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Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications

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Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

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Table of contents

Executive Summary

The Priority Medicines (PRIME) scheme was launched to enhance EMA support to the development of medicines that target an unmet medical need with the aim to help patients to benefit from these therapies as early as possible. This is achieved by optimising the medicines development plans and speeding up their evaluation.

Experience to date has shown that applicants face challenges to complete quality and manufacturing development and data requirements during development of medicines for early access. This document provides guidance, in a 'toolbox approach', by summarising scientific elements and regulatory tools, available in the existing EU regulatory framework, that can be applied to support the development and completion of Module 3 quality data packages in the preparation of marketing authorisation applications (MAA) of designated PRIME medicinal products.

This toolbox guidance follows on from the Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)[1], held jointly with the US Food and Drug Administration (FDA) on 26 November 2018, which sought to identify scientific and regulatory solutions to challenges commonly experienced by Applicants of PRIME applications in completing Module 3 data requirements in time for the MAA.

1. Introduction (background)

The European Medicines Agency (EMA) launched the PRIME scheme to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.

To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data.

Once a candidate medicine has been selected for PRIME, the Agency will:

- appoint a rapporteur from the Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy to provide continuous support and help to build knowledge ahead of a marketing-authorisation application;
- assign a dedicated contact point from EMA and a dedicated EMA Quality specialist. Other team support will be involved as needed (e.g. Inspections Office)
- organise a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts, so that they provide guidance on the overall development plan and regulatory strategy;
- provide scientific advice at key development milestones, involving additional stakeholders such as health-technology-assessment bodies, to facilitate quicker access for patients to the new medicine;
- review the available information on supply chain to establish the need for an inspection and to co-ordinate any inspections during the assessment;

[1] Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies (https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough)

- confirm potential for accelerated assessment at the time of an application for marketing authorisation.

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, the Agency wishes to support applicants with guidance regarding their pharmaceutical development programme and flexibility on the provision and type of data packages in the context of a MAA taking into consideration the overall benefit/risk of the product. Specific guidance includes 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.

This toolbox guidance summarises scientific and regulatory approaches which can be considered and applied by Applicants, tailored to their product development in question, to facilitate the development and preparation of robust quality data packages. A well prepared and robust Module 3 will support timely access to the medicine for patients whilst providing assurance that product quality and efficacy and patient safety are not compromised. Similarly, applicants should ensure that manufacturers are compliant with EU GMP and are inspection ready at the time of submission.

The scientific and regulatory approaches described in this document can offer flexibility in terms of the time point for full completion of certain quality data packages when there is an unmet medical need and should always be considered in the context of the specific benefit/risk of the product.

Nevertheless, while regulatory tools can support timely access, they do not reduce the product quality requirements in a MA dossier. The data needed to demonstrate quality, safety and efficacy in line with Annex I of Directive 2001/83/EC is expected to be provided in the MAA dossier.

Therefore, Module 3 marketing authorisation dossier data requirements must be in line with scientific guidelines and technical requirements according to the EU legislation (Annex I of Dir. 2001/83/EC). Alternative data sources (e.g. platform/pilot scale data) can be considered provided their relevance to the product in question is established. In case of ATMPs, the content of the application can be adapted under a risk-based approach specific to ATMPs (according to Annex I, part IV of Directive 2001/83/EC).

For an optimal use of these regulatory tools, applicants aiming at early access are strongly encouraged to initiate dialogue with regulators as early as possible to discuss their overall development plan, including their quality programme and compliance of the supply chain, to ensure there is a mutual agreement on the dossier expectations and they are prepared to address any uncertainties, avoid delays, enable an accelerated assessment (if applicable) and ultimately achieve a successful MAA.

2. Scope

The scope of this document is on medicinal products that have received PRIME designation by the CHMP[2] and includes medicinal products containing chemical, biological and/or biotechnologically derived substances and Advanced Therapy Medicinal Products (ATMPs).

[2] Enhanced early dialogue to facilitate accelerated access of Priority Medicines (PRIME) (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/enhanced-early-dialogue-facilitate-accelerated-assessment-priority-medicines-prime_en.pdf)

It is recognized that some of the tools described in this document may be considered on a case by case basis, and prior to agreement with regulators, for other products intended for early access that address an unmet medical need.

3. Legal and regulatory basis

This guideline should be read in conjunction with EU legislation (Annex I of Dir. 2001/83/EC and 2001/20/EC), which details Module 3 data requirements, and scientific guidelines and technical requirements according to the EU framework, in particular:

- EudraLex- Volume 2B- Notice to Applicants
- 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)
- ICH M7 (R1) (assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk).
- ICH Q6A (specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances).
- ICH Q6B (specifications: test procedures and acceptance criteria for biotechnological/biological products).
- 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).
- ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle management).
- 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).
- EMA Meeting Report: Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications (EMA/CHMP/BWP/187162/2018).

*This list is not exhaustive, and other guidelines may also be of relevance.

4. Scientific Tools

4.1. Introduction

In the context of this document, the term ´scientific tools´ refers to scientific concepts, principles or technologies used for development, manufacture and quality risk management of medicinal products. Examples include modelling, analytical or platform technologies.

Of note, during the Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies[1] the term 'scientific elements' was used for the term 'scientific tools'.

4.2. General scientific tools

4.2.1. Prior knowledge

Prior knowledge is a term used in ICH (e.g. Q8, Q10 and Q11) and EMA guidelines. A definition of this term was discussed at a Joint BWP/QWP workshop with stakeholders on prior knowledge and its use in regulatory applications held at EMA in 2017[3] (EMA/CHMP/BWP/187162/2018). A definition was agreed and published in the workshop meeting report. Prior knowledge includes company knowledge from development and manufacturing experience (e.g. experience based on similar compounds, products and processes) as well as reference to scientific and technical publications or application of established scientific principles e.g. within chemistry.

The availability of prior knowledge, if demonstrated to be relevant for the product in question, could be good basis for shifting the time-point for completion of certain quality studies. Prior knowledge may also make some development studies redundant. If the knowledge is not related to experience with the molecule in question, but based on a similar molecule, then the applicability of the knowledge to the new molecule needs to be justified, and the knowledge also needs to be communicated in the dossier for the new molecule in the form of a summary discussion or inclusion of supportive data. Where relevant, reference to previous filings should be made, but sufficiently comprehensive information should be presented in the dossier for the new molecule making it possible to determine that it is representative for the product in question.

Prior knowledge information should be included in the CTD in the section where the product specific information otherwise would be, together with argumentation on how the information is relevant.

Prior knowledge can also stem from "platforms", which means that, for example, similar formulation, manufacturing process and/or analytical testing is used across many different molecules within a group. Such groups can include monoclonal antibodies, viral vector vaccines or oligonucleotides. In such cases the number of products already included in the platform and other information on the extent of knowledge available, together with information on the qualification of the new molecule to the platform is essential in order to assess the applicability of the platform.

4.2.2. Risk assessment

As indicated in ICH Q8 and Q9 risk assessment is a systematic science-based process of organizing information to support a risk decision to be made within a risk management process. It consists of the

[3] Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications https://www.ema.europa.eu/en/events/joint-biologics-working-party-quality-working-party-workshop-stakeholders-relation-prior-knowledge

identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. This tool is typically used as part of the pharmaceutical development to evaluate the formulation and manufacturing processes to understand the impact of material attributes and process parameters on product quality, define their criticality and inform the studies to be conducted. With the use of the identified risk profile the applicant shall justify the extent of data available in the various sections of the MAA dossier.

It is important to note that this process starts at the beginning of product development and matures over time, as the knowledge of the product and its characteristics increases. Nonetheless, applicants, using the risk-based approach, are expected to present in the application dossier the picture of the risk profiles as it is at the time of MAA. The potential risk resulting from incomplete data packages at time of approval is considered by Regulators in the context of the benefit-risk assessment during the MAA review.

Although risk-based approaches may also be applicable for non-PRIME products, it is worth noting the difference, i.e. that the level of residual risks that can be accepted for non-PRIME products compared to PRIME products (which are intended for an unmet clinical need) may be lower (e.g. it is more likely to accept a lesser degree of assurance for a life-saving product compared to a product where well-documented, usable alternatives exist).

For further guidance on the risk/based approach specific to the development of ATMPs, please refer to the dedicated EMA guideline (EMA/CAT/CPWP/686637/2011).

4.3. Scientific tools related to process validation

Process validation is a lifecycle activity; a continuum from early clinical product and process development through to a fully mature commercial process and maintenance of the process in a state of control during routine commercial production.

For products in an early access program, the main challenge is when sufficient data are considered to be available to support approval. A departure from the traditional requirement of data from a minimum of three process performance qualification (PPQ) batches can be accepted by regulators when there is a strong benefit/risk of the product in question. In this regard, there are several tools (described below) which can facilitate flexibility in the extent and type of process validation data required prior to approval. Such approaches need to be accompanied by clear plans which outline how the process validation data available support the effectiveness sand reproducibility of the commercial process and how process validation data, based on an appropriate protocol, will continue to be gathered in the post-approval phase.

4.3.1. Process validation protocols

A process validation protocol, also known as a process validation scheme, is a plan describing what data will be gathered and how it will be analysed (see EU GMP Annex 15 and CHMP process validation guidelines). Normally it is expected that most validation activities are finished at the time of MAA but even today certain validation protocols are accepted as substitutes for a final validation report. Examples of such protocols (for biological products) include resin lifetime studies, introduction of new cell banks, and introduction of new reference standards. For accelerated procedures it may be acceptable, on a case-by-case basis and supported by a risk assessment, to defer some process validation activities to the post-authorisation phase and submit protocols for the studies to be performed and their acceptance criteria. The scope of validation protocols could be expanded to include other validation activities, for example hold time studies, transport validation, reprocessing etc.

Proposals for the use of protocols in additional areas of process validation should firstly be discussed with EMA. Contrary to post-approval change management protocols (PACMPs) (see section on regulatory tools), process validation protocols are not followed by an implementing variation as they cover aspects already described in the dossier.

4.3.2. Concurrent validation

Concurrent validation is defined in Annex 15 of the EU Guidelines for GMP as 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 commercialisation of the validation batches. If concurrent validation is proposed, it should be appropriately justified based on patient need, and its acceptance will depend on the benefit/risk balance. The decision to carry out concurrent validation must be documented in the Validation Master Plan and approved by authorised personnel including the Qualified Person (QP).

In exceptional circumstances, concurrent validation may also be appropriate where there is a small patient population, resulting in batches only being manufactured infrequently. In such cases, the expected batch utilisation and approximate timeframe of future batch manufacture should be described.

The acceptance of concurrent validation is on a case-by-case basis and will depend on the extent of supportive data available. It should be supported by robust application of quality risk management. Any proposal for concurrent validation should also be accompanied by a supporting protocol. The protocol should therefore contain all the relevant tests and acceptance criteria which the concurrent validation batch must fulfil before it can successfully pass validation and be certified by the Qualified Person. In addition to the release specifications, the tests registered in the protocol should include all relevant in-process controls and process parameters to support a conclusion that any given batch of product will be uniform. The proposed acceptance criteria for all tests should be appropriately justified and met. Prior Knowledge can also be useful for justification of the protocol parameters and acceptance criteria. It is also recommended to place the concurrent process validation batches on stability.

When concurrent validation is used, evidence should be provided to demonstrate i) that studies performed for process evaluation are appropriate representations of the commercial process, and ii) that the control strategy will properly verify that the process has performed as intended. It is recognised that in the case of accelerated development, the level of process understanding may still be evolving. Nonetheless, acceptance of a concurrent validation approach for active substances and/or finished products requires sufficient process evaluation data to justify that the parameters and acceptance criteria included in the protocol are suitable for concluding that the process is in a state of control and that the product is uniform.

Where available, data from other non-PPQ batches (including clinical batches) manufactured using the commercial manufacturing process can be used as supportive data to justify that the process is in a state of control. Supportive process evaluation data e.g. small-scale data can also be used provided that they are appropriate representations of the commercial process.

The number of PPQ batches to be submitted prior to licensure will depend on the data package. It is generally expected that data from at least one formal process validation batch from the commercial manufacturing process will be available prior to approval. In exceptional cases, it may be acceptable not to have successfully manufactured any PPQ batches prior to approval. This will have to be supported by a comprehensive risk-based approach and will depend on the extent of Prior Knowledge

which can be leveraged and other supporting validation data from non-PPQ batches or small scale batches. Provision of interim process validation data during MAA review is also desirable.

A concurrent validation approach may have implications for the timing and scope of GMP inspections. Concurrent validation proposals should therefore be discussed pre-submission with the relevant EU supervisory authority.

For products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes), the data from the concurrent process validation batches should be submitted post-approval. However, formal regulatory approval will generally not be required for release of concurrent validation batches to the market. However, depending on the benefit-risk ratio evaluation, formal regulatory approval could be required for release of concurrent validation batches to the market. Several mechanisms exist to request the submission of the post-approval process validation data, for example a Recommendation, a Specific Annex II condition to the Commission Decision for a Conditional Marketing Authorisation). The most appropriate mechanism will be decided case-by-case and will depend on the overall data package and level of risk.

4.3.3. Deferral of the submission of certain process validation data

Aside from concurrent validation, it may be possible under certain circumstances to defer certain process validation activities to the post-approval phase. This would allow for a mixed approach where some process validation data are available prior to authorisation and other data is provided post-approval. To manage the provision of additional data post approval, regulatory tools (e.g. recommendations, protocols, variations (see section on regulatory tools) will be agreed by Regulators and Applicants.

4.3.4. Decoupling active substance and finished product process validation

In order to avoid delays in finished product PPQ activities, it may be acceptable, under certain circumstances, to manufacture finished product PPQ batches using active substance batches which were produced prior to formal active substance process validation, provided the active substance batches were manufactured under GMP. If this approach is chosen, it should be demonstrated that such active substance batches are sufficiently representative of the commercial manufacturing process and will meet their intended specifications for quality and purity.

4.3.5. Continuous process verification

Continuous process verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8). Continuous process verification can be used in addition to, or instead of, traditional process validation (ref. CHMP guideline on process validation for finished products EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1).

When there is extensive prior knowledge on a particular manufacturing process and it comprises extensive in-line, on-line or at-line controls, continuous process verification could be used to validate the manufacturing process and facilitate early access since the robustness of the manufacturing process can be demonstrated in the dossier by a discussion on the appropriateness and feasibility of the continuous process verification strategy in the development section, supported with data from at least laboratory or pilot scale batches, and a continuous process verification scheme in 3.2.R. Actual

data generated during continuous process verification at production scale should be available at the site for inspection.

4.4. Scientific tools related to control strategy

4.4.1. Initial filing with a more "constrained" control strategy

As articulated by ICH Q8 to Q11, the more knowledge an applicant has of their product and process, the more flexibility can be afforded in the approved control strategy. For products undergoing an accelerated development timeline, product and process knowledge (e.g., uncertainty on the criticality of attributes, their control by the manufacturing process, and analytical capability) may still be evolving at the time of filing. Thus, the amount of data available to support its control strategy at the time of approval may be reduced compared to a product undergoing a standard development. In order to facilitate faster access for patients, some process development and evaluation studies could be deferred to the post-approval phase, depending on the benefit/risk balance. In order to support the deferral of such data, applicants may choose to file with a more constrained control strategy. Such a constrained control strategy could encompass some or all of the following elements:

- Additional specification tests
- Additional in-process controls
- Additional process parameters
- A higher number of critical process parameters
- Narrower ranges for critical process parameters (CPPs)

Applicants should justify how the tighter control of the manufacturing process supports the deferral of some process development and evaluation studies. For example, in the case where process evaluation studies to demonstrate clearance of a certain impurity are not available at the time of registration, a release test or IPC could be registered until those studies are complete and support discontinuation of routine testing. As another example, during a standard development timeline, data from small-scale process evaluation studies may be used to justify the classification of a process parameter as non-critical. Where such process evaluation studies are still ongoing, some process parameters could default to critical until the data is available post-approval to support their downgrading. Ranges of process parameters could also be narrowed until data is available showing that a wider range of process parameter inputs does not impact the relevant critical quality attributes (CQAs) outputs of that manufacturing step.

Once suitable data has been gathered post-approval, an appropriate variation could be submitted to "relax" or de-constrain the control strategy e.g. downgrade/remove process parameters, widen ranges etc. The process evaluation data required to support the relaxing of a control strategy could be agreed during the initial assessment phase as part of a PACMP.

When planning the timing of process development and process evaluation work, the major consideration of which (if any) process development studies could be deferred should be that the safety and efficacy of the product must still be assured at the time of approval.

4.4.2. The acceptance and use of *in-silico* models and purge factor calculations.

A control strategy that is based on product and process understanding and utilisation of risk management principles will lead to a combination of process design and control and appropriate

analytical testing, which can also provide an opportunity to shift controls upstream and minimize the need for end-product testing.

ICH M7 foresees the use of in-silico models in the control of mutagenic impurities and defines four potential approaches to the development of a control strategy (section 8.1), where option 4 is relies on understanding of process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity does not need to be listed on any specification).

The risk assessment can in this case be based on knowledge of physicochemical properties and process factors that can influence the fate and purge of the impurity. Where justification based on scientific principles alone is not considered sufficient, analytical data to support the control approach is expected.

It is important to demonstrate that the fate of impurities/purge argument for the impurity is robust and will consistently assure a negligible probability of an impurity residing in the final drug substance above the acceptable limit.

In addition, for Lifecycle Management purposes section 8.5 of ICH M7 also states that in some cases, the use of statistical process control and trending of process measurements can be useful for continued suitability and capability of processes to provide adequate control on the impurity. Statistical process control can be based on process parameters that influence impurity formation or clearance, even when that impurity is not routinely monitored.

From these excerpts from ICH M7 it can be seen that in-silico calculations of carry-over of genotoxic impurities can be justified, where it has been shown that carry-over and purge calculations are based on physicochemical parameters. The physicochemical parameters in themselves may be collected both from calculations and measured data from experiments.

However, in many cases the programs and algorithms used by Applicants for carry-over calculations have not been fully transparent to the Authorities, in some cases hampering the assessment and acceptability of in-silico purge calculations.

In order to address this, topics that may be of interest for further discussions include:

- Discussion on what parameters of purge calculations should be/can be transparent in an MAA
- Insight into the software used for purge calculations from side of the Authorities
- Possibility of mutually recognised software for purge calculations
- Follow-up on regulatory issues that may follow from the use of such calculations, e.g. how to handle a database that changes over time as more data is added/or removed (evolving databases)

4.4.3. Front-loading of control strategy activities/ CMC development plan

In accelerated development programs, development of a robust control strategy may be on a critical path. By front-loading of process development activities, a more robust quality data package may be available to support the control strategy at the time of MAA approval. This could include early planning of small-scale studies required to establish process parameter ranges and conducting risk assessment activities to identify and mitigate gaps in process development and evaluation.

4.5. Approaches related to GMP compliance

4.5.1 Launching from an investigational medicinal product site

According to the European legislation, all medicinal products for human use manufactured or imported into the Union, including investigational medicinal product (IMP) and medicinal products intended for export, should be manufactured in accordance with principles and guidelines of good manufacturing practice (GMP). In addition, according to Article 40 of Directive 2001/83/EC and Article 13 of Directive 2001/20/EC (as amended), the manufacturers of these medicinal products are subject to the holding of an authorisation, covering marketed or investigational medicinal products.

In certain cases, to facilitate timely patient access to medicines that address unmet medical needs, the Agency could allow at the time of submission of the dossier, an investigational product manufacturing authorisation holder as the site of manufacture. A commercial manufacturing authorisation issued under Article 40 of Directive 2001/83 confirming that the IMP manufacturer is authorised to manufacture marketed products will be required at the time of the Opinion of the MA. Therefore, the applicant should ensure that the necessary application for the relevant MIA is submitted to the relevant supervisory authority in time to allow inspection prior to the grant the Opinion, otherwise the CHMP will ask the supervisory authority to carry out an inspection and the application will be delayed until the MIA has been granted. In such circumstances, evidence that an adequate level of compliance to GMP to manufacture marketed products is in place, that an effective Pharmaceutical Quality System has been implemented , and that manufacturing and supply processes have been designed and validated using robust and efficient Quality Risk Management prior to certification and release of the marketed batches. The use of a Comparability Assessment exercise (See 4.6) could be considered and applied for the evaluation of GMP gaps to support the certification and release of the marketed batches. In the case the manufacturing site authorised under the Article 13 of Directive 2001/20/EC will not be the site will perform final batch release of any marketed batches, the Qualified Person of the MIA holder authorised under Article 40 of Directive 2001/83 should be involved into the evaluation of the level of GMP compliance.

4.5.2 Alignment of quality review and GMP inspections

During the granting of a marketing authorisation (MA), a GMP inspection could be required in order to assess the GMP compliance of a site. Submission of the supply chain information in advance of the submission is necessary to evaluate, the need for a GMP inspection and to co-ordinate any requested inspection within the assessment procedure.

During accelerated timelines, it is important to ensure the quality review and GMP inspection activities are aligned and appropriate mechanisms to share knowledge and information obtained through inspection or assessment activities are utilised by the Agency to facilitate the evaluation of a MAA.

4.5.3 Use of biological starting material manufactured under a lower level of GMP

The establishment of new seed/cell lots/banks and viral seed stocks should be done in accordance with the guidelines and principles of GMP (refer to Annex 2 or Part IV GMP for ATMPs). The level of GMP increases in detail from early to later steps in the manufacture of biological active substances but GMP principles should always be adhered to. Under exceptional conditions, it could be acceptable to use starting material (e.g. MCB) that may be considered by the applicant to have been manufactured under a lower level of GMP, provided documentation is available to confirm traceability, and prevention of contamination, including information related to components used during development with potential impact on product safety, and that an extensive characterisation and testing have been carried out. A

documented risk assessment should be conducted to identify the testing requirements necessary to ensure the quality of the starting material and the medicinal product. Sufficient documentation should be available on the production of the starting material and also a comprehensive viral safety study complying to GMP should be performed. The competent authorities will evaluate the risk assessment and should agree to the proposed strategy in the context of the assessment of the marketing authorisation application/clinical trial authorisation application.

4.6. Scientific tools related to stability

In accelerated development programs, standard stability data packages may not be feasible and alternative paths may be needed while still assuring the stability of the product.

4.6.1. Stability models generated from stability of structurally similar molecules (Biotech)

In accordance with ICH Q5C stability data fully covering the period of the claimed shelf life is requested for biological products which could delay the MA approval of PRIME products with accelerated development. For a biologic PRIME product, trends in stability data, and therefore the claimed shelf life, could be extrapolated using predictive stability models generated from prior knowledge of the stability of structurally similar molecules. In such cases, it may be possible to approve a shelf life which is longer than the available product-specific real time stability data. Success of this type of approach requires evaluation and justification that the risks in extrapolation of stability data are appropriately mitigated by sufficient prior knowledge of the stability of similar products and commitments to report deviations from the expected stability trends and out of specification results.

The data used to generate the predictive stability model should be provided in the dossier. The types of products from which the model was derived should be described. In order to justify the use of a predictive stability model, the Company should provide a rationale for any statistical analyses used and for the parameters used to show that the current product fits the model generated using data from other products. Data from stress studies could be submitted to further support the shelf life.

The trend in the stability model is considered of greater importance than 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 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 fits the model, while considering the change over the proposed shelf life, it should be possible to set release acceptance criteria which would assure that the clinically relevant quality attribute limits are met at the end of shelf life. As real time stability data are generated post-approval, the company should verify on a continuous basis that the stability of the product continues to fit the predictions of the model. This should be supported by commitments to report deviating trends, out of specification (OOS) results etc., and what actions will be taken in case the results no longer fit the model.

There are situations where the models do not fit. It is 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.

It may be possible to leverage data from other presentations when establishing the shelf life. For example, using stability data from a vial presentation to establish the shelf life for a pre-filled syringe presentation. For such approaches it should be demonstrated that the results from different presentations show similar trends, this information can then be included in the model and extrapolated

to the intended commercial presentation. There should be no major changes to the production apart from the container closure system.

It is acknowledged that the principles will be difficult to apply to other groups of products than those used to establish the model (i.e. a model based on monoclonal antibodies is unlikely to apply in general to other types of recombinant products). The generation of a predictive stability model and its application should be agreed in advance with the agency.

4.6.2. Stability based on supportive knowledge (small molecules)

It is acknowledged that in some cases general prior knowledge of the stability of an active substance can be gained from similar molecules e.g. within the same class, considerations of functional groups in the molecule and the relevant environment regarding e.g. pH and moisture. Prior knowledge may also be available on the stability of products containing similar molecules. Knowledge can also be gained from the use of accelerated stability using more challenging conditions of temperature and humidity, and modelling of the results. With regards to predictions of chemical stability these accelerated stability approaches are well established.

This prior knowledge or results from modelling could be used as supportive information to claim a re-test period beyond the time-point justified by the results from long-term studies and extrapolation as per ICH Q1E. In this case, a commitment to inform the regulators immediately if the stability of the active substance/medicinal product is not as anticipated and restrict the retest period/shelf life accordingly should be provided. This should be accompanied by a second commitment to submit the remaining quality data which would otherwise generally required (e.g. at least 12 months under long term storage and maximum 12 month extrapolation) when available, if not otherwise agreed with the agency.

Regardless of the approach taken, regular ICH studies should be run in parallel and additional stability commitments provided, as described in ICH Q1A.

In justified cases, it may be acceptable not to define a re-test period for an active substance, and instead test it before use. This could be relevant if a constrained control strategy is used, or if other supportive knowledge is available.

4.7. Scientific tools related to comparability (biologicals)

A risk-based approach, such as the one developed for ATMPs[4], can potentially be used to tailor the comparability study by identifying CQAs impacted by manufacturing changes. This will allow for a reduced comparability package focusing only on the relevant CQAs. Based on this, a justified set of release, (accelerated) stability and/or characterization data can be used to demonstrate comparability.

The following aspects are taken into account.

4.7.1. Using prior knowledge to tailor comparability studies

Prior knowledge based on e.g. the same platform or from similar products can be used to predict the impact of specific manufacturing changes. A risk-based approach could potentially be applied to tailor the comparability study by identifying CQAs most likely to be impacted by manufacturing changes. This could allow a company to justify proportionate requirements on the comparability data.

[4] 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.

The applicability of prior knowledge on which the choice of quality attributes to be studied in the comparability exercise should be justified by the representativeness of the data for the product in question. After the initial comparability studies an analysis of the need for additional studies should be performed taking into account the residual uncertainties from the initial comparability studies, before the final comparability exercise can be submitted.

4.7.2. Risk based identification of CQAs

Comparability studies are expected to be comprehensive. (ICH Q5E states: *Generally, quality data on the pre- and post-change product are generated, and a comparison is performed that integrates and evaluates all data collected, e.g., routine batch analyses, in-process control, process validation/evaluation data, characterisation and stability, if appropriate).*

However, in case of development of medicines for early access it could be justified to have a less comprehensive comparability exercise limited to identified relevant Critical Quality attributes (CQAs). A risk-based strategy is used to identify and select CQAs. CQAs are identified in a risk assessment by evaluating for each of the qualitative or quantitative characteristics whether and to what extent it could potentially contribute to the efficacy or a specific safety risk of the product. Then, as a second step, considering the type of the change introduced (e.g. change to process step) and the available prior knowledge, the potential impact of such change to each CQA is considered. Based on that risk assessment the comparability study could be limited to a justified set of CQA.

A risk-based approach also takes into account the type of change made to the manufacturing process and how this relates to the prior knowledge used to predict and select the relevant impacted CQAs.

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.

4.7.3. Separate assessment of individual changes

In case multiple changes are introduced there are two possible scenarios: either all the changes are introduced at the same time, or each change (or combination of some changes) is introduced in different stages of development of the manufacturing process.

In the case of introduction of all changes at the same time, it is generally expected that comparability will be demonstrated for the combined introduction of these changes. However, separate assessment of individual changes could be acceptable when it is justified that the impact is independent for each of the different changes (i.e. there are no interactions). The acceptability of separate comparability data should be duly justified (dependent on the type of change, type of manufacturing process and type of product).

In case of sequential introduction of the changes to the manufacturing process at different stages of development, it is generally acceptable to provide serial (sequential) comparability data, demonstrating comparability between each of the development stages.

Depending on the change made it may not be necessary to assess its impact all the way to the finished product. It may be sufficient the assess of the impact on a particular step of a limited number of steps, by demonstrating comparability for a relevant intermediate after modified manufacturing step(s).

For any scenario, the comparability between the product used for the clinical trials and the commercial process has to be fully justified.

4.7.4. Statistical tools for comparability

Statistics may provide useful information to support comparability even though any statistical approach has its own limitations and strengths. Those limitations should be well understood and documented before conduct of the comparability exercise and in order to make informed decisions on the comparability utilizing the statistical results.

In any case, it is essential that an appropriate pre-specified plan with a justification for the statistical approach chosen and the comparability acceptance criteria proposed for the relevant quality attribute selected according to a risk-based approach is provided in the regulatory submission.

Inclusion of side-by-side analysis of individual values with accompanying descriptive statistics to summarize data (e.g. min-max and 3*sigma ranges) is recommended, particularly when comparing a limited number of samples/batches. Likewise, suitable graphical representations (e.g., individual values scattergrams) could be provided, allowing the identification of possible shifts within the acceptance criteria.

In case there are only very few batches available (sometimes in combination with large variability e.g. autologous cell products) a statistical tool may not be useful to demonstrate comparability, in such cases a comparison with historic ranges may be the best approach.

Further consideration could also be given to the draft CHMP reflection paper on statistical methodology for the comparative assessment of quality attributes (EMA/CHMP/138502/2017) and the meeting report "Workshop on the reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development" (EMA/CHMP/579441/2018).

4.7.5. Comparability and Stability

In general, full real time stability studies are not required to support comparability. Nevertheless, stability data can be relevant to understand the impact of manufacturing changes. In this regard, it is more reasonable to focus on dedicated stability studies under accelerated or stress conditions that can be of value to identify possible differences. Such pre/post-change comparability stability studies done using relevant accelerated conditions on representative material could also be acceptable to support a shelf life claim based on pre-change or platform real time stability data.

4.7.6. Comparability for ATMPs

ATMPs in general are characterized by starting materials of inherent variability (for cell/tissue-based products), complex biological features and manufacturing processes. Therefore, ATMPs are outside the scope of the ICH Q5E guideline and a specific Q&A document is available: Comparability considerations for Advanced Therapy Medicinal Products (ATMP)- EMA/CAT/499821/2019.

The Q&A document should be read in conjunction with this Toolbox document.

4.7.7. Need for additional (non)clinical data

In case full comparability of the CQAs related to safety and efficacy cannot be demonstrated, additional (non) clinical data may be needed before approval of the MAA. In exceptional cases, based on a risk-benefit assessment, these could be post-approval clinical studies.

5. Regulatory tools

5.1. Introduction

EMA is committed to enabling early patient access to new medicines, particularly those that target an unmet medical need or are of major public health interest. The Agency seeks to support the medicine development process from an early stage and to offer regulatory mechanisms to help promising new medicines reach patients as early as possible, without compromising their quality, safety and efficacy. In this context, the Agency EMA has different procedures available to establish an early dialogue with regulators and support prospective planning. These include:

a) **scientific advice/protocol assistance** during development, whereby the EMA provides medicine developers advice on the most appropriate way to generate robust evidence on a medicine's benefits and risks. This supports the timely and sound development of high-quality, effective and safe medicines, for the benefit of patients. Scientific advices are particularly suitable to agree with the EMA on tailored development approaches such as filing with an initial more restricted control strategy, concurrent validation approaches, prior knowledge etc.

Applicants can also request a parallel scientific advice or a consultative advice with EMA and US FDA to optimize product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies in both regions. The agencies conduct this procedure under the auspices of the confidentiality arrangement between the European Commission, the EMA, and FDA.

Further information can be found on the dedicated EMA website (references below).

b) **pre-submission meetings between applicants and the EMA/(Co-) Rapporteurs.** The meetings should take place approximately 7 months prior to the anticipated date of submission of the application. They are a vital opportunity for applicants to obtain procedural, regulatory and legal advice from the EMA and the Rapporteurs, and discuss issues specific to their upcoming application. The EMA product team is available to address any questions MAHs may have regarding their MAA. Further information can be found on the European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure (EMA/24037/2019) (references below).

In addition, the EU regulatory framework contains a number of regulatory tools or strategies that can be used and adapted to facilitate timely patient access to medicines that address unmet medical needs.

The available regulatory tools are further detailed below.

5.2. Regulatory tool 1: accelerated assessment

The accelerated assessment is a procedure reserved to medicinal products of major therapeutic interest (recital 33 and Article 14(9) of Regulation (EC) No 726/2004). Relevant information on the eligibility criteria, applicable evaluation timelines, procedure to apply for an accelerated assessment can be found on the dedicated EMA webpage (see references below).

This procedure is intended to shorten the active review time of a MAA from 210 to 150 days and therefore to potentially secure an earlier access of the medicine to patients. In order to achieve this, applicants should aim at filing a complete MA dossier and avoid the submission of data during the review, to avoid the timetable is reverted to normal due to major objections raised during the evaluation (e.g. major objections include concerns related to an insufficient control strategy,

redefinition of active substance starting materials, comparability between clinical material and commercial product not fully demonstrated).

Applicants are encouraged to discuss proactively with regulators their intention to apply for accelerated assessment and any issues related to the dossier, and follow any scientific advice received, to ensure appropriateness of an accelerated assessment procedure and a possible way forward to address any potential obstacles. Adequate planning regarding manufacturing authorisation requirements, GMP compliance and any potential GMP inspection should also be taken into consideration to prevent delays (see GMP section). Applicants should ensure that manufacturing sites are inspection ready at the time of submission of the application.

5.3. Regulatory tool 2: conditional marketing authorisation (CMA)

This is a tool available for medicinal products aiming at the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or medicinal products to be used in emergency situations in response to public health threats. In this case, a marketing authorisation may be granted prior to the submission of comprehensive clinical data provided that the benefit-risk balance of the product is considered positive and the benefits of immediate availability outweighs the risk of less comprehensive data than normally required, i.e. the medicines is able to address an unmet medical need. Such conditional marketing authorisations are subject to specific obligations, aiming at generating the missing data and confirming the favourable benefit-risk profile.

Conditional marketing authorisations should be restricted to situations where only the clinical part of the application dossier is less complete than normal. Incomplete pre-clinical or pharmaceutical data should be accepted only in the case of a product to be used in emergency situations, in response to public health threats.

Conditional marketing authorisations are valid for one year and can be renewed annually. During this period, the holder will be required to complete these specific obligations (ongoing or new studies, and in some cases additional activities) with a view to providing comprehensive data to address uncertainties and confirming that the benefit-risk balance is positive.

The legal basis for conditional marketing authorisation is Article 14-a of Regulation (EC) 726/2004 as further defined in Commission Regulation EC No 507/2006 and information on the requirements to be met and application process are described in the CHMP guideline on the scientific application and practical arrangements on the CMA (EMA/CHMP/509951/2006, Rev.1) and the dedicated EMA webpage (see references below).

5.4. Other regulatory tools:

Post-approval change management protocols (PACMPs)

The concept of PACMP was introduced in the EU through the Commission's Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01) that supports the Variations Regulation (Commission Regulation (EC) No 1234/2008).

A PACMP enables a stepwise approach in the assessment of changes. The protocol would describe the specific changes that a company would like to implement during the lifecycle of the product (e.g. to add a new manufacturing site, to upscale a manufacturing process) and how these would be prepared and verified. The results from the pre-defined studies would be submitted post-approval through a

variation to implement the change. This approach enables an early assessment of the strategy to be pursued, thereby lowering the reporting category of the implementing variation, which in turn reduces the overall regulatory review and implementation time (ref. EMA Q&A on PACMP-EMA/CHMP/CVMP/QWP/586330/2010).

Post-authorisation measures (PAMs)

The intention of PAMs is per se not to facilitate early access or facilitate deferral of data generation. PAMs are means for regulators to request any additional data that from a public health perspective, are needed to complement the available data. These can be categorized as specific obligation [SOB], annex II condition [ANX], additional pharmacovigilance activity in the risk-management plan (RMP) [MEA] or recommendation [REC].

The existence of these 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. Based on the assessment of the committee(s), PAMs are classified into their appropriate legal framework under which they will be enforced.

The PAM selected depends on the criticality of the data set/measure in relation to the clinical use of the product and its impact on the benefit/risk. For example, a recommendation may be issued to further consider the implementation of a more sensitive analytical method for characterisation or batch release purposes; or to review and, if necessary, revise product specifications once more batch data become available.

*While not a regulatory tool, it is acknowledged that in certain cases some data generation to support approval may be on-going at the time of MAA (e.g. stability, process validation studies) and applicants may submit the missing data as part of the responses to the list of questions or list of outstanding issues. When this situation is foreseen applicants are encouraged to discuss this approach upfront with regulators and seek agreement to ensure there is a mutual understanding.

References

- Annex I of Dir. 2001/83/EC
- EudraLex- Volume 2B- Notice to Applicants
- EudraLex Volume 4 (Good Manufacturing Practice), Guidelines on Good Manufacturing Practice
- ICH M7 (R1) (assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk)
- ICH Q1A Stability testing of new drug substances and drug products
- ICH Q1E note for guidance on evaluation of stability data
- ICH Q5C Stability testing of biotechnological/biological products
- ICH Q6A (specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances).
- ICH Q6B (specifications: test procedures and acceptance criteria for biotechnological/biological products).
- 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).
- ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle management).
- 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). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf
- CHMP Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-manufacture-biotechnology-derived-active-substances-data-be-provided_en.pdf
- Guideline on the risk-based approach according to Annex I, part IV of Dir 2001/83/EC applied to Advanced Therapy Medicinal Products (EMA/CAT/CPWP/686637/2011). 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
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- Draft Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/138502/2017). https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-statistical-methodology-comparative-assessment-quality-attributes-drug_en.pdf
- CHMP Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 (EMA/CHMP/509951/2006, Rev.1) https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf
- EMA Meeting Report: Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies) (EMA/CHMP/BWP/812924/2018). https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime_en.pdf
- EMA Meeting Report: Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications (EMA/CHMP/BWP/187162/2018). 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

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