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Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need

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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 for marketing authorisation applications (MAA) of designated PRIME medicinal products and certain marketing authorisation applications targeting an unmet medical need as pre-agreed with the European Medicines Agency (EMA).

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 EMA and 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 early access applications in completing Module 3 data requirements in time for the MAA.

1. Introduction (background)

The 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. In exceptional cases, PRIME designation may also be granted to applicants from the academic sector and micro-, small- and medium-sized enterprises (SME) at an earlier stage of development based on non-clinical data and first-in-human studies which indicate adequate exposure and tolerability.

Once a candidate medicine has been selected for PRIME, EMA 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;

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>)

- review the available information on supply chain to establish the need for an inspection and to co-ordinate any inspections during the assessment;
- 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 data requirements during development of products in [early access](#) approaches.

In order to address and overcome these challenges, EMA 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 covers prior knowledge, risk assessment, process validation, specification setting, GMP compliance, stability testing, and comparability, 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 (see section 4.5).

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 understanding 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 primary scope of this document is on medicinal products that have received PRIME designation by the CHMP² 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 recognised that some of the tools described in this document may be considered, on a case by case basis, and subject to prior agreement with EMA, for certain products intended for early access that address an unmet medical need, but where PRIME status may not have been requested by the applicant. Therefore, applicants are recommended to liaise with EMA during their product development to confirm that the tools described in this document can be applied to their product. In this context, references to PRIME applications throughout this guideline may also apply to certain marketing authorisation applications targeting an unmet medical need.

3. Legal basis

This guideline should be read in conjunction with EU legislation (Annex I of Dir. 2001/83/EC, Directive 2001/20/EC and the Regulation on Advanced Therapy Medicinal Products (EC) No 1394/2007), 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 including guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

Other relevant EU guidelines, especially those mentioned in the reference list, should also be consulted.

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 Therapies¹ 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 2017³ (EMA/CHMP/BWP/187162/2018). A definition was agreed and published in the workshop meeting report. Prior knowledge includes knowledge from development and manufacturing experience (e.g. experience based on similar compounds, products and processes)

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>

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 a good basis for shifting the time-point for completion of certain quality studies, or supporting an alternative approach to data requirements for certain quality studies (e.g. stability studies, process validation, justification of specification). Prior knowledge may also make some development studies redundant. If the knowledge is not related to experience with the product in question, but based on a similar product, 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 product making it possible to determine that the prior knowledge is representative for the product in question.

Prior knowledge information should be included in the MAA dossier in the section where the product specific information otherwise would be, together with justification 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 products within a group. Such groups can include, for example, monoclonal antibodies (mAbs), viral vector vaccines, mRNA vaccines, viral vectors for gene therapy, expression vector system (e.g. Baculovirus expression vector system), genetically-modified cell therapies, 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 product to the platform is essential in order to assess the applicability of the platform. Information required in Module 3 may include comparative descriptive details for all the products for which data is used.

4.2.2. Risk assessment

As indicated in ICH Q8 and Q9, risk assessment is a systematic science-based process of organising 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. 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. Risk assessments are also used to evaluate dossier elements such as attribute critically, appropriateness of models and prior knowledge and to inform the overall control strategy. With the use of the identified risk profile the applicant should 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 the replacement of certain conventional data by alternative supporting data packages at time of approval is considered by regulators in the context of the benefit-risk assessment during the MAA assessment. This risk-based approach can lead to agreement in providing additional quality data during assessment or post-approval if the clinical benefits clearly outweigh the risks.

Risk-based approaches may also be applicable for non-PRIME products which are intended for an unmet clinical need. The level of residual risks that can be accepted for such products will reflect the extent to which a product meets an unmet clinical need i.e. EMA 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 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).

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. The tools below describe flexibilities for products where process validation data would normally be required prior to approval (e.g. biological products, chemical products manufactured using non-standard processes).

For products in an early access program, where data from process validation (also referred as process performance qualification (PPQ) in this guideline) batches would normally be required prior to approval, flexibility on the timing of submission of this data can be accepted by EMA when there is a strong benefit-risk balance 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 and reproducibility of the commercial process and how process validation data will continue to be gathered in the post-approval phase, based on an appropriate protocol.

