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SCIENCE MEDICINES HEALTH

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Qualification of novel methodologies (QoNM) for medicinal product development

Procedural Guidance to applicants

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1. Introduction

The EMA Qualification of Novel Methodologies (QoNM) provides a voluntary, scientific pathway to support development, evaluation and regulatory endorsement of innovative methodologies in specific contexts of use. In this guidance, the term 'methodologies' refers to approaches allowing to generate evidence that supports regulatory benefit-risk assessment and decision making related to medicinal products throughout their lifecycle (development, use or monitoring of medicinal products pre- or post-authorisation).

QoNM promotes innovation, fosters collaboration among developers and stakeholders, and aims to integrate novel scientific approaches into medicinal product development and regulatory assessment. QoNM is open to any type of applicant.

QoNM provides development support and endorsement for novel methodologies intended for general regulatory acceptance. Published qualification opinions allow for application of qualified innovative methodologies for evidence generation by any medicinal product developer and thereby advance research and development of medicinal products and increase efficiency of regulatory assessment.

Broad applicability of the methodology beyond single medicinal product developments or single developers and external validity of the Context of Use are prerequisites for a qualification opinion in any case.

Proprietary methodologies may be in scope for QoNM, provided they will be accessible for medicinal product developers broadly if qualified.

While regulatory qualification translates into efficiency gains for both applicants and regulators, a qualification opinion is not a prerequisite for the regulatory acceptance of a novel methodology. A methodology may also be considered acceptable within a regulatory submission (e.g. Scientific advice, MAA) when the data provided demonstrate that it is "fit for purpose" for the specific medicinal product development and a defined context of use.

Methodologies solely intended for evidence generation in specific medicinal product development programs are discussed as part of product specific Scientific Advice.

Depending on the stage of development and the maturity of supporting evidence, applicants can request:

- **Qualification Advice** on the scientific rationale, preliminary data and the qualification plan for further development of a methodology to support a future qualification opinion in specified contexts of use. It allows for targeted refinement and early alignment with regulatory expectations. Detailed advice will be provided to applicants in a confidential letter. High-level information on qualification advice requests will be published on the EMA QoNM webpage to promote transparency, foster collaboration and avoid duplication of efforts. EMA may also propose publication of a Letter of Support when a novel methodology cannot yet be qualified but is considered promising based on preliminary data and the targeted context of use. Letters of Support can facilitate collaboration, data sharing and support utilisation of methodologies under development in collaboration with other developers for further evidence generation towards a qualification opinion.
- **Qualification Opinion** on the acceptability of a methodology in specific contexts of use to generate evidence for regulatory assessment and decision-making related to medicinal products. If successful, a draft qualification opinion together with the assessment of the supportive evidence will be published for consultation by stakeholders and the scientific community, ensuring thorough scientific scrutiny and discussion before final adoption by the EMA's Committee for Medicinal

Products for Human Use (CHMP). Publication of a final qualification opinion confirms that a methodology in the defined context(s) of use is accepted for evidence generation to support regulatory decision making.

Based on experience gathered since 2008, insights from various workshops and input from stakeholders, this updated guidance provides information on: methodologies considered in- and out of scope for QoNM; support to prepare for QoNM requests; the QoNM process, operations, timelines, outputs; considerations regarding the evidence expected to support qualification opinions, as well as considerations for lifecycle management of qualified methodologies.

2. Legal basis

The legal basis for providing scientific advice on medicinal product development is laid down in Article 57(1)(n) of Regulation (EC) No 726/2004 of the European Parliament and the Council.

Qualification advice and qualification opinions are provided without prejudice to requirements laid down in other potentially applicable legislation to be considered by methodology developers, e.g. the General Data Protection Regulation (GDPR, Regulation (EU) 2016/679), the Medical Device Regulation (MDR, Regulation (EU) 2017/745), the In-Vitro Diagnostics Medical Device Regulation (IVDR, Regulation (EU) 2017/746) and the Artificial Intelligence Act (AI Act, Regulation (EU) 2024/1689). These regulations may apply to technologies or devices which are used as part of the methodology to be qualified. It is the responsibility of the methodology developer to identify and meet the requirements as per applicable regulations for a specific use case.

A qualification opinion confirms acceptability of evidence generated by the methodology within its specified context of use and considering the specific regulatory question addressed for benefit-risk assessment of medicinal products by the CHMP; it does not provide certification or CE marking for medical devices, in vitro diagnostics or medical device software which may be used as part of the methodology. It is for developers and users to ensure that all components of the methodology are used and certified in line with the provisions of applicable EU regulations.

QoNM requests are subject to fees and fee incentives/waivers according to the applicable EMA fee regulation.

3. Scope

QoNM supports the development, evidentiary-strategy planning and regulatory approval of innovative methodologies. These may fill a gap in evidence generation to support regulatory benefit/risk decision making or promise to offer clear advantages over existing approaches (e.g. quality of evidence, feasibility, efficiency of evidence generation). Methodologies may pertain to any phase of medicinal product development or lifecycle, including quality development, non-clinical studies, clinical trials, and post-authorisation activities.

