proposed to explore how better to link inspectors to concurrent validation activities (e.g. protocol and data) in the context of an ongoing manufacturing site inspection.**
4. **Management of OOS and possible administration of cells/tissues that are contained in a cell / tissue- based ATMP that is OOS in cases of autologous treatment.**
5. **Possible use of Master Cell Bank (MCB) and/or Working Cell Bank (WCB) not manufactured under GMP, batch release from a laboratory based in a third country**

5a. – 7a. Biological Breakout session. Process validation & control strategy, comparability and stability

5a. Case studies on process validation & control strategy

Session lead: S. Barry (BWP member, EMA)

Industry case studies

Approaches to Setting Specification Acceptance Criteria. R. Keane (Biogen)

Acceptance criteria for specifications are often set strictly based on the range of values observed in clinical batches. It is unlikely that this approach adequately captures the true attribute ranges that reflect acceptable quality, safety and efficacy profiles, and that are expected based on the long term behaviour of the manufacturing process. This is likely to be an acute challenge for products developed through accelerated routes which will typically have considerably less direct manufacturing experience at the time of approval. The proposal discussed was to establish acceptance criteria that provide a high level of confidence in continued product safety and efficacy, and that are based on the appropriate level of available knowledge at the time of approval.

The initial MAA/BLA approval would include a prospective plan agreed between the regulators and developer to re-examine these acceptance criteria once a sufficient number of batches are available. For well characterised biological products the proposal is that the acceptance criteria approved in the initial MAA/BLA would be set primarily on a combination of the clinical specifications, prior knowledge, and documented risk assessments. Additional confidence in these criteria is proposed to be enhanced as required by post-approval confirmatory commitments, appropriate ongoing commitments to provide interim data, underpinned by an appropriate Quality Management System per ICH Q10 and supported by cGMP inspection activities. This proposal builds on available concepts such as ICH Q8 (R2), discussions on the use of prior knowledge and the Biophorum Operations Group 2014 Position Paper Continued Process Verification: An Industry Position Paper with Example Plan <Reference>.

The goal of this proposal was to agree in the initial MAA/BLA and later confirm appropriate acceptance criteria for products developed rapidly to address critical unmet medical needs. Acceptability of proposals such as this will be critical to ensure continued global supply of these products to patients by avoiding a high risk of batch rejection through overtight specification acceptance criteria from a highly restricted data set.

Ebola case study on process validation and control strategy. T. Pepper (MSD)

This presentation focused on the Company's approach to comparability and process validation and the informal and formal interactions with EU and US regulators regarding the CMC approaches taken to accelerate product development for a candidate Ebola vaccine (designated V920). The vaccine was granted PRIME and BT status in June 2016. MSD intends to file marketing applications in the EU and US in 2019. Following approval by EMA, MSD will seek rapid pre-qualification by the WHO and then the vaccine will be registered in African countries where Ebola is endemic.

V920 consists of a Vesicular Stomatitis Virus (VSV) that has been genetically engineered to contain an envelope glycoprotein from the Zaire Ebola virus (designated rVSVΔG-ZEBOV-GP). The clinical development program was conducted very rapidly, with twelve Phase 1, 2, and 3 trials ongoing during the 2014-2016 Ebola outbreak.

After MSD joined the development program together with multiple collaborators in late 2014, the goal was to build up capacity to manufacture the vaccine using expedited CMC approaches to accelerate product development and characterization. Clinical lots were made at a Contract Manufacturing

Organization (CMO) and clinical consistency evaluation was performed using lots made at a Biological Pilot Plant prior to scale up of the process and transfer to the final manufacturing facility.

A “tailored” process validation approach is being pursued with parallel/overlapping DS and DP validation activities; for example, as DS PPQ lot 1 data are available, these data will be used to start DP PPQ lot 1 such that overlapping DS and DP PPQ lots will be manufactured.

Throughout this rapid development, advanced CMC data was shared with both US and EU Agencies when available to gain access to timely regulatory advice that could be acted upon and ahead of the MAA submission.

In summary, early and frequent informal and formal discussions with EMA and FDA under PRIME and BT have facilitated development of an Ebola vaccine.

Transparent and open communications between the company and both agencies and review of the advanced CMC data submissions allowed the continued progress of the project, limiting the potential risk to submission of the Marketing Application by enabling alignment with regulator's expectations.

Feedback on key aspects of the control strategy and comparability protocol including setting of acceptance criteria and setting clinically relevant specifications through expedited Agency interactions have enabled the company to focus on the remaining items that are needed to complete the dossier.

Comparability protocols were discussed under the IND by CBER/FDA and in the EU under the PRIME Scheme.

Panel discussion

Regulators: S. Barry (BWP member, EMA), E. Lacana and A. Byrnes (CDER, FDA); Industry: R. Keane (Biogen), T. Pepper (MSD), A. Lennard (Amgen)

Regulators accepted the difficulties in **setting meaningful specifications** when very few batches are available at the time of approval. The future natural variability in the manufacturing process cannot be captured on the basis of traditional statistical limits based on low numbers of batches.

One proposal was to use **the clinical specifications for the commercial product**. For this approach, the concern from regulators is that clinical trial specifications can be far wider than available batch data. Industry emphasised that clinical trial specifications are based on product knowledge and prior knowledge, and clinical qualification is still ongoing at the time of approval. Industry felt that any gaps in knowledge related to clinical qualification could be mitigated by appropriate plans/protocols which include regulatory commitments covering areas of trending, investigation and reporting of out-of-specification (OOS) results, description of the quality management system etc. Industry proposed that the totality of these approaches should be sufficient for initial approval until more clinical experience and data is available.

It was agreed that in certain cases it may be possible to register specifications which are wider than the batch data available at the time of approval. However, regulators want to see a **clear plan** for establishing appropriate specifications as the **product knowledge** increases post-approval. Industry pointed out that there are several sources of information which could be provided such as a full breakdown of the quality management system, SOPs for investigating OOS results etc., however such sources of information may be challenging to review during an approval procedure. The most appropriate content of such plans remain to be agreed.

One approach which was accepted in principle is to use post-approval ongoing/continued process verification to identify any batches which are within specification but are nonetheless considered to be atypical. The identification of such batches would trigger a root cause analysis. The potential actions to

be taken for such batches, which are within specification, but out-of-trend could be presented in the regulatory file.

The final specifications could be set on the basis of analysis of additional batch information and product understanding, or trending analysis, after a sufficient number of batches have been manufactured. As for all products, clinical qualification should be addressed when establishing the final specifications.

Regulators highlighted that such approaches provide assurance that approval of specifications, which are wider than the available batch data, will be adjusted if necessary once sufficient data is available. The most appropriate means of including elements of trending and statistical process control in the regulatory file remain to be worked out.

The role of the pharmaceutical quality system (PQS) in monitoring the specifications was discussed in this regard. The benefits of increased interaction between assessors and inspectors were emphasised in terms of developing a clear understanding of how the PQS relates to monitoring of specifications. It was highlighted that such novel approaches to setting specifications are part of an ongoing process which requires communication and collaboration between industry and regulators.

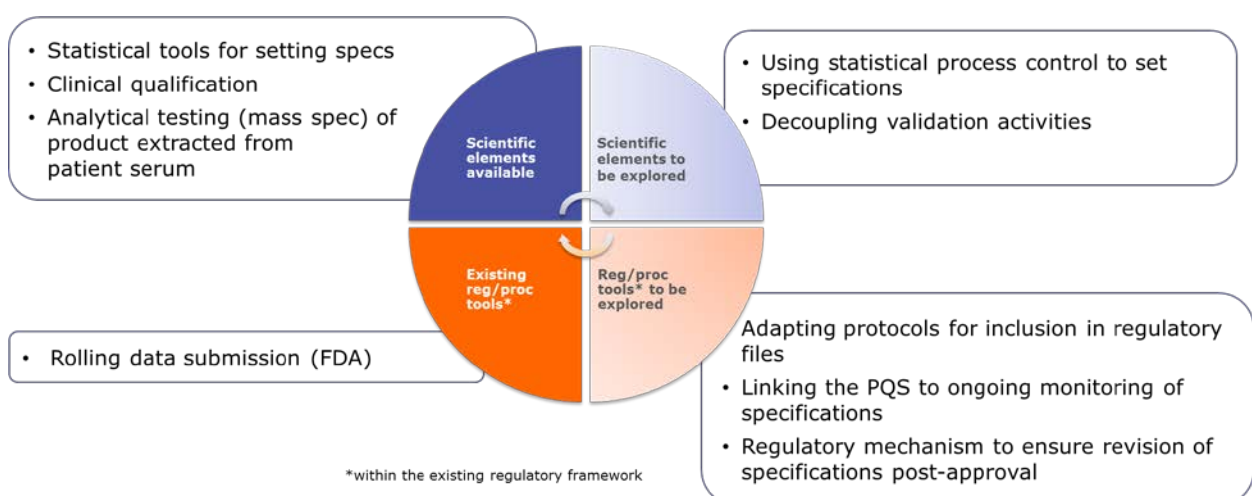
The challenges of conducting comparability studies in a time-sensitive manner, when moving from a contract manufacturer to a pilot plant, were discussed. Agreement can be sought on the analytical comparability protocol prior to submission of the regulatory file.