4.3.1. 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 balance for the patient, where the validation protocol is executed concurrently with commercialisation of the validation batches. Situations of unmet medical need can fall under exceptional circumstances. Applicants are encouraged to liaise with EMA to ensure there is common understanding on the specific case. Similarly, as described in the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, concurrent validation may be acceptable where there is limited availability of the starting materials and/or where there is a strong benefit-risk balance for the patient. 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. 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).

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 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 QP. 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 the process has performed as expected and any given batch of product will be consistent. 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. The concurrent process validation batches should be placed 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 assure 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/investigational medicinal product 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. Where data from non-PPQ batches is used to support process validation, consideration should be given to method performance and the quality attributes studied. If the non-PPQ batches were tested using methods different from the registered commercial analytical methods, this should be justified.

The number of process validation batches to be submitted prior authorisation 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 manufactured any process validation 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 assessment 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 prior to submission with the relevant EU supervisory authority.

Data from the concurrent process validation batches should be submitted post-approval. Formal regulatory approval will generally not be required for release of concurrent validation batches to the market, unless otherwise determined during assessment as being necessary based on the benefit-risk evaluation. Any decision on the requirement for formal regulatory approval for release of concurrent validation batches will be communicated to the applicant prior to MA approval⁴. Several mechanisms exist to request the submission of the post-approval process validation data, for example a Recommendation or an 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 Additional requirements apply to products under Official Control Authority Batch Release (e.g. vaccines, plasma derived products).

4.3.2. 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, Guidelines on Good Manufacturing Practice specific to advanced Therapy Medicinal Products, and CHMP process validation guidelines). Whereas it is normally expected that most validation activities are completed at the time of MAA and process validation data included in the MAA dossier, certain validation protocols may be accepted as substitutes for a final validation report. Examples of such protocols include resin lifetime studies, introduction of new cell banks, introduction of new reference standards, hold time studies, transport validation, reprocessing etc. For PRIME/early access products it may be acceptable, on a case-by-case basis and supported by a risk assessment, to defer other process validation activities, in addition to those mentioned above, to the post-authorisation phase. Such proposals should first be discussed with EMA.

Protocols can be submitted in lieu of supportive validation data prior to approval and should include the studies to be performed and their acceptance criteria. Provided that the results are in accordance with the agreed protocol, submission of the data post-approval is not a requirement. Such protocols are handled differently to post-approval change management protocols (PACMPs), where a subsequent variation is required before implementing the change.

4.3.3. Deferral of the submission of certain process validation data

Aside from concurrent validation, it may be possible 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. Some examples include, but are not limited to, transport validation, column lifetime validation, hold time validation, validation of reprocessing etc. 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 process validation activities, it may be acceptable to manufacture and supply finished product process validation batches using active substance batches which were produced prior to formal active substance process validation, provided the active substance batches were manufactured and controlled under GMP in full accordance with the applied manufacturing process. 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.

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. The robustness of the manufacturing process can be demonstrated in the development section of the dossier by a discussion on the appropriateness and feasibility of the continuous process verification strategy, 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

It is recognised that expedited development programs have a number of challenges related to control strategy: e.g. limited manufacturing and clinical experience, difficulties in assessing if the process is consistent due to a limited number of manufactured batches, process and method validation studies not finalised, and an understanding of criticality and interactions which is not fully developed. Despite this, these products are still expected to be safe and efficacious with a positive benefit-risk balance. Flexibility in what quality information is required for marketing approval will depend on factors such as product and process knowledge, analytical capability and the quality system. Whenever possible it may be a good practice to frontload certain process development activities. 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

4.4.1. Initial filing with an adapted control strategy to offset the reduced level of knowledge on the product and process

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 the 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 an adapted control strategy to offset the reduced level of knowledge of the product and process due to the expedited development. Such an adapted 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)

Careful considerations should be given to the potential implications for the approach taken e.g., for patient-specific products such as autologous products, to assure that measures are in place, consistent with current guidance, to decide the best course of action for the patient in the event of a batch which is out of compliance and/or out of specification.