Methodologies considered for QoNM should have broad applicability in the sense that they can be applied in different drug development programmes by different developers. This demands transferability/external validity of results across settings (yet within the Context of Use), accessibility of the tools needed to apply the methodology and an adequate level of documentation which can be published, allowing other developers to apply a qualified methodology in line with conditions sufficiently described in a qualification opinion. This ensures that valid conclusions can be drawn from evidence generated applying qualified novel methodologies irrespective of specific investigational medicinal product (IMP) development programs. For proprietary methodologies where the information published as part of the qualification opinion is limited for reasons of commercial confidentiality and

does not enable direct application, arrangements with the owner of the methodology may have to be sought to access the qualified methodology.

Questions concerning the use of novel methodologies exclusively in the development of an individual medicinal product, or exclusively within a single developer's pipeline (e.g. use of in-house tools), may be addressed through product-related Scientific Advice or through Broad Scientific Advice, respectively.

QoNM can relate to methodologies that require use of (a) device(s), but it does not encompass the device(s) per se; nor does it provide certification/CE marking for medical devices, in vitro diagnostics or medical device software which may be used as part of the methodology. Depending on the methodology's context of use, MDR/IVDR applicability may need to be verified. Developers are encouraged to liaise early with relevant regulatory authorities as per e.g. MDR/IVDR/AI-Act to confirm the need for a clinical investigation or performance study application in the targeted context of use. Irrespective of CE marking considerations, characterisation and description of device performance is important for QoNM and device characteristics will be published in qualification opinions as reference for future use and lifecycle management of a qualified methodology with similar devices (see e.g. Stride velocity 95th centile).

Below, categories and criteria are mentioned clarifying which methodologies are typically within or outside the scope of QoNM. This overview is not exhaustive, given that QoNM is open to future innovative methodology developments. Developers are generally recommended to contact the EMA Scientific Advice Office as part of QoNM early interaction support to confirm eligibility before submitting a formal QoNM request (see information below).

3.1. Eligibility criteria

- Methodologies must relate to specific applications in the development, use or monitoring of medicinal products pre- or post-authorisation, considering the expected role of such methodologies in the development and benefit/risk evaluation of medicines.
- Methodologies should address gaps related to evidence generation or offer advantages or alternatives to existing approaches.
- Qualification proposals must specify (a) well defined context(s) of use (CoU) linked to a clearly identified question in development and lifecycle of medicinal products and contribute to regulatory decision-making; the ensemble of data space, CoU and method(s) informs a qualification opinion.
- Methodologies should be intended to become broadly accessible and applicable by medicinal product developers at large once qualified.
- Proprietary methodologies are in scope for QoNM if they are intended to become accessible broadly for procurement by medicinal product developers and marketing authorisation holders. Scoping meetings as part of QoNM early-interaction support (see details below) will allow clarifying whether these criteria are met.
- Willingness to publish an appropriate level of detail regarding the methodology, its application and performance characteristics as well as the evidence supporting its scientific validity in a qualification opinion is key. For non-proprietary methodologies, this should enable medicinal product developers to apply the qualified methodology in development programmes. For proprietary methodologies, the evidence supporting scientific validity will be published, while commercial confidentiality related to proprietary elements of the methodology will be considered. The content of draft and final qualification opinions will be agreed with applicants before publication.

3.2. In scope

The table below provides a non-exhaustive summary of common methodology categories in scope for QoNM. Whether a specific methodology is in scope for QoNM can be confirmed as part of QoNM early-interaction support.

Category	Examples / Context
(Bio) Marker	Prognostic/predictive, can be derived by application of various technologies (e.g. chemical, physical or digital measurements)
Outcome measure	Allows measurement of effects of an intervention, e.g. based on imaging, lab test, patient-/observer-reported outcomes, performance tests (e.g. outcome measure using DHT tool)
Data source	Patient registries, electronic health data sources
Methodologies for data analysis and decision support	Applications of statistical methods, modeling and simulation methods and approaches, artificial intelligence/machine learning based tools, manufacturing models
Non-clinical methodologies	Studies or tests conducted in vitro, in silico, or in chemico, or in vivo related to the investigation of the safety and efficacy of a medicinal product (e.g. simple and complex human cell-based assays, microphysiological systems including organ-on-chip, computer modelling, other non-human biology-based test methods, and animal-based tests)

3.3. Out of scope

- Methodologies that are not intended to directly support the generation of evidence to support benefit-risk assessment of medicinal products fall outside the scope of QoNM (e.g. methodologies for drug candidate selection or supporting clinicians identify the best therapeutic approach).
- Technical solutions or devices per se (e.g., biochemical assays, software, hardware, sensors, wearables). For context: QoNM may qualify a mobility measure as a clinical outcome assessment *derived from* measurements of a wearable technology/sensor, but not the specific wearable device used to generate the mobility measure. Technical solutions or devices which are part of a methodology may need to comply with other regulations and QoNM is without prejudice to potential requirements from applicable EU regulations as outlined above (e.g., GDPR, CTR, MDR, IVDR, AI-Act).
- Methodologies with no intended general application or broad accessibility and not intended for publication as qualification opinion. Qualification advice may still be available if the focus is entirely on the planning of evidence generation to validate a complex novel methodology and not its role in the development of specific medicinal products. Eligibility can be clarified during QoNM early-interaction support.
- Scientific tools and methodologies, including models and statistical methods already used in the regulatory context.
- Frameworks and guidelines for development and use of methodologies typically fall outside the scope of a qualification opinion; qualification advice might be possible; interested parties should seek early-interaction support.