The benefits of transparent and open communications between the company and both agencies were highlighted, however FDA emphasized that any rolling assessment of data is only conducted in cases of urgent clinical need. The level and intensity of regulator/industry interaction should be viewed as a spectrum based on benefit risk and unmet patient need. Nonetheless, the positive experiences in terms of communication and interaction can be built on. It was also reflected on how best to increase inter-agency cooperation before, during and after the MAA/NDA assessment of PRIME/Breakthrough products.

Scientific elements or regulatory/procedural tools collected from Session 5a Case studies on process validation & control strategy

(Note that scientific elements/regulatory tools also covered in sessions 2 and 3 are not repeated in the below diagram).

Session 5. Control strategy/process validation - Bio



Several current and new tools are available to help in setting meaningful specifications for products under accelerated development. Approval of specifications wider than the available batch data is

possible. In such cases, regulators want to see a clear plan for how data will continue to be gathered post-approval. Regulatory protocols can be developed which outline how trending analysis will be monitored as part of the PQS. It is not practical to include a full description of the PQS in the dossier, however, elements of how the PQS is used in practice to gather the data can be included. Statistical process control can also be leveraged to provide further assurance that the specifications are appropriate. To improve certainty around comparability issues, analytical comparability protocols can be agreed up front between regulators and industry.

Main points identified for further follow-up:

- 1. Using pre-agreed batch analysis trending approaches supplemented by product understanding and statistical elements to set and confirm appropriate specifications**
- 2. Exploring the applicability of different protocol and plan types for inclusion into regulatory filings**
- 3. How the PQS can be best leveraged in the context of initial approval and post-approval to provide assurance that the specifications are appropriate**

Setting meaningful specifications based on the totality of the evidence including clinical data can be challenging when only a few batches have been manufactured. A Q&A document could include a mock example as to how this could be achieved. This could provide certainty for industry and serve as a reference for assessors. Such an example plan could include example batch data and the outline of how an ongoing process verification plan could be used to present the trending analysis to regulators. It could highlight how a statistical plan can be agreed in a PACMP at the time of approval so that meaningful specifications are established once sufficient batch data is available.

6a. Comparability

Session Lead: M. Hoefnagel (BWP member, EMA)

Industry case studies

Risk-based assessment of comparability for a mAb. A. Clinch (UCB)

Accelerated development brings a number of CMC challenges, not least the development of a commercial process within considerably reduced timelines. With respect to comparability, making changes late in development brings challenges, especially with reduced timelines and potentially limited pre-change data.

ICH Q5E already allows for a risk-based assessment of comparability, through the assessment of "relevant" quality attributes. However, applicants tend to be conservative and perform full comparability assessments of changes as a matter of course, including extensive characterisation. This may not be necessary, depending on the extent of the changes.

An example of a risk-based assessment of comparability was presented. This is a multi-step approach, beginning with an assessment of the potential impact on quality attributes for each individual change. Other considerations include whether the analytical methods are capable of detecting changes in the quality attributes and whether there are any other relevant data that could support the comparability exercise, such as small-scale data, platform data and/or prior knowledge. Each assessment is justified, and this forms the initial comparability exercise. After the studies, the data are reviewed, and if comparability is demonstrated, there are no further actions, but if there are any issues, then the risk assessment is repeated and additional studies are performed.

Examples of different comparability packages devised using the risk assessment tool were provided.

ATMP comparability challenge case study. M. Jeschke (Novartis)

The presentation focused on the challenges encountered during manufacture of autologous products leveraging experience from the commercialization of a CAR T cell product. Due to the high-unmet medical need, and thus short development time lines, in conjunction with limited process and product understanding, process changes are inevitable, even late in development or post-approval. Compared to Biopharmaceuticals comparability exercises are required more frequently for ATMPs, they are usually more complex, and analytical data might not suffice to demonstrate comparability.

A robust risk assessment of the impact of proposed process changes is the basis for the decision on whether comparability studies are required as well as the design of the studies. The defined process map governing the change control was presented and general requirements, concepts and principles for comparability study design for CAR T cell products, were discussed. Manufacturing of batches for comparability is usually done at full scale, using 'Split apheresis' due to high donor/patient variability. The use of surrogate starting material, e.g. from healthy donors is possible but its suitability needs to be well justified. A side-by-side stability program or short-term stress testing (in-use stability) is needed if the change has the potential to affect product stability. As cell products cannot be fully characterized, the inclusion of a matrix of functional assays is valuable. The analytical program to show comparability of the product quality before and after process changes, includes measures of process performance (e.g. growth rate, cell volume, viability); results of QC release testing; biological activity (product functionality) measuring responsiveness to target cells, such as cytotoxicity, cytokine profile, proliferation; and additional cell characterization (non-GMP) such as cell population analysis / immunophenotyping. Understanding of assay variability is critical to set appropriate comparability acceptance criteria.

Approaches to Comparability. M. Alai-Safar (Kite Pharma)

The presentation was prepared based on a licensed CAR-T cell product, YESCARTA.

Process comparability is the Key to managing process changes. Process characterization has been performed in support of comparability studies. The process characterisation programme involves a formal risk assessment of quality attributes based criticality using the 2 dimensions of severity and likelihood.

Process characterization studies have been executed to determine the impact on relevant product quality attributes and process performance, at scale.

Several comparability studies have been performed to support the introduction of process changes and process transfers to new manufacturing sites. Both equivalence and expectation approaches were used.

Under both approaches, comparability included demonstrating a number of process parameters meeting the expected established ranges.

Long-term stability data may not be required for comparability purposes of CAR-T cell products, if supported by risk assessment. The basic consideration is that CAR-T cell products are very stable under their normal storage conditions (in the vapour phase of liquid nitrogen ($\leq -150^\circ\text{C}$)). A short-term study (e.g. one month) may provide the supportive data.

A question was posed: Can comparability be executed with surrogate material at scale as part of process characterization, followed by concurrent validation using patient material? Can the product be released after meeting approved protocol acceptance criteria prior to filing the data package with regulators in order to expedite availability to the patient? Views in relation to these questions were provided in the Panel discussion.

Panel discussion

Regulators: M. Hoefnagel (BWP, EMA), T. Solstadt-Saunders (BWP, EMA), M. Menezes-Ferreira (BWP, EMA), E. Lacana and M. Ramanadham, (CDER, FDA), and A. Byrnes (CBER, FDA); Industry: A. Clinch (UCB), M. Jeschke (Novartis), M. Alai-Safar (Kite Pharma)

Two related issues were discussed:

*Question 1: **Launching from clinical manufacturing**: Is analytical comparability of clinical vs. commercial material in BLA/MAA and clinical comparability post-approval (commitment) acceptable?*

*Question 2: Is comparability with **surrogate material** from at scale non-GMP manufacture, followed by concurrent validation using patient material acceptable?*

An EMA colleague clarified that when validation is done with healthy donor materials it is difficult to set appropriate specifications, because healthy donor and patient materials may not have the same behaviour. Therefore it would be good to have a comparison between patient and healthy donor materials to understand the representativeness of the healthy donor material for the actual product. This should at least include the critical part of the process.

*It was clarified by an FDA colleague that **launching with only clinical manufacturing** is feasible if the facilities are GMP compliant. Comparability exercise could be done after the BLA is approved when comparability from clinical to commercial manufacturing is carried out. If analytical differences are observed, additional clinical data may be required. Furthermore, depending on the product and the disease study only on healthy volunteer material for analytical comparability might not be appropriate, because patient material may be very different, as a result of the disease or, for example, in oncology setting due to the effects of chemotherapy on the cells.*

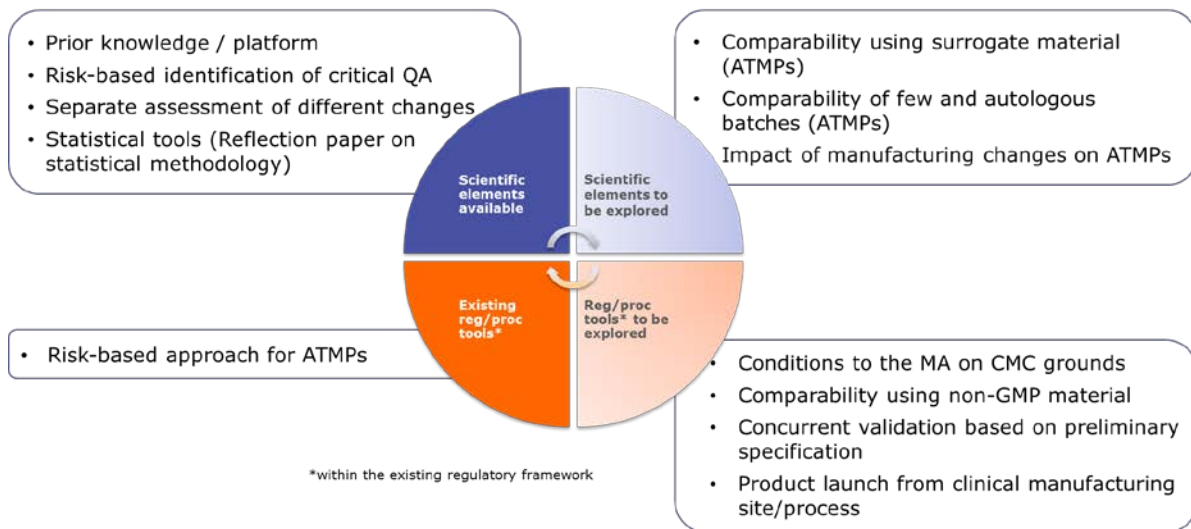
*An Industry representative asked if it would be possible to apply for a marketing authorisation with a validated clinical manufacturing process and to **validate the commercial manufacturing post approval**. An FDA colleague commented that sometimes validation at the clinical facility can be acceptable to have the product faster on the market but there should be appropriate validation data.*

Furthermore an EMA colleague suggested that if there is some remaining material left from the patient it should be retained for analysis to avoid the use of surrogate material. Although it was also cautioned that using patient material could be non-ethical. Often the autologous batches consist of limited material, and for some treatments, the more material the patient gets back the better (clinical benefit).

*An EMA colleague stated that **concurrent validation with patient material** is accepted at the moment for products under conditional approval and for ATMPs, when there is limited availability of the starting materials and/or where there is a strong benefit-risk ratio for the patient. For some and that for some products, in specific indications, this may be the only way to validate the commercial process with patient material.*

Due to the focus of the workshop on CMC aspects of comparability, aspects of clinical comparability linked to CMC changes and requirements for clinical exposure of commercial material, were not discussed. Clinical aspects of comparability are a potential topic for future discussion in a different forum.

Session 6. Comparability - Bio



Several tools exist which can be used in the strategy to demonstrate comparability between the different development phases of the manufacturing process. Prior knowledge from similar products (platforms) or different products can be used to assess the impact of specific manufacturing changes. Separate assessment of individual changes could be acceptable when the expected impact is also expected to be independent for the different changes. Separate comparability data could be acceptable (dependent on the type of change, type of manufacturing process and type of product). Statistical tools can be useful in comparability settings where sufficient batch data are available. The risk-based approach for ATMP is an established regulatory tool that permits adaptation of the data in MAA to the specific risks of the product.

Development of more knowledge of the **impact of manufacturing changes on ATMPs** is needed for an adequate risk assessment. Most of the currently available knowledge is present in registration dossiers and not publicly available. It would be of great benefit if this information was published. To make this possible, it should be considered that this can be done in a "safe haven" fashion to remove any potential hesitations, other than competitive considerations. An effort to publish this information generated by Industry and learned societies could be considered.

Main points identified for further follow-up:

A number of scientific elements and regulatory tools were identified and highlighted which warrant further elaboration by Regulators in a Q&A/guidance document. The below points are identified specifically for joined EMA-FDA follow-up:

- **Comparability using surrogate non-patient material (e.g. healthy donor material) at scale and follow up with concurrent validation using patient material**

For some products the use of patient (or patient-specific) material for demonstrating comparability is not possible (often for ethical reasons or due to limited availability). Development of scientific knowledge on the difference between healthy donor materials and patient materials in relevant manufacturing processes is needed. It would be useful if (all) existing experience would be published. That would be good resource to assess new comparability cases.

While it could be acceptable to demonstrate comparability using healthy donor material, this should eventually be confirmed when product is manufactured for patients. For these situations **Concurrent**

validation (based on preliminary specification) validation could be acceptable (for ATMPs see also GMP for ATMPs guideline).

- **Risk-based identification of critical QA impacted by manufacturing changes and studied in a comparability exercise**

A risk-based approach (RBA) could potentially be used to narrow the comparability study by identifying CQA impacted by manufacturing changes. This could yield proportionate requirements on the comparability data based on risk as evaluated and justified by the company. The regulatory acceptability of such an approach should be further evaluated and regulatory guidance could be developed.

- **Product launch from clinical manufacturing site / process**

Product launch from clinical manufacturing (site/process) can be acceptable for products with an established potential to address an unmet medical need. Transfer to the commercial site/process requires appropriate (often extensive) comparability data to ensure product efficacy and safety. This may also include clinical comparability data that have to be obtained post-approval.

- **Comparability of non-GMP material (see also session 4 on GMP)**

Comparability using non-GMP material is an issue that sometimes arises when material used in a clinical study was manufactured in a facility without an official GMP license (e.g. a research site outside of the EU) or when for a comparability study material is manufactured in a non-GMP facility. Regulatory tools to deal with these situations have to be established.

- **Comparability of few and autologous batches**

Comparability of few and autologous batches is challenging, because of the inherent variability a limited number of batches is rarely sufficient to reliably demonstrate comparability. Split batch manufacturing could help to partly overcome this. Further evaluation of the use of few batches (e.g. from studies using different healthy donor batches using similar manufacturing processes) could provide additional information that can be used in a risk assessment and to formulate the post-approval requirements for confirmation.

- **Conditions to the MA on CMC grounds (See session 9 Regulatory Tools)**

7a. Stability

Session lead: M. Welin (BWP member, EMA)

Industry case study

Stability: Predictive Stability Models to Extrapolate Shelf-life. A. Lennard (Amgen)

Obtaining sufficient stability data for a drug product in an accelerated development program is typically on the critical path to support a desired shelf-life of at least 24 months. It is proposed that stability data trends for a biologic BTD/PRIME product be extrapolated using mathematical models that are supported by predictive stability models generated from prior knowledge stability of structurally similar molecules. Such extrapolation takes elements from ICH Q1E, typically applied to small molecules, and reinterprets the biologic stability guideline ICH Q5C by applying expectations for 'primary lot' stability data using the predictive stability model. Success of this type of approach requires acceptance that risks in extrapolation of biologic stability data are appropriately mitigated by stability prior knowledge on similar products and post-approval commitments.

The predictive stability model would be mapped onto a mathematical extrapolation, of the real-time, real-condition BTD/PRIME stability data. The Sponsor should provide a rationale for any statistical analyses used and for the parameters identifying fit, both within the model and to the real-time stability of the BTD/PRIME product. The proposed modelling would be verified on a continuous basis as product stability data are obtained and backed up by commitments to report new trends, OOS results etc. The generation of a predictive stability model and its application should be agreed in advance with the agency.

Example IgG stability data were provided, for typical stability-indicating attributes, to illustrate predictive stability modelling. For frozen drug substance, since no attributes change over time under these storage conditions, the risk for extrapolation is considered very low. Drug product (stored liquid) data were provided for high molecular weight 'dimer', cation-exchange acidic and basic peaks, and potency that support extrapolation of the BTD/PRIME product stability data trends.

Proposals were presented to support extrapolated BTD/PRIME stability data, in the absence of applicable prior knowledge stability models that included analyses of accelerated stability data, additional stability time-points, enhanced commitments and limited 2-fold extrapolation.

Panel discussion

Regulators: M. Welin (BWP member, EMA), E. Lacana (CDER, FDA), A. Byrnes (CBER, FDA);
Industry: A. Lennard (Amgen), M. Goese (Roche)

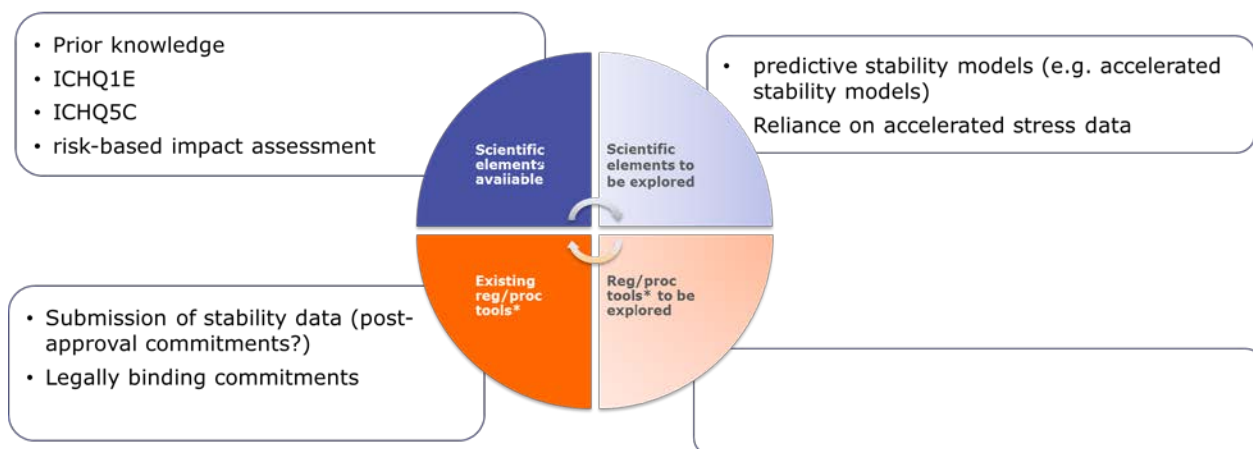
The panel discussed the use of models in Accelerated Stability Assessment Protocols. This question would deserve a meeting on its own for more discussions on how much data would be needed to verify the model etc. In general, the panel felt that the principle could be acceptable. Stressed data could be submitted to further support the claims. What matters is the trend, not the actual levels of degradation seen in different products. The trends should then be applied to what could be claimed as clinically qualified levels for each quality attribute for the BTD/PRIME product and the release requirements back-calculated from the level observed at the intended shelf-life.

In cases where the data for the new product follows the model, it should be possible to set acceptance criteria based on the model, with the provision that the product specific stability will be monitored and action would be taken in case the results no longer fit the model. Even if not strictly in line with ICH Q5C, this would follow the same principles that are applied for clinical trials.

There are situations where the models do not fit. Regulators highlighted that it was important to find out why and apply this knowledge to new products in order to decide early on if the model would fit or not. If the latter, applicants need to justify stability claims by product specific data or redesign the molecule/ formulation to avoid these problems by removing the features. Industry experience was that for one product the model did not fit. There was an extra event occurring with a product (linear increase of HMW species). Product knowledge and accelerated data can help to predict this.

Scientific elements or regulatory/procedural tools collected from Session 7a Stability.

Session 7. Stability



Standard stability requirement in line with Q5C may not be feasible for accelerated access product as this may delay the submissions. Making use of prior knowledge and accelerated stability studies may be helpful for Applicants to base their claims on shelf life in cases of incomplete data sets. In cases where the data collection is carried out post-authorisation, applicants should submit protocols to support these studies.

Main points identified for further follow-up:

▪ Predictive stability models

The proposal is interesting and may help to set a commercially acceptable shelf life to a product even if full time, product specific data have not been submitted. Further work is needed to understand the possibilities and weaknesses of the proposed model.

▪ Reliance on accelerated / stress data

Accelerated and or stress stability data have in the past not been acknowledged to the same extent for biological products compared to small molecules. A lot of data has however been gained over the years and it would be useful to further discuss the predictability of accelerated/ stressed data to support a claimed shelf life beyond what has been shown by real time data. Stressed data may also help in understanding if the product will follow the predictive stability model as described above.

5b. – 6b. Chemical Breakout session, control strategy and stability

5b. Control strategy

Session lead: K. Olofsson (QWP member, EMA)

Industry case study

Impurity Control Strategy for an Oncology drug. A. Teasdale (Astra Zeneca)

A case study that focused on the accelerated development of an anti-cancer agent was presented. The challenges articulated mirrored those experienced by many, specifically including the lack of large batch data to allow establishment of a specification. The example sought to highlight the very real risk of establishing limits based on product performance alone, using a very small data set; that this could lead to specification failures that could ultimately limit access of the medicine to patients. It was stressed that a balanced approach was needed, one that took into account both batch data and pre-clinical data.

In contrast to the challenge of establishing appropriate limits for non-mutagenic impurities, the case study highlighted how key principles within ICH M7 are much more closely aligned to the adoption of a true risk based approach. Principles include safety limits that take into consideration both patient population and study duration. Also discussed was the importance / value of flexible options to demonstrate control; in particular option 4 within ICH M7 where control can be demonstrated through use of purge concepts. This relates to the prediction of removal based on a comparison of the physico-chemical properties of an impurity and relating this to the process conditions employed, using this to numerically calculate and predict the potential removal of the impurity in question.

Panel discussion

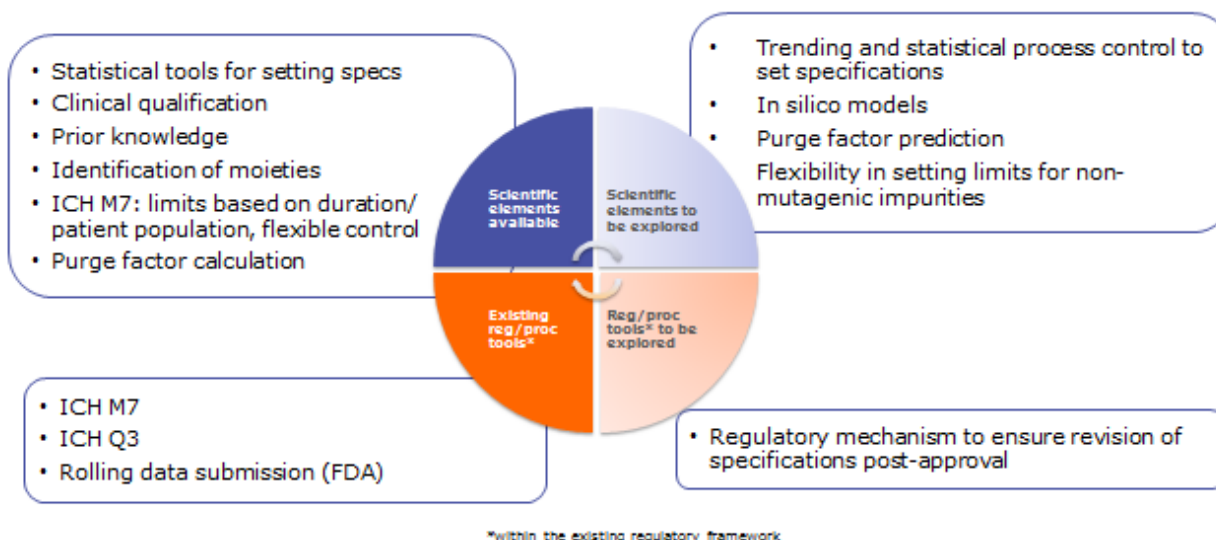
Regulators: K. Olofsson (QWP member, EMA), M. Ramanadham, S. Furness and R. Sood (CDER, FDA);
Industry: A. Teasdale (Astra Zeneca)

Regulators questioned how the predicted purge factors are validated. The case study presenter explained that there is a systematic bias due to solubility and that the method under predicts by a factor of 10.

It was indicated that a software that would make the predictions for reactivity is being developed. This is an example where prior knowledge can be converted to established knowledge. Preliminary results from the risk of contamination of nitrosamines in the synthesis of candesartan supported that the method could be useful.

Another question from the audience on how the industry would manage changes during the lifecycle and if systematic re-evaluations would be made regularly was raised. From the audience, the response was that lifecycle changes with the potential to impact the control strategy, such as process changes or changes to the input materials, are evaluated systematically in the same way as for the original filing. The type and amount of data to be presented should be determined on a case-by-case basis.

Session 5b. Control strategy - CHE



Statistical tools that can assist in the interpretation of data and the setting of limits in specifications are available. An alternative to this approach is clinical qualification, which provides valuable data but is dependent on time and resources. Prior knowledge is an existing scientific element which may relate to knowledge on the relevant substance or formulation, it could be platform knowledge, or it could also be more general knowledge covered in scientific publications. Prior knowledge may be used to define the control strategy.

Identification of moieties, e.g. chemical groups or substituents that are known to be reactive and/or genotoxic, is an important aspect in the control of toxic and/or genotoxic impurities. The identification may be made by prior knowledge or by in-silico methods. Limits should be set with reference to ICH M7 and ICH Q3. Purge factor calculation is a tool to predict the likelihood of carry-over of impurities from one step to another or to the final drug substance based on the physico-chemical properties of the related substance. These calculations can give an estimation of the likelihood that an impurity persists in the manufacturing chain over one or several steps and can, if properly justified and validated, be used as a tool to justify its control strategy.

Main elements identified for further follow-up and for EU-FDA joint follow-up:

1. The acceptance and use of **in-silico models and purge factor calculations**. Specifically, it may be of importance to discuss what level of information on the methods and their respective validations need to be presented in an MAA.
2. What can be learned from how option 4 of ICH M7 has been successfully implemented in product control strategies?
3. What data would be necessary to support **setting of limits** and qualification of impurities based on **non-clinical (e.g. in-silico) safety studies**?
4. **The regulatory mechanisms to ensure revision of specifications post-approval**. This may be of importance as the Authorities may have limited insight in the exact mechanisms of the methods and it is not evident how an evolving database should be handled.

6b. Stability

Session lead: T. Agasoster (QWP member, EMA)

Industry case study

Supporting Accelerated Development - Stability approaches. R. Ogilvie (Pfizer)

A joint case study from several companies (GSK, Pfizer, Astra Zeneca, Novartis and Vertex) was presented. Evaluating stability of a drug substance or drug product at normal storage conditions bring the 'real time' cost of these studies to a development program. These studies can constitute the critical path to many development and medicine supply situations (such as commencing clinical investigation, making development changes or post-approval changes and indeed in readying a program for registration). Utilising alternative approaches to the evaluation of stability and using more 'aggressive' (but relevant) conditions of temperature and humidity can more rapidly provide data to model and predict stability under normal storage conditions. Such accelerated stability approaches are now a well-established field, with many papers and monographs providing 'prior knowledge' of how science has progressed in this field since e.g. ICH Q1 guidance was established.

This presentation included several examples, from different companies, to show how accelerated stability evaluation can expedite the start of clinical investigation, manage drug substance and drug product changes and even support stability issue resolution by using modelling, prediction and stability comparison. Development changes and 'late-breaking' challenges can result in rapid development programs under PRIME / Breakthrough and it is of great value if there are means of managing these events without having to wait for real time stability data. The examples showed how accelerated stability approaches can support rapid development by taking the 'real time' stability study clock off the critical path, allowing data generation under normal conditions to become confirmatory rather than pivotal in developing product understanding.

Increased regulatory allowance for such data to be used provides very valuable time saving opportunities for a rapid CMC development program.

Panel discussion

Regulators: T. Agasoster (QWP member, EMA), S. Furness and R. Sood (CDER, FDA); Industry: R. Ogilvie (Pfizer), A. Kuzmission (Vertex), M. Ganapathy (MSD)

An industry representative emphasised that accelerated stability approaches should enable the managing of any post-approval changes to maintain robustness and supply as efficiently as possible.

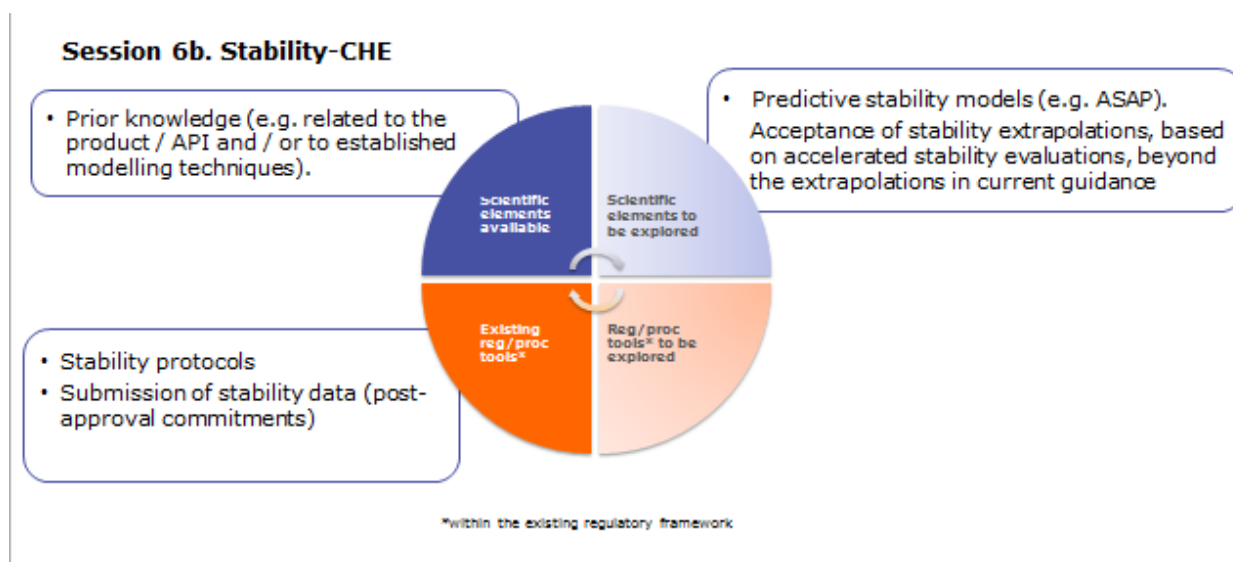
With regards to chemical stability predictions these accelerated stability approaches are well-established prior knowledge, and can also provide knowledge of the degradation pathways. For physical stability tests such as dissolution, there is less knowledge/experience on whether these accelerated approaches can make accurate predictions. Therefore drug substance stability is easier to predict using these approaches than drug product. Representatives from Industry mentioned that companies have started to make investigations related to accelerated stability testing of physical attributes, including dissolution (see references).

An industry representative expressed the view that the ICH Q1 guideline on stability was conservative and over its time. Industry felt that, in the EU guideline on quality documentation for clinical trials, the guidance on extrapolation of ICH stability data could be interpreted in a strict way by some assessors. It was stressed that for PRIME products under development addressing an unmet medical need, the generation of stability data could be on the critical path and limit the progress of initial clinical trials. The difficulty is that at the stage of an application for a Phase I clinical trial it is not known whether it will be a PRIME product or not. A representative from QWP, EMA recognized this, and pointed out that quality assessors should be open to consider accelerated stability approaches, supplemented with other

data where relevant, especially for phase I studies for products with a potential unmet medical need. If some assessors hesitate to consider such data, it may be due to lack of data/information/sound justification, and/or lack of experience with this kind of data since this is a relatively new field. In addition to the accelerated approach for phase I studies, normal ICH stability studies should be run in parallel. This will reduce the risk associated with clinical material going OOS during its assigned expiration period, since the company will be able to react quickly should the stability trend from concurrent studies, being run under ICH storage conditions, show clinical material being at risk of going out of specification.

A representative from QWP, EMA indicated that allowing such stability approaches, in general, and for MA applications (e.g. for generics where there are alternatives in the market or for new chemical entities where there is no previous knowledge), would be difficult. For variations it would be easier to accept, given the knowledge already acquired on the product. This concept is also described in the draft ICH Q12 in Chapter 8 on Post-approval changes for marketed products, on a stability data approach.

Scientific elements or regulatory/procedural tools collected from Session 6b Stability.



Prior knowledge is an existing scientific element which may relate to knowledge on the relevant substance or formulation, it could be platform knowledge, or it could also be more general knowledge covered in scientific publications. This was discussed as one of the elements available to support the assignment of a re-test period/shelf-life.

Predictive stability models (ASAP) is a scientific element to be explored. They have been described in many publications for degradation processes, and may for such reactions be seen as prior knowledge. This strategy has to some extent been used for post approval changes. The benefits of ASAP include rapid availability of model data and also knowledge of the degradation pathway. The model should be justified by demonstration of its predictive nature for the relevant parameters.

With regards to the regulatory tools, at present it is possible to extend a shelf life/re-test period based on additional data during MAA review or after approval (e.g. through a post-approval protocol and stability commitment) based on the data available including extrapolation as per ICH Q1E, if applicable.

Other ways of updating the shelf life post-approval based on on-going stability studies could be explored. It could be worth exploring further if, in some cases, an extended shelf life can be allowed

which is to be restricted if the real-time results are not as expected. In other cases, an initial (limited) conservative shelf-life could be defined based on the data provided, which can be extended post-approval. Which of these alternatives to select could depend on the stability of the active substance/product and the supportive modelling data available.

Main elements identified for further follow-up and for EU-FDA joint follow-up:

1. Consider the development of some **guidance / Q&A on the use and acceptance of accelerated stability data** (e.g. predictive stability models to define shelf-life and / or to verify that established shelf-life is not impacted by process improvements).
2. Exploration of how applicants can utilize a **combination of prior knowledge of product and API stability**, extrapolation of real-time and accelerated stability data and modelling to ensure provision of data to support shelf-life establishment is not the critical path to provision of an accelerated product to patients.

8. Summary of the afternoon sessions (Biologicals & Chemicals)

M. Hoefnagel (BWP member, EMA) and J. Limberg (QWP member, EMA)

The biologicals and chemicals groups reconvened and a summary of the discussions held at the separated sessions was provided in order to provide each subgroup with an overview.

9. Regulatory tools to support early access

Session lead: D. Hernan (Quality Office, EMA)

Presentations

Industry perspective & case study: *Regulatory tools to support early access – Industry perspective.* Y. Momonoi (Celgene)

The industry perspective for the session on “Regulatory tools to support early access” focused on two aspects, the use of Agency meetings during development and the use of PACMPs. To illustrate different types of interactions during development, three scenarios for a site addition of an ATMP were explored; frequent interactions with an Agency, separate Agency meetings, and the parallel scientific advice (PSA). Informal frequent communications between a Sponsor and an Agency best supports accelerated development with rapid turnaround on feedback but may be limited in scope in terms of the type of topics that can be discussed. Separate Agency meetings may be a shorter process than the PSA in terms of receiving feedback from at least one Agency. With a PSA, a Sponsor can receive EMA and FDA recommendations at the same time, but receiving one agreed plan is not guaranteed. Establishing a PACMP or a comparability protocol in a post-approval setting for rapidly developed products can be a challenge since the understanding of the manufacturing process may still be evolving, making it difficult to meet the information requirements. PRIME/BTD products may have complex manufacturing processes, often without prior knowledge. They undergo rapid development to meet patient needs and the clinical plan evolution. As such, rapid change implementation is often required to ensure expedited product development and continued supply. For this reason, expansion and more flexibility around existing regulatory tools, such as more interactions with the Rapporteur outside the formal SA and flexibility and dialogue around the required information for PACMPs, are desirable.

The aim of this session was to follow-up on the scientific challenges discussed earlier and explore the existing regulatory tools in EU and US regulatory frameworks and how these could be adapted to facilitate timely patients access to medicines that address unmet medical needs.

In EU, these include early access tools such as i) accelerated assessment that allow for a faster authorization procedure; ii) conditional marketing authorisation in case of a non-comprehensive clinical data package which is subject to certain requirements to be met, including conditions to the marketing authorisations (i.e. specific obligations) to be fulfilled post-authorisation to address uncertainties and confirm the benefit/risk; or iii) PACMPs that allow for the post-approval generation of data based on an agreed protocol. Other pre-authorisation tools available to enable early dialogue with regulators and support prospective planning are: a) scientific advice/protocol assistance during development, including parallel EMA-FDA scientific advice and consultative advice (which are available to all products); b) the PRIME scheme, and c) pre-submission and d) clarification meetings with the Rapporteurs and EMA.

It was stressed that the use of early access tools can facilitate a faster evaluation procedure, but do not reduce the data requirements at the time of MAA submission. The data needed to demonstrate quality, safety and efficacy have to be provided in the MAA dossier.

Applicants aiming at early access are strongly encouraged to discuss in advance their overall development plan, including their quality program, with regulators to be prepared on how to address uncertainties, avoid delays, and enable an accelerated assessment (if applicable) and ultimately achieve a successful MAA.

FDA Regulators' presentations on regulatory tools. A. Byrnes (CBER, FDA)

This presentation described 1) how sponsors of products in expedited pathways can communicate with FDA, and 2) potential CMC flexibilities that may be available.

Dr. Byrnes noted that communication is the most important tool available when a sponsor desires CMC flexibility, and enhanced communication opportunities are available for products with Breakthrough or CBER Regenerative Medicine Advanced Therapy (RMAT) designation. During the investigational stage, sponsors can interact with FDA during major milestone meetings (e.g., initial breakthrough designation, end of phase 2, pre-NDA/pre-BLA) and can also communicate between milestones (amendment submission to the IND). Challenging topics may require repeated interactions, for example comparability protocols, potency assays and stability protocols. During review of marketing applications, there are opportunities for both formal status updates and for ad hoc communications such as teleconferences. After licensure, communication continues via formal supplement submissions to the license, as well as meetings and teleconferences if needed.

Dr. Byrnes emphasized that the goal is always to ensure the availability of a quality product at the time of license approval, but within this framework there may be some flexibility available, as described in FDA's 2014 guidance: "Expedited programs for serious conditions – drugs and biologics." Specific examples of potential flexibilities include stability assessment, concurrent release and comparability protocols. There is also potential flexibility in the timing and order of module submissions to a license application (a "rolling" application), but module 3 must be complete at the time of submission, and the review clock starts after all modules have been submitted. FDA encourages discussion of major CMC issues during the investigational stage so that challenging CMC issues can be resolved by the time that module 3 is submitted.

Panel discussion

Regulators: C. Blanc (Procedure Management, EMA), C. Bouygues (RA Office, EMA), Z. Hanaizi (PRIME coordinator, EMA), K. Olofsson (QWP member, EMA), M. Hoefnagel, (BWP member, EMA), A. Byrnes (CBER, FDA), M. Ramanadham and E. Lacana (CDER, FDA); Industry: Y. Momonoi (Celgene), D. Wilkinson (Biogen), M. Goese (Roche)

During the panel discussion, the **opportunities available in PRIME** were further explained: early appointment of Rapporteur and kick-off meeting with the full assessment team where applicants can flag issues and topics key for their development and discuss them, and redirect to SA if required. The importance of having regular interaction to follow the progress and, if needed, organize an ad-hoc interaction with the Rapporteur or follow-up SA was stressed.

The use of the **EMA-FDA parallel scientific advice** was also discussed. An industry representative asked whether it would be possible to get PMDA views in the consultative advice. It was noted that this is something that could be explored in the future but at present the procedure involves EMA and FDA only. Experience so far has shown that there has been little overlap between PRIME and SAKIGAKE products that would justify the additional complexity of adding PMDA to this parallel procedure.

Industry expressed their wish for more informal discussions during development, MAA/NDA evaluation and post-approval phase. Regulators remarked the need to have records of the discussions/review in case the assessment team changes in order to document the interaction and not to give contradictory guidance. EMA clarified that pre-submission discussions on critical issues on PRIME products are expected to be channeled through the scientific advice procedure, thus enabling a response from the Agency's committees and working parties.

In this context, industry indicated the usefulness of having a meeting between regulators and industry to discuss specific topics (e.g. for CAR-T therapies stability requirements, solutions for comparability studies when you cannot use healthy donor material) to share learnings and find solutions.

However, it was also highlighted that the PRIME guidance foresees the possibility for other interactions: in case the applicant identifies a topic warranting further discussion with regulators, they should contact the EMA who will advise on the suitable way to address the matter. Where appropriate, the Agency can support interactions with the **CHMP/CAT Rapporteur** (e.g. ad-hoc teleconferences) with a view to resolve minor issues or for the applicant to provide updates on their development.

Overall, it is expected that the applicant keeps the EMA and Rapporteur informed on the implementation of the scientific advices received and on the progress made or hurdles encountered on the development programme.

FDA colleagues explained that it is just as important for MAH's and manufacturing sites to coordinate manufacturing and GMP readiness as it is for assessors and inspectors to coordinate their respective activities to facilitate development, approval, and implementation of a breakthrough or PRIME product.

Although **PACMP** is a very useful tool, it was recognized that in some cases it can be challenging for industry to use these for accelerated fast-evolving programs.

Following the morning discussion, regulators clarified that when required, especially in the context of SA for ATMPs, the interaction between assessors and inspectors is established. Since GMP issues can be a blocking issue in some applications, Industry is advised to raise relevant questions at the kick-off meetings and/or SA procedures.

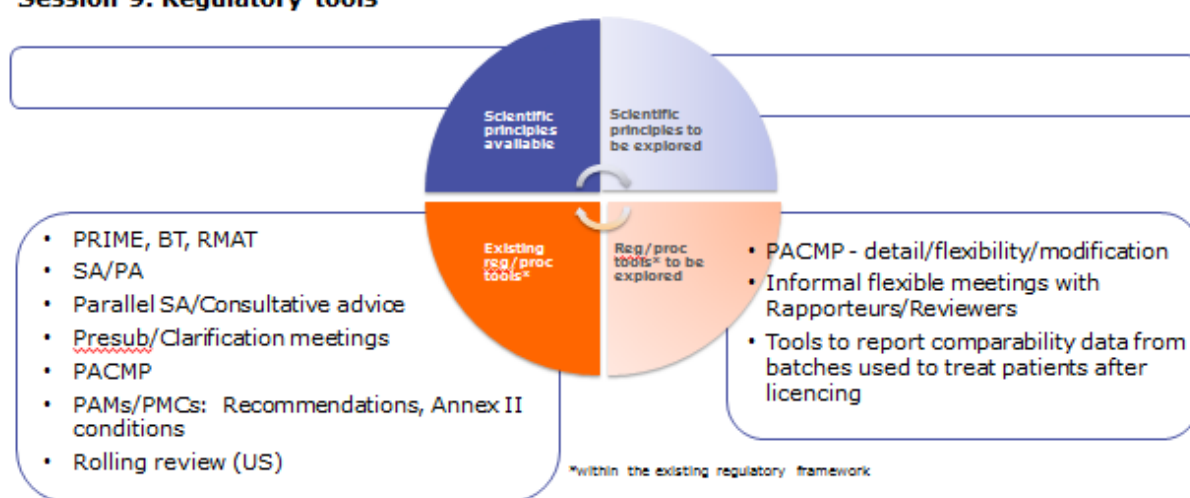
Industry was recommended to establish a strict coordination between the applicant and the CMOs across the board. There have been cases where manufacturing facilities were not ready or not aware of the development program.

Industry enquired about exceeding an acceptable range of a process parameter, in an accelerated program filing a constrained manufacturing process. Regulators indicated that the approach should be similar as for OOS, e.g. trigger an investigation, ensure there is no impact to product quality and submit relevant information to the Agency to reassure that it does not impact product safety and efficacy, etc. Depending on the clinical indication wider process ranges could be proposed (e.g. acute versus chronic use).

During this panel discussion industry also highlighted the specific importance of stakeholder workshops, such as this one, and encouraged the regulators to consider a similar follow-up event with industry.

Scientific elements or regulatory/procedural tools collected from Session 9 Regulatory tools.

Session 9. Regulatory tools



Main elements identified:

PRIME specific tools: For PRIME these regulatory tools include: early CHMP Rapporteur appointment, appointment of EMA quality specialist to follow the development of the product, kick-off meeting with multidisciplinary expertise from EU network to discuss the development plan, EMA and/or EMA and FDA Scientific Advice/ Protocol Assistance /Parallel scientific advice/Consultative advice at key development milestones/decision points and a pre-submission meeting prior to filing. Note that Scientific Advice/ Protocol Assistance Parallel scientific advice/Consultative Advice are also available for non-PRIME designated products. It should also be considered whether PRIME support can also be extended to the post-authorisation phase to facilitate lifecycle management.

EU early access tools for PRIME & non-PRIME products: During the assessment EU regulatory tools include: the accelerated assessment (faster review), conditional marketing authorization, and the establishment of specific obligations/conditions/post-authorisation measures (recommendations, or Annex II conditions, specific to quality shortcomings, in very exceptional circumstances) during the assessment to address uncertainties affecting the benefit/risk of the product. During the review clarification meetings to discuss concerns raised by the CHMP and applicant's strategies to address them can also be held to ensure there is a mutual understanding on the issues and way forward.

US FDA tools associated with Breakthrough Designation & RMAT: For products with BT and RMAT designation, regulatory tools include: increased opportunity for meetings with the FDA and intensive guidance on efficient drug development, beginning as early as phase 1. These meetings include an initial comprehensive BT (or RMAT) meeting, which is meant to provide an overview of the

state of development of the program. Senior managers attend meetings for BT and RMAT products. Meetings for BT and RMAT products are scheduled as type B meetings, which offer faster turnaround time than other types of meetings. For marketing applications, BT and RMAT products are eligible to be considered for rolling review, if FDA agrees. Rolling review allows for complete modules to be submitted at different times. In addition, BT and RMAT products may be eligible for priority review (faster review) of marketing applications.

Post-approval change management protocols (PACMPs): PACMP is an existing tool within the EU and US regulatory frameworks with great potential to facilitate the completion of comprehensive quality data packages for accelerated developments, where incomplete data packages are present at the time of submission. The applicant presents a summary of his strategy to conduct/complete the studies post-approval. The relevant data is subsequently submitted for review when available. This stepwise approach is aimed at achieving a faster and more predictable implementation of changes post-approval, since the MAH will have obtained prior agreement from the Regulatory Authorities about the proposed strategy and tests to be conducted.

PACMPs are not a new tool and are available for all type of submissions, but their full potential remains to be further explored (e.g. within the ICH Q12 framework).

The challenge to prepare PACMP or comparability protocols for rapidly developed products in the scenario where the manufacturing process is still evolving is noted. In this regard, more interactions with reviewers outside the formal Scientific Advice procedure and flexibility and dialogue around the required information/adequate level of detail in an accelerated setting for PACMPs is requested.

Tools for comparability reporting post-marketing: Regulatory tools to report comparability data from batches used to treat patients after approval should be better clarified. For example, if these lead to change(s) in the established conditions (e.g. specifications) a variation/supplement would be required; whereas if the additional data to be submitted are to provide re-assurance of the interim limits agreed at the time of approval and no changes on these is to be made, the submission of these through a post-approval measure (PAM) –recommendation could be considered.

The following points were identified for specific EMA-FDA follow-up:

- **PACMP: level of detail to be included, flexibility, modification**
- **Tools to report comparability data from batches used to treat patients after licensing**

10. General discussion, summing up and way forward

Discussion

To conclude, **S. Ruiz**, *BWP chair/CAT member/CHMP co-opted member*, emphasised that regulators recognize the way innovation is changing the regulatory and scientific environment, which brings with it the need for dialogue and communication with stakeholders in order to jointly overcome the challenges faced. In this sense, the workshop provided a unique opportunity and the views expressed by industry colleagues were very welcomed. Regulators have listened to the various scientific challenges and both EU and US FDA regulators will aim to work on a global response to the challenges. She concluded by thanking the organising committee, consisting of both EMA/EU NCA and FDA colleagues for the work done in preparation of the workshop.

K. Pugh, *QWP chair*, valued the way that the workshop encouraged honest views to be expressed on both sides, regulators and industry. He pointed out that several points have been raised that require

further reflection and communication between industry and regulators. These will be reflected upon and followed up as appropriate in order to facilitate the early access to these medicines.

On behalf of FDA, **L. Graham**, *Director of the Division of Internal Policies and Programs (DIPAP) at CDER*, emphasized the shared goal of all parties present at the workshop, to want to get these products to the patients as soon as possible whilst assuring adequate product quality. She reminded that standards should not change because of a drug being 'breakthrough', however there is flexibility in how industry meets these standards. L. Graham also stressed to the audience to take further advantage of the communication channels that have been opened in this area in order to address the scientific challenges. In her view, the meeting suggested that we (EU, FDA, Industry) are moving towards a common understanding of the challenges and there may be the need for additional guidance on certain topics, which may need to go beyond current ICH guidelines in order to have the required flexibility.

She indicated that CDER/OPQ has an interest in evaluating the effectiveness of their policy documents, such as guidances (e.g. what's working, what's not working, identifying gaps). As part of those efforts, they need to gather feedback from stakeholders. Meetings like this provide one avenue for gathering that feedback. She emphasized the value of proactive, early, concurrent communication & dialogue between all parties.

A. Hidalgo-Simon, *EMA's Head of Specialised Scientific Disciplines Department* pointed out that this forum highlights the need for global involvement, which could be further extended to other regions in the future (e.g. Japan). The efforts by Industry to come with one voice were appreciated and the collaborative and multidisciplinary nature of the discussions (including quality assessors and inspectors and several product classes) provide a valuable perspective. She also highlighted the Agency's commitments to full support for those novel medicines with a high public health value, which includes developments following early and accelerated access approaches.

Dr. Hidalgo Simon reiterated that this event should be seen as a starting point for the discussions between EMA and FDA (in relation to accelerated programs) and mentioned that the interest from stakeholders for further events such as this one is well noted.

11. Key conclusions from the workshop

Problem statement/motivation

The timely development and delivery of good quality medicines to patients for unmet medical needs is a core motivation for Regulators and Industry alike. To support this early access, EMA and US-FDA launched the PRIME or Breakthrough Designation schemes. These bring about clinical development programs which move quickly into patients and/or pivotal studies. As a result, quality developments adaptation to these time limited scenarios is becoming necessary.

Scope/deliverables

The workshop provided a forum for Industry stakeholders, US-FDA and European Regulators (Assessors and Inspectors), who have expertise in small molecules, biological/biotechnological products and ATMPs, to discuss Quality (CMC) challenges that may arise with accelerated development and early access scenarios. Challenges and solutions were explored by means of a combination of real case studies, regulators' perspectives and panel discussions.

Scientific elements and regulatory tools which already exist, or which would benefit from exploration, to help address such development challenges, were identified and discussed throughout the sessions.

It was also evident that current paradigms for Quality should evolve so that emerging scientific knowledge and guidance and different regulatory pathways can be harnessed to support a timely access to new medicines, whilst ensuring quality remains at the heart of development and manufacturing, and safety and efficacy are not compromised. Mechanisms to facilitate post-approval improvements and allow continued dialogue between applicants and regulators are similarly essential. There was thus a consensus across all parties that many novel and existing approaches when applied effectively to product development and manufacturing can significantly contribute to deliver new products to patients with robust Quality packages.

The development of medicines for areas of unmet medical need thrives in an environment of increased collaboration and communication between industry and regulators. Frameworks such as PRIME and Breakthrough Designation can also provide opportunities to apply novel scientific elements and regulatory tools in a coordinated and product-specific manner to address some of the key challenges (e.g. development of control strategies, generation of process validation, comparability and stability data in shortened timeframe, new development approaches, innovative products, global developments and supply chains).

With many developments being carried simultaneously in different regions, the alignment of technical requirements between Europe and USA provides a good opportunity to stimulate and facilitate the global development of these priority medicines for the benefit of patients.

Next steps

The workshop discussions have brought to the surface several areas amongst scientific elements and regulatory tools that, in the view of the organizing committee, would merit further discussion and elaboration. The organizing committee proposes these topics for consideration by EMA and FDA for future work (i.e. workplans of the relevant committees and working parties):

❖ **Scientific areas to be explored:**

- Priorities for **Biologicals** (Models for the prediction of stability, batch analysis trending approaches/product understanding & statistical elements for specification setting)
- Priorities for **Chemicals** (exploring the use of ASAP models to predict stability, the use of in-silico models and purge factor calculations to set specification limits for impurities)
- Priorities for **ATMPs** (Comparability; Practical management of out-of-specification products [for autologous products (see recently published Question and Answer developed by CAT¹)] ; Quality development paradigm for autologous products)

❖ **Regulatory tools/procedures (for all products)**

- Avenues for provision of data during post-authorisation in addition to the established procedures (i.e. PACMPs, variations, recommendations, Annex II conditions)
- PACMPs (flexibility in timelines, detail and scope, specific guidance on PACMP application for ATMPs)
- CMC development plans (or 'quality lifecycle plans') specific to PRIME quality packages as a tool to describe the Quality development and product lifecycle planning.

¹ Questions and answers on the use of out-of-specification batches of authorised cell/tissue-based advanced therapy medicinal products (EMA/CAT/224381/2019)

- Continuation of PRIME product support in the post-authorisation phase and opportunities for communication
- Strengthened inspector-assessor interaction during the development phase (e.g. scientific advice)

❖ **Follow-up by Industry**

- Industry consortia to help generate and disseminate scientific findings relevant to the field through collaborative studies and publication of results
- Sharing of their proposals on use of certain scientific elements and regulatory tools with Regulators (for EU: EMA interested parties meetings, scientific advice procedures, kick-off meetings etc.)

❖ **Joint EU-FDA actions**

- Use of models for stability and shelf life determinations
- Innovative process validation approaches
- Launch from the clinical manufacturing site

❖ **Toolbox guidance**

In addition, the organizing committee proposes to develop a 'Toolbox- guidance' for PRIME products, which shall summarise the identified scientific elements/regulatory tools that are already available in the EU to address some of the challenges faced during the development of products under PRIME and generation of robust quality packages for MAA review . This toolbox will include scientific elements/regulatory tools applicable to small molecules, Biologicals/Biotechnological products and ATMPs.

It is also suggested to consider the above topics for further discussions, which may be useful for further development of regulatory guidance in Europe, the US and globally, and the evolution of joint guidance.

Glossary

The glossary contains definitions, where available in the regulatory framework and/or refers to other guidance documents or other EMA/FDA documents (e.g. workshop reports) where these concepts are explained further.

Accelerated stability program (ASAP): accelerated stability study which is executed for a duration of few days or weeks, using a range of temperatures, humidity conditions and storage times to predict and model long term active substance or finished product stability behaviour. It is based on isoconversion and the humidity-corrected Arrhenius equation. This definition refers to chemical entities only.

Concurrent validation: Validation carried out in exceptional circumstances, justified on the basis of a strong benefit-risk ratio for the patient, where the validation protocol is executed concurrently with the commercialisation of the validation batches (EU GMP Annex 15), instead of completed before the start of routine production. The decision to carry out concurrent validation must be justified, documented in the validation master plan (VMP) for visibility and approved by authorised personnel.

For ATMPs, the use of concurrent approaches is possible in cases of limited availability of the starting materials and where there is a strong benefit-risk ratio for the patient (see Guidance on GMP for ATMPs).

Continued / ongoing process verification: Documented evidence that the process remains in a state of control during commercial manufacture (EU GMP Annex 15).

Continuous process verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8).

Post-approval change management protocol (PACMP): A protocol which describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified. It is a step-wise approach in the assessment of changes, which allows an early evaluation of the strategy for the change and a later separate evaluation of the data produced based on the agreed strategy. Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the MAH will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.

Post-authorisation measures (PAMs): At the time of finalising a procedure or in follow-up of a signal evaluation, regulators may request that the applicant/MAH should provide additional data post-authorisation. This may be necessary from a public health perspective to complement the available data with additional data about the safety and, in certain cases, the efficacy or quality of authorised medicinal products. Such post-authorisation measures (PAMs) may be aimed at collecting or providing data to confirm the assessment of the quality, safety or efficacy of medicinal products in the post-approval setting.

The existence of such a system of PAMs does not aim at promoting premature approvals of marketing authorisations or post-authorisation procedures. The background and rationale for requesting PAMs will be described in the relevant assessment, which will present the context and nature of the PAM.

Prior knowledge (including platform technology): is an established term which is used in ICH Q8, Q10 & Q11 and various EMA guidelines, although this term is not formally defined. Prior knowledge is an established tool that is explicitly or implicitly used for informing decisions during pharmaceutical development and lifecycle management. In the context of pharmaceutical development and regulatory applications prior knowledge can be:

- internal knowledge from a company's proprietary development and manufacturing experience (e.g. historical experience based on similar compounds, products and processes, including data modelling, application of 'platform technologies', knowledge from previous filings),

- external knowledge such as reference to scientific and technical publications (including vendors data, literature and peer-reviewed publications). The application of established scientific principles (e.g. chemistry, physics and engineering principles and mechanistic understanding from studies evaluating structure-function relationships) is also considered to be prior knowledge.

Definition as laid down in *Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications* can be found at

(https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-party/quality-working-party-workshop-stakeholders-relation-prior-knowledge-its-use-regulatory-applications_en.pdf)

Protocols: In the context of this workshop, this term has been used to describe existing protocols that are an integral part of the MAA in module 3 such as stability protocols, cell bank qualification protocols, process validation schemes and design space verification schemes. These protocols are to be distinguished from PACMPs (Post-approval change management protocols (see above)).

Quality by design: A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8, R2).

Risk Assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (ICH Q9).

A risk assessment tool can be used to evaluate the potential impact of the manufacturing change on the CQA attributes. Uncertainties can be identified using risk assessment.

Risk-based approach for ATMPs is an established regulatory tool that permits adaptation of data in the MAA dossier to the specific risks of the product (see Part IV of Annex to Directive 2001/83 and EMA Guideline on the risk-based approach: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-according-annex-i-part-iv-directive-2001/83/ec-applied-advanced-therapy-medicinal-products_en.pdf).

Risk management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk (ICH Q9).

Statistical tools: A Draft Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development has been published (<https://www.ema.europa.eu/en/statistical-methodology-comparative-assessment-quality-attributes-drug-development>). This paper reflects on the use of statistical methods and its limitations in the demonstration of comparability.

References (as proposed by Industry stakeholders)

EMA website on PRIME: <https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines>

FDA website for expedited program guidance:

<https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf>

https://www.ema.europa.eu/en/documents/other/general-principles-european-medicines-agency-food-drug-administration-parallel-scientific-advice_en.pdf

ICH M7 (R1) (assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk)

ICH Q8 (R2) (Pharmaceutical development).

ICH Q9 (Quality risk management).

ICH Q10 (Pharmaceutical quality system).

ICH Q11 (Development and manufacture of drug substances (chemical entities and biotechnological / biological entities)).

Annex 15. EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines.

EudraLex Volume 4 (Good Manufacturing Practice), Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products
(https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf)

CHMP Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1).

EMA Questions and answers on post approval change management protocols
(EMA/CHMP/CVMP/QWP/586330/2010).https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-post-approval-change-management-protocols_en.pdf

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