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 in-process control could be registered until those studies are complete and support discontinuation of routine testing. Also, 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 revise the commercial final 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 [ref. EMA Questions and answers on post-approval change management protocols (EMA/CHMP/CVMP/QWP/586330/2010)].

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 ensured 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 minimise 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 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 active 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 concept of *in-silico* models and/or purge factor calculation may also be applied when chemical synthesis is used to manufacture larger molecules out of scope of ICH M7 (e.g. antibody drug conjugates). 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 active 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 EMA, in some cases hampering the assessment and acceptability of *in-silico* purge calculations.

4.4.3. Setting of specifications

It may be possible to establish specification acceptance criteria/limits which are wider than the release data of batches used in clinical studies. In this case, the limits should still be appropriately justified in terms of clinical impact (i.e., product knowledge as it relates to safety and effectiveness). Importantly, additional sources of information beyond clinical experience are always considered when establishing specifications for any program, not just PRIME. However, it is recognised that setting specification acceptance criteria wider than clinical experience is frequently required specifically for PRIME programs.

Such additional sources of information could include, but are not limited to, *in vitro* data, animal data, published information, prior knowledge specific to a development platform, and the impact of potential CQAs from related development programs. In using information from other products, a comparison and justification for any differences between products should be provided. This comparison can include, for example, context of use (e.g. dosage forms, dosing regimens, route and duration of drug administration, clinical indications, and the intended patient populations), chemical characteristics, mechanism of action, analytical testing, manufacturing processes, formulations, and container closure systems.

The justification of specification limits for CQAs should be linked to clinical performance rather than solely derived from statistical methods such as tolerance intervals. Statistical analysis of a limited number of batches could result in specification limits which are too broad and cannot be justified clinically.

4.5. Approaches related to GMP compliance

4.5.1. Launching from an investigational medicinal product manufacturing site

According to EU legislation, all medicinal products for human use manufactured or imported into the EU, including investigational medicinal products (IMPs) 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, EMA could allow at the time of submission of the dossier, an investigational product manufacturing authorisation holder as the site of manufacture. Nonetheless, a commercial manufacturing authorisation issued under Article 40 of Directive 2001/83 confirming that the IMP manufacturer is authorised to manufacture products to be marketed will be required at the time of the opinion to the MAA. Therefore, the applicant should ensure that the necessary application for the relevant Manufacturing and Importation Authorisation (MIA) is submitted to the relevant supervisory authority in time to allow a GMP inspection prior to adoption of the opinion to the MAA. 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, although the IMP manufacturing experience can be taken into account, evidence that an adequate level of GMP compliance 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 a robust and efficient Quality Risk Management prior to certification and release of the marketed batches has to be provided. In this context, the use of a comparability assessment exercise (See 4.7) could be considered and applied for the evaluation of GMP gaps. In case the manufacturing site authorised under the Article 13 of Directive 2001/20/EC will not be the site that 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 in the evaluation of the level of GMP compliance.

In exceptional circumstances, it may be possible to place on the market the existing inventory of batches which have already been manufactured for use in pivotal clinical studies. In such cases, applicants should engage as early as possible with the relevant Regulatory Authority to seek prior agreement. Information should be provided, for example, to support that the batches were manufactured under GMP and the comparability of product manufactured with the clinical and commercial manufacturing processes. In addition, any batches distributed commercially will need to comply with the approved labelling.

4.5.2. Alignment of quality assessment and GMP inspections

During the MAA assessment, a GMP inspection could be required in order to assess the GMP compliance of a site. Submission of the information on the sites responsible for manufacturing, testing, EU batch release and distribution in advance of the MAA submission is necessary to evaluate the need for a GMP inspection and to co-ordinate any requested inspection within the timelines of the assessment procedure.

For accelerated procedural timelines, it is important to ensure that the timing of the quality assessment and GMP inspection activities are aligned, and appropriate mechanisms to share knowledge and information obtained through inspection or assessment activities are utilised by EMA to facilitate the overall evaluation.

4.5.3. Use of biological starting material manufactured under an appropriate 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 active substance starting material (e.g. a MCB developed in an academic setting) that may be considered by the applicant to have been manufactured under an appropriate level of GMP. This requires that 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 using appropriately qualified assays according to the approved control strategy. A documented risk assessment should be conducted to identify the testing requirements and/or other measures 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. A comprehensive viral safety study complying to GMP should also be performed, where relevant. The competent authorities will evaluate the risk assessment and the

proposed control 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 approaches may be used to demonstrate the stability of the product.

Based on scientific justification, which may include prior knowledge and/or data from development/pilot scale batches of the same formulation, it may be possible to submit less data than described in ICH guidelines. Data may cover shorter times (e.g. 6 months) than those recommended in available guidelines. In some cases, where a consistent stability pattern is seen, it may be acceptable to include data from less than 3 primary batches. Data from clinical batches may be used to support the shelf life, but any subsequent changes to the product or process should be explained, and it should be considered whether these changes could impact product stability. Applicants are encouraged to initiate dialogue with EMA to discuss their use of alternative stability approaches to ensure there is a mutual agreement on the dossier expectations.

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

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 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 that commitments to report deviations from the expected stability trends and out of specification results are provided.

The data used to generate the 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 stability model, the applicant 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 accelerated and stressed studies could be submitted to further support the proposed 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 be applied to what could be claimed as clinically qualified levels for each quality attribute, 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, more stringent release acceptance criteria should be set 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 applicant 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 apart from the container closure system.

The approach to use (models based on) prior knowledge to extend the claimed shelf life can in principle be applied to all types of biologicals (including e.g., mAbs and other therapeutic proteins, vaccines, viral vectors, cell therapy products). However, it is acknowledged that the principles will be difficult to apply to other groups of products and formulations than those used to establish the model (e.g. a model based on mAbs is unlikely to apply in general to other types of recombinant products). Especially for complex products, the prior knowledge is expected to be based on very similar products (e.g. same viral vector with a similar genetic construct carrying a different gene of similar size).

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 or utilising prior knowledge of molecular stability from other formulations of the same molecule. 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 should be provided to inform EMA immediately if the stability of the active substance/medicinal product is not as anticipated, and restrict the retest period/shelf life accordingly. This should be accompanied by a second commitment to submit the remaining quality data which would otherwise generally be required (e.g. at least 12 months under long term storage and maximum 12 months extrapolation) when available, if not otherwise agreed with EMA.

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 an adapted control strategy is used, or if other supportive knowledge is available.

4.7. Scientific tools related to comparability (biologicals)⁵

A risk-based approach, such as the one developed for ATMPs⁶, can potentially be used to tailor the comparability study. This will allow, for example, a reduced comparability package focusing only on the

⁵ The guidance below on comparability strategy is intended for biologicals, although it is acknowledged that several elements could potentially be applied for other product types. If developers intend to use such a strategy to other products it is recommended to seek advice from the competent authorities.

⁶ 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.

relevant CQAs (4.7.2) or the use of prior knowledge (4.7.1). Based on this, a justified set of release, (accelerated) stability and/or characterisation data can be used to demonstrate comparability.

A risk-based approach to the number of lots used for comparability studies could be justified. For example, the number of process validation lots used in comparability could follow the strategy for process validation lot manufacture (Section 4.3) or additional representative lots may be justified.

It is recognised that the level of comparability that needs to be demonstrated is dependent on the development phase. However, the recommendations given in this section are intended for later development stages in which clinical studies are ongoing or have been performed and a full comparability exercise is required.

Differences that are the result of enhancements of the process, leading to improvements in quality (e.g., improved purity profile) are generally acceptable.

Considerations in the sections below should be taken into account.

4.7.1. 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 these CQAs. Firstly, 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 CQAs.

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.

4.7.2. Using prior knowledge to tailor comparability studies

Prior knowledge (see 4.2.1), based on e.g. the same platform or from similar products, can be used to predict the impact of specific manufacturing changes.

The applicability of prior knowledge to 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. Firstly, it should be considered if additional chemical-physical, immunological or other data are needed. If required due to non-comparable results that can have impact on the relevance of the safety and/or efficacy data gathered so far, the comparability exercise should proceed with the generation and evaluation of non-

clinical and/or clinical comparability data as necessary to contribute to the conclusion of comparability of the product (see 4.7.7.).

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 active substance/finished product. It may be sufficient to assess the impact a particular step or a limited number of steps, by demonstrating comparability for a relevant intermediate after the modified manufacturing step(s).

For any scenario, comparability between the product used for the clinical trials and the product manufactured with 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 conducting the comparability exercise in order to make informed decisions on comparability when utilising the statistical results.

In any case, it is essential that an appropriate pre-specified plan is provided in the regulatory submission 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.

Inclusion of side-by-side analysis of individual values with accompanying descriptive statistics to summarise 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) a statistical tool may not be useful to demonstrate comparability, in such cases a comparison with historic ranges may be the best approach in which pre- and post-change data would be expected to fall within a range supported by product attribute and assay knowledge. High assay variability also necessitates to have sufficient repeats in the assay to demonstrate comparability.

Further consideration could also be given to the 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 characterised 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.

The principles of comparability described in this document do apply to ATMPs. This toolbox guidance should be read in conjunction with the Question and Answer document on Comparability considerations for Advanced Therapy Medicinal Products (ATMP), (EMA/CAT/499821/2019).

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 - benefit-risk assessment, this information could be gathered through 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. EMA seeks to support the medicine development process from an early stage and to offer regulatory mechanisms to help promising new medicines reach patients as early as possible, without compromising their quality, safety and efficacy. In this context, procedures are already available to establish an early dialogue with regulators and support prospective planning. These may not be limited to PRIME products and they include:

a) **scientific advice/protocol assistance** during development (which may also comprise the post-approval phase), 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 seek agreement on tailored development approaches such as filing with an initial adapted 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 optimise product development and avoid unnecessary testing replication or unnecessary differences in

testing methodologies in both regions. The agencies conduct this procedure under the auspices of the confidentiality arrangement between the European Commission, the EMA, and the US FDA.

Further information can be found on the dedicated EMA webpage (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 applicants 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 also contains a number of regulatory tools or strategies, which are not limited to PRIME products, 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. Accelerated assessment

The accelerated assessment is a tool reserved for 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 assessment 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 MAA dossier and avoid the submission of data during the assessment, to avoid the timetable reverting to 210 days 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 EMA 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 MAA.

5.3. Post-approval change management protocols (PACMPs)

The concept of PACMPs was introduced in the EU through the European 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 an applicant 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 planned

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 regulatory review and implementation time (ref. EMA Q&A on PACMP-EMA/CHMP/CVMP/QWP/586330/2010).

5.4. 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 categorised as specific obligation [SOB], annex II condition [ANX], additional pharmacovigilance activity in the risk-management plan (RMP) [MEA] or recommendation [REC].

PAMs should not be seen as a tool to allow 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 PAMs are classified according to the appropriate legal framework under which they will be enforced.

The type of PAM applied depends on the criticality of the missing data in relation to the clinical use of the product and its impact on the benefit-risk balance.

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 MA assessment (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 (e.g. at the pre-submission meeting) and seek agreement to ensure there is a mutual understanding.

References

- EMA website on PRIME scheme: <https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines>
- EMA website on support to early access: Support for early access
- 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
- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-4/2017_11_22_guidelines_gmp_for_atmps.pdf
- CHMP Q&A on Comparability considerations for Advanced Therapy Medicinal Products (ATMP) (EMA/CAT/499821/2019) https://www.ema.europa.eu/en/documents/other/questions-answers-comparability-considerations-advanced-therapy-medicinal-products-atmp_en.pdf

- Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017).
https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-statistical-methodology-comparative-assessment-quality-attributes-drug-development_en.pdf
- 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
- EMA Post-authorisation measures: questions and answers.
<https://www.ema.europa.eu/en/human-regulatory/post-authorisation/post-authorisation-measures-questions-answers>
- 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 webpage on conditional marketing authorisation: <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation>
- EMA webpage on accelerated assessment: <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment>
- 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).
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- EMA Scientific advice and protocol assistance: <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance>
- European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf
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(EMA/636600/2014). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-meetings-applicants-responses-questions-received-european-medicines-agency-scientific_en.pdf