- Methodologies in scope of ongoing regulatory guideline development on ICH or EU level may be out of scope for QoNM. Eligibility will be clarified during early-interaction support.

4. Preparing QoNM

Innovation Task Force

Innovation Task Force (ITF) briefing meetings offer a forum for informal discussion during conceptual and early stages of innovative methodology development. ITF briefing meetings establish early dialogue and provide opportunity to explore scientific, technical and regulatory considerations with experts from the European Medicines Regulatory Network (EMRN). ITF meetings are advisory and allow exploring the most suitable regulatory pathway (e.g. QoNM or Scientific Advice) to achieve a targeted regulatory outcome. ITF meetings are free of charge.

QoNM early interaction support

Applicants considering a QoNM request should contact the EMA Scientific Advice Office for informal early interaction support well in advance of a planned submission of a QoNM request via this mailbox:

EMA-Qualification-support@ema.europa.eu

Early interaction support will:

- address remaining questions after applicants will have considered available QoNM procedural guidance and related information thoroughly,
- clarify whether methodology and targeted context(s) of use are in scope for QoNM, and
- confirm documentation requirements to ensure submission of high-quality briefing packages enabling a timely and efficient process.

A Scientific Officer from the EMA Scientific Advice office will review the inquiry submitted via the EMA-Qualification-support inbox and reply in writing within 14 days.

Applicants may request an **informal 1-hour virtual scoping meeting** indicating why such a meeting would be beneficial. Granting scoping meetings is at the discretion of the EMA Scientific Advice office. Aspects which could support requests for a scoping meeting are e.g. limited regulatory experience of the applicant, highly innovative methodology or need to clarify whether methodology and context of use are in scope for QoNM and whether QoNM or other EMA support mechanisms will be best suited at a given stage of methodology development.

If a scoping meeting is granted, it will be scheduled within 6 weeks following the request. Developers will need to provide a short description (20 pages max.) of the methodology and its development, mentioning the targeted context(s) of use, the stage of development including a concise high-level overview of the studies/evidence already available, an outline of the qualification plan for further development, the targeted regulatory outcome (i.e. qualification opinion, qualification advice with/without Letter of Support), questions for discussion during the scoping meeting and an overview on interactions with other regulatory bodies they might have had. A meeting presentation should be provided at least two business days prior to the scheduled scoping meeting.

QoNM early-interaction support is free of charge.

Additional support

EMA is committed to supporting the development and qualification of innovative methodologies across the range of stakeholders. Early regulatory engagement is crucial for effective and efficient planning of evidence generation to demonstrate the validity of novel methodologies. Stakeholders, particularly those with limited experience interacting with the EU regulatory system — e.g., small and medium-sized enterprises (SMEs), biotech companies, academic institutions, public-private partnerships, and consortia — are encouraged to use EMA's available tailored platforms for early dialogue and support. These engagement opportunities help stakeholders determine whether the QoNM platform is appropriate for obtaining regulatory support and endorsement for their methodologies in the specifically targeted Context(s) of Use. Relevant EMA contacts include:

- SME office, for small and medium sized enterprises: sme@ema.europa.eu
- Stakeholder Department (public-engagement@ema.europa.eu), facilitating engagement with patients, consumers and healthcare professionals
- Academia office, for academic developers, entities not engaged in economic activities, research consortia and public-private partnerships: academia@ema.europa.eu
- Questions linked to patient registries: emaregistries@ema.europa.eu

5. Operations

General arrangements

The EMA Scientific Advice Office manages the QoNM procedure. Each request is assigned to an EMA scientific officer and an administrative assistant as primary contacts, responsible for providing scientific support and managing procedural administration, respectively.

The scientific evaluation is conducted by a specialised group of experts called the 'Qualification Team' (QT), appointed by the CHMP. This team is led by two coordinators (members of CHMP and/or SAWP) who oversee scientific evaluation of protocols, data, analyses and conclusions. Additional experts from the EMRN are included in line with the expertise required. The Qualification Team comprises at least five members. A patient representative will be invited to join the Qualification Team if meaningful in the context of the methodology and its specific context of use under consideration (e.g. PROM development as secondary efficacy endpoint, DHT based performance tests). The EMA stakeholder department will identify and invite patient representatives from the database of registered patient representatives based on the condition concerned.

If the required expertise is limited within the EMRN (e.g. for highly innovative methodologies) external experts may be involved in line with EMA's Conflict of Interest (CoI) policy. If external expert participation is not feasible but the Qualification Team during its review and deliberations identifies the need for broader scientific input, a targeted **stakeholder consultation** may be organised with support from the EMA stakeholder department. For such consultations, scientific questions will be drafted by the QT to avoid disclosure of confidential procedural information or data from the briefing package. The EMA stakeholder department will approach relevant learned societies, healthcare professional and patient organisations, or academic institutions with a request to nominate suitable candidates. A stakeholder consultation - if required - is part of the initial review of a QoNM request. Therefore, no information sharing with or input from the applicant is foreseen at the time of a possible stakeholder consultation. Input received from external experts during a stakeholder consultation will contribute to the primary assessment and will be reflected in the Scientific Discussion of the List of Issues shared with applicants to prepare a discussion meeting.

Procedure

The QoNM procedure is based on the Scientific Advice procedure but allows for additional flexibility. Provided the documentation submitted for review is of high quality and comprehensive, this allows for an efficient and timely process. If additional time is required, timelines can be adapted (e.g. for the review of large evidence packages by the Qualification Team or for applicants to address issues identified during the assessment which may require generation, analysis and submission of additional data). A detailed overview of the procedure is provided below.

Outputs

Qualification advice

In case of qualification advice, applicants receive a detailed confidential letter providing the CHMP's assessment and recommendations for further evidence generation towards a future qualification opinion.

High-level information regarding the qualification advice—including a descriptive title, targeted context(s) of use, applicant name, methodology type, and public enquiry contact—will be published on the EMA website. The specific information to be made public will be subject to review and approval by applicants prior to publication.

Qualification opinion

If a methodology can be qualified, a draft qualification opinion will be published for 6-weeks of consultation. This consultation allows the CHMP to share information broadly, inviting scientific scrutiny and discussion from the wider stakeholder community.

In a qualification opinion, an appropriate level of detail regarding the methodology, its application and performance characteristics as well as the evidence supporting its scientific validity will be published. For non-proprietary methodologies, this should enable medicinal product developers to setup and apply the qualified methodology in development programmes. For proprietary methodologies the evidence supporting scientific validity will be published, while commercial confidentiality related to proprietary elements of the methodology will be considered. The content of draft and final qualification opinions will be agreed between applicants and EMA before publication.

Comments received during consultation will be reviewed by the Qualification Team and shared with the applicant. Relevant input will inform amendments of the qualification opinion before its final adoption by the CHMP. All comments received, along with EMA responses, will be published as part of the final qualification opinion.

If a qualification opinion request cannot be agreed, the outcome will be a confidential qualification advice Letter with high-level information published on the EMA website as described above (‘qualification advice’).

Letter of Support

EMA may propose publishing a **Letter of Support** for methodologies which cannot be qualified yet but are deemed promising based on preliminary data and the targeted context(s) of use. If agreed by applicants, Letters of Support publicly recognize methodology developments, can promote collaboration, and encourage data sharing. Letters of Support include a concise summary of the methodology, context of use, available data, ongoing studies, and plans for future evidence generation. Applicants will review and approve Letters of Support before publication.

Post procedure

Applicants may request clarification after receiving a Qualification Advice Letter. Clarification aims to address potential errors or language that the applicant finds unclear or imprecise. However, any new information provided by the applicant will not be considered during clarification but can be addressed in a follow-up request.

Follow-up procedures should be considered if, e.g.:

- Additional advice is required.
- Evidence generated following qualification advice recommendations is expected to support a qualification opinion.
- Lifecycle management measures stipulated in a qualification opinion require assessment of newly generated supportive evidence to confirm continued validity of the methodology.
- The applicant seeks qualification of the same methodology in a different context of use.

Follow-up procedures adhere to the same timelines and fee considerations as initial requests.

Involvement of non-EU regulatory agencies

Currently, there is no formal parallel process for Qualification of Novel Methodologies with non-EU regulatory agencies. However, confidentiality agreements with agencies such as the US FDA, PMDA, WHO, Swiss Medic, and Health Canada generally allow representatives from these bodies to attend EMA QoNM meetings as observers (and vice versa).

Applicants interested in involving external observers will need to proactively contact the relevant agencies to identify interested representatives and obtain their commitment to join the QoNM discussion meeting as well as their agreement to share contact details. Applicants must provide EMA with these details in good time — preferably before the formal start of the EMA QoNM procedure — to enable timely invitations.

If a Qualification project is reviewed in parallel by different agencies and there are confidentiality arrangements between EMA and these agencies, ad-hoc exchanges may be arranged which may increase opportunities for scientific consensus and alignment of evidence requirements for qualification.

6. Procedure

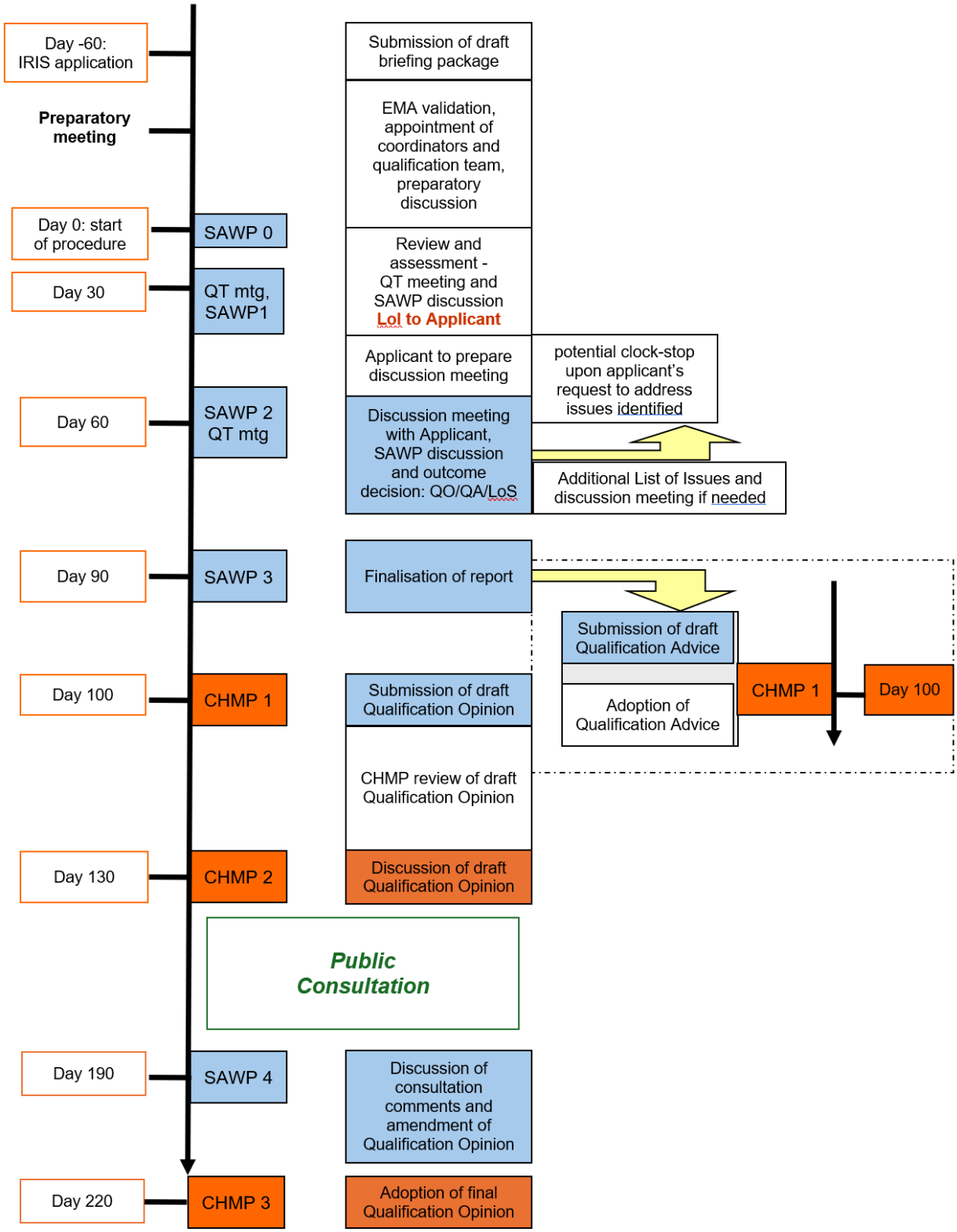

Figure 1: QoNM procedure flow

The QoNM procedure follows the meeting schedule of Scientific Advice Working Party (SAWP) as published annually on the Scientific Advice webpage. Indicated timelines reflect usual needs. However, the QoNM procedure affords flexibility. Complex requests with extensive documentation may require additional review time by the Qualification Team, and applicants may request clock stops to address issues or evidentiary gaps identified during the regulatory review.

Day -60

Request submission, appointment of qualification team, validation with optional preparatory meeting

Request submission

Requests must be submitted online via EMA's secure IRIS platform.

A complete draft dossier must be uploaded at the time of request submission (see briefing document template(s) for qualification request).

To submit a request, a methodology specific research product identifier (RPI) is required. Developers approaching EMA for the first time with the novel methodology will need to request a new RPI by contacting ScientificAdvice@ema.europa.eu. (RPI guidance).

Reports of prior informal discussions at EMA or minutes from interactions with other regulatory bodies internationally should be submitted as supportive appendices. Please indicate whether qualification advice or qualification opinion is requested. Requests for qualification opinion may be reverted to qualification advice during the procedure if the submitted evidence is not considered adequate to support the targeted Context(s) of Use.

Appointment of the qualification team

For each qualification request, EMA assigns a dedicated scientific officer and an administrative assistant who serve as primary contacts for applicants.

A tailored Qualification Team, reflecting the specific expertise required, is nominated to conduct the scientific review. Two coordinators, members of CHMP or SAWP, will lead the assessment. Additional team members with relevant expertise are selected from EMA committees, working parties, and the broader EU expert network. This approach ensures involvement of suitable experts and effective collaboration between specialists in emerging technologies or methodologies and experts in regulatory assessment.

Typically, a Qualification Team consists of at least five members, two coordinators from CHMP and/or SAWP, and three experts selected based on the specific methodological and scientific requirements (e.g. biostatistics, digital health technologies, imaging techniques, -omics, AI, modelling & simulation, (pharmaceutical) quality, non-clinical testing, 3Rs, translational research, clinical outcome assessments, RWE, clinical therapeutic area).

The Qualification Team will be supported throughout the process by the assigned EMA Scientific Officer.

Request validation with optional preparatory meeting

Applicants may request a virtual preparatory meeting. The main objective of this interaction is to clarify procedural aspects and to optimise the information included in the draft briefing package to ensure that review and assessment are based on optimal documentation. Preparatory meetings will be hosted by the Scientific Advice Office and chaired by the EMA scientific officer. Members of the qualification team may join as appropriate, allowing for an informal high-level scientific discussion based on a presentation by the applicant. Key points for optimising the briefing package identified during the meeting will be shared in writing by the EMA Scientific Officer within 48 hours after the

meeting. Preparatory meetings have proved highly valuable to optimise the quality, efficiency and timeliness of the review and therefore are strongly encouraged.

If no preparatory meeting is requested, the EMA Scientific Officer will perform a validation check of the draft briefing package and provide written validation comments for the applicant to optimise the briefing package before validation.

Day 0

Start of the procedure

Day 0-30

Review and assessment, qualification team meeting, List of Issues:

The information provided in the validated briefing package will be reviewed and assessed by the coordinators and qualification team experts. The coordinators will draft two independent reports which will be shared with qualification team members for comments and will be discussed during a qualification team meeting. A List of Issues will be drafted, and the coordinators will present the outcome of the deliberations during the qualification team meeting to the SAWP. After discussion, SAWP will adopt the List of Issues including a preliminary scientific discussion of the review findings to be shared with the applicant to prepare a discussion meeting. The List of Issues will be shared with the applicant in the week after the SAWP meeting. Based on the feedback provided in the List of Issues, applicants may consider submission of additional data or further analyses to address issues raised. If one month is too short to address the issues raised, applicants may request a clock-stop for a pre-defined, reasonable period which will be considered by the QT coordinators and the EMA scientific officer.

Day 60

A virtual discussion meeting with the applicant (potentially including patient representatives and/or observers invited by the applicant from other regulatory agencies) will be scheduled during the following SAWP meeting. Discussion meetings are a default element of the Qualification procedure. After the discussion meeting, the applicant will be asked to provide minutes within one week. These minutes serve as a record of the applicant's understanding of the meeting and can further address and clarify issues which may have emerged during the meeting. They will not be commented on and do not serve as an official outcome summary but will be considered by the Qualification Team when drafting the final report (Qualification Advice Letter, Letter of Support or qualification opinion).

Day 70-90

Joint report and SAWP review:

A draft joint report will be prepared by the qualification team coordinators in consultation with the qualification team members, reflecting also additional information received from the applicant in the context of the discussion meeting and will be shared with SAWP members. During its next plenary meeting, SAWP will discuss the qualification team report, ensure its scientific quality and consistency and will provide input on the possible need for further actions to support the qualification request.

Based on the validated briefing package, the input received from the applicant during the discussion meeting and the deliberations at SAWP, the qualification team will recommend to SAWP whether the procedure should be eligible for a qualification opinion or a qualification advice with/without Letter of Support. If deliberations after the discussion meeting indicate need for further clarification, a second List of Issues may be drafted. It will be for the Qualification Team to decide whether another discussion meeting is also considered meaningful to address issues, or whether a written response by the applicant could be sufficient.

Based on the initial assessment and the information received in reply to Lists of Issues, the SAWP will recommend one of the following procedural outcomes:

- **Qualification advice for future studies**: Based on the report of the qualification team, SAWP may recommend adopting a qualification advice on studies to support future qualification for the proposed context of use. This outcome is envisaged when prospective advice on planned studies to support future qualification has been requested, or when the supportive evidence submitted is not considered adequate to support a qualification opinion. Once additional evidence will have been generated, the applicant may request a qualification opinion as a follow-on request. For promising methodologies addressing unmet measurement needs, publication of a Letter of Support may be proposed to provide visibility and facilitate scientific collaboration and data sharing. In this case, a Letter of Support will be drafted by the Qualification Team and shared with the applicant for review, comments and agreement before publication.
- **Qualification opinion for public consultation**. Based on the report of the qualification team, SAWP may recommend the adoption of a qualification opinion on the acceptability of the method for evidence generation to inform regulatory decision-making in the specified context of use. The CHMP will receive the draft qualification opinion for review one month in advance of discussion in the CHMP plenary. The draft qualification opinion will be amended to reflect the comments and the discussion at the CHMP level.

If a request for qualification opinion cannot be endorsed based on the supportive evidence submitted, the procedure will instead result in qualification advice.

The EMA scientific officer will update the applicant after SAWP discussion.

Day 100

CHMP adoption of qualification advice:

The CHMP will discuss and adopt qualification advice for future studies. A confidential detailed report (Qualification Advice Letter) will be sent to the applicant. High-level information will be published on the QoNM webpage (descriptive qualification advice title, targeted context of use, applicant, type of novel methodology, contact for public enquiries). This completes a qualification advice procedure.

If a Letter of Support is proposed by the SAWP and agreed by the applicant, drafting by the Qualification Team, review by the applicant and publication will follow usually within 3 months after adoption of the Qualification Advice Letter.

Day 130

CHMP adoption of draft qualification opinion and start of public consultation:

Following review and discussion, the CHMP plenary may adopt a draft qualification opinion.

The draft qualification opinion including supporting information/annexes to be published will be forwarded to the applicant for review to confirm the information included is accurate (5 working days). For proprietary methodologies, the applicant may suggest removal of information considered commercially confidential. The final content will have to be agreed between EMA and applicants before a draft qualification opinion can be published.

The draft qualification opinion including the assessment report and supporting documentation is released for **6 weeks public consultation**, with proactive notification of relevant learned societies, patient organisations and other relevant stakeholders to ensure input and scrutiny by the scientific community and stakeholders.

Day 220

Adoption of the final CHMP qualification opinion:

Stakeholder input received during the public consultation will be shared with the applicant (for review and comments) and considered by the Qualification Team and SAWP to potentially amend and finalise the qualification opinion, as appropriate. CHMP may adopt this final qualification opinion, whereby the CHMP confirms the proposed methodology as an acceptable regulatory standard in specified contexts of use.

Communication and training:

The final CHMP qualification opinion together with supportive documentation will be made publicly available on the EMA website. The EMA/CHMP may organise training sessions/workshops on high-impact qualified methodologies and reflect in relevant existing guidelines as part of regular guideline revisions.

7. Considerations on generating evidence for qualification

Methodologies in scope for QoNM comprise a wide variety of tools in specific contexts of use to generate evidence for regulatory assessment and decision making related to medicinal products. Requirements for development, evaluation and regulatory endorsement largely depend on the specific methodologies involved, the question(s) of interest and context(s) of use. Considerations for methodology developers when planning studies aimed at demonstrating the validity of novel methodologies in support of eventual qualification can therefore only provide a general framework with a certain level of specificity.

Question of interest

Methods for evidence generation in the medicinal product lifecycle or for improving medicinal product development usually enable addressing a scientific question of interest. This question and how the novel methodology is to be integrated in product development and regulatory review should be explicitly described.

Plans for generating evidence for qualification

The qualification procedure allows flexibility by giving qualification advice on sufficiently mature (pre-specified) qualification plans. Feasibility studies, pilot data or preliminary results, if available, can support this. Early engagement is recommended, and qualification advice usually precedes a request for qualification opinion as it will allow for efficient generation of supportive evidence based on an agreed qualification plan. Therefore, applicants are encouraged to come for qualification advice with a pre-specified plan describing already available data, current knowledge gaps, and future data collection and analysis plans. See also comments on the Planning and the Learn/Confirm paradigm below.

In general, evidence demonstrating the reliability and accuracy of proposed new methodologies generated according to a pre-specified plan, separating exploratory from confirmatory steps, is considered more robust than evidence generated in a data-driven process. Usually, independent validation/testing with an appropriate data set is needed as a confirmatory step. Prospective validation is always preferred and for some methodologies (e.g. when using artificial intelligence technologies), it will be required.

Planning and assessment can follow a framework for establishing credibility of a new methodology, e.g. outlined in the draft ICH M15 guideline for model informed drug development and should use a risk-based assessment of key elements as described below.

Context of Use (CoU)

The "Context of Use" (CoU) is a description of the methodology and its specific role and scope to answer the scientific question of interest. It should be a concise, clear and explicit description of how and in what setting a novel methodology will be applied for evidence generation within medicinal product development and lifecycle.

The following elements should be considered when drafting a CoU statement:

- Category of methodology (e.g. plasma biomarker/clinical outcome assessment/NAM in context of 3Rs),
- intended role in evidence generation (e.g. for enrichment of clinical trial populations, as primary/secondary efficacy endpoint, for safety monitoring, to replace animal studies),
- population and disease context (e.g. diagnosis/condition, severity),
- study context (e.g., type of non-clinical studies, interventional/observational clinical studies, phase of clinical studies),
- information on in- and outputs (e.g. specimen/matrix, type of device/software used, scanners, assays, timepoints for measurement)
- limitations/exclusions (e.g. qualification limited to one or few CT/MRI/WSI scanners, or for AI-based methodologies whether intended for full automation or to assist human decision making).

The CoU governs the scope of claims about the methodology's utility—e.g., whether it supports patient selection, measures treatment response, identifies sub-populations, optimises dosing strategies, simulates clinical scenarios, serves as a (surrogate) endpoint, or provides patient-/observer-reported outcome measures. The CoU description should also outline how the methodology will be applied in the intended environment (quality, non-clinical or clinical setting) and which other essential technologies are needed for application (standardised procedures for generating information on e.g. biological systems or patients in studies, such as imaging methodologies).

The CoU plays a critical role for defining the evidence required for qualification. A methodology intended for confirmatory efficacy demonstration typically requires more robust supportive evidence than one used solely in early exploratory research (e.g. meta-analyses, prospective studies vs. observational studies or retrospective analyses).

A well-defined CoU guides exploration and validation study designs and analyses. It should be operationally specified to a level of detail that can support quantitative criteria for evaluation. The level of evidence required for successful qualification will depend on the impact for regulatory decision-making in a risk-based approach. It is usually best to begin with a narrow lower impact CoU and broaden it as data and experience grow.

Risk-based assessment

Developers should evaluate the risks and impact of new methodologies at the planning stage and when validation data and data generated during the life cycle of a new methodology are available. Assessment should comprise key elements outlined in the following paragraph and should focus on the scientific question of interest and CoU.

Risk-based assessment systematically evaluates the impact of a new methodology (weight of the new methodology in regulatory decision-making considering the contribution of other relevant information to address the scientific question of interest), the potential consequences of an incorrect decision (significance of an adverse outcome concerning the question of interest e.g. regarding efficacy or patient safety), how the new methodology contributes to a potential incorrect decision (with a justified description of the risk on a scale from low to high) and the impact of the new methodology (contribution of the evidence generated relative to its intended context of use considering regulatory expectations or standards).

The higher the risk and impact on regulatory decision-making, the more robust will the evidence base need to be to support qualification.

The evaluation of inherent risks and impact on regulatory decisions involves subject matter experts covering technical and quality/non-clinical/clinical domains. It is expected that for this task applicants involve experts and interested parties as e.g. patients or healthcare providers and similarly for assessment of qualifications experts from the regulatory network and invited interested parties will contribute.

Planning stage and the learn/confirm paradigm

Developers should propose a qualification plan leading to qualification of a new methodology. The steps of the development process should be clearly and comprehensively documented.

The appropriateness of the proposed new methodology should be justified (rationale why the proposed new methodology is suitable to answer the scientific question of interest considering related key assumptions and required data).

Criteria for evaluation should be pre-defined to establish the acceptability and validity of a new methodology, including explicit validation criteria and sufficient details on metrics used.

New methodologies used across the medicinal product lifecycle can involve parts for which assessment of data for validation is not in the remit of EMA (e.g. evidence needed for conformity assessment for CE marking, evidence for validation of a biomarker assay) or which are a tool/subpart used for the new methodology. It may be beneficial to separate the description of performance data for this part with the relevant details needed for qualification (e.g. reproducibility, repeatability) from other aspects of validation, e.g. clinical performance of a methodology that uses a medical device or biomarker assay, or final performance of a quality control system.

Typically, the development process is divided into different phases. The exploratory ('Learn') phase includes early studies to characterise feasibility, setup and preliminary performance. Modifications to the novel methodology and/or its CoU at this stage can frequently be found necessary. The confirmatory ('Confirm') phase comprises larger, more rigorous studies that are intended for validation/testing to demonstrate the validity of the new methodology in line with the CoU. Major modifications at this stage may require additional confirmatory experiments.

Each step of the development needs appropriate planning and pre-specification.

Methodology-specific considerations

Specific considerations pertain to the evidence requirements to support various categories of novel methodologies (refer to section 3.2); however, an in-depth discussion of these issues falls outside the scope of this procedural guidance. Future Question and Answer documents dedicated to particular methodology categories will address these considerations. As high-level examples, few considerations

pertaining to clinical outcome assessment (COA) and surrogate endpoint qualification as well as 3Rs testing approaches are mentioned below.

COAs should demonstrate content validity as well as adequate psychometric properties (e.g., reliability, validity, responsiveness) in larger samples of the target population and enable an understanding of the sensitivity to detect change and which changes reflect clinically meaningful shifts in the patient's health status/QoL (MCID: minimal clinically important difference) if applicable; relationship to established outcome measures ('anchors') should be investigated. Instrument burden, administration mode (paper vs. electronic) and language, literacy or cultural factors can impact on COA performance and feasibility and need to be considered.

Surrogate endpoints typically require prospective trials measuring both the surrogate and the related final clinical outcome; usually, clear trial-level and typically individual level surrogacy based on meta-analysis of multiple studies investigating different treatment modalities are needed to address the high regulatory impact surrogate endpoints have, in particular if they are intended to serve as primary efficacy endpoints replacing established clinical outcomes in confirmatory studies.

Considerations regarding qualification of 3Rs testing approaches (e.g. NAMs) can be found in the 3RsWP Guideline on the principles of regulatory acceptance of 3Rs testing approaches (Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches). Definition of a specific context of use is considered critical for the determination of the performance standards aimed to establish being fit for purpose and guide qualification.

Submission stage and evidence for demonstration of validity

Developers should describe the evaluation and validation process. Due to the large range of new methodologies in scope of qualification, the description will need different elements, and not all recommendations outlined below apply to each new methodology.

Generally, the evaluation should contain a discussion of key results and conclusions from validation steps, e.g. performance of tools involved (e.g. performance of a medical device part, biomarker assay) and overall performance of the new methodology. It should be described how key results compare to and fulfil pre-specified criteria in line with appropriate research questions. Conclusions on the acceptability of the performance of the new methodology with a view to the (operationalised) research question and Context of Use should be provided. A rationale for the chosen evaluation methods and performance metrics should be provided already at the planning stage. Relevant deviations from the plan should be described and discussed.

A summary of the evidence assessment should be provided. As for risk-based assessment, this usually involves multidisciplinary assessment by subject matter experts from interested parties covering the technical domain and domain of application (quality, non-clinical, clinical). The evidence assessment should include a discussion of limitations.

8. Lifecycle management considerations

Case-by-case consideration

Lifecycle management of qualified methodologies is important and should be proactively planned and agreed upon between qualification opinion holders and regulators on a case-by-case basis and documented in published qualification opinions. Special consideration is necessary for methodologies involving rapidly evolving technologies such as e.g. Digital Health Technologies (DHTs) and Artificial Intelligence/Machine Learning (AI/ML) related approaches as well as dynamic data sources, including

registries and other Real-World Evidence (RWE) data sources, where e.g. model degradation, changes in disease understanding/classification, population drift and changes in underlying data characteristics may occur over time.

Methodology developers should discuss the need for and propose detailed, prespecified and documented plans to monitor, assess, and maintain the robustness, reliability, and continued validity of the methodology as part of the QoNM request. These plans must clearly address version control, ongoing validation, governance responsibilities, and the criteria and procedures for triggering regulatory communication or updates, ensuring the methodology consistently aligns with its qualified Context of Use.

Regulatory guidance and standards to consider

Over recent years, various regulations, guidelines and standards related to pharmaceuticals, analytical methods, medical devices and emerging technologies have become available (e.g., ICH guidelines Q2(R2), Q10, Q12, Q14; ISO 13485, ISO 14971; IEC 62304; EU Medical Device Regulation (EU) 2017/745 (MDR); EU In Vitro Diagnostic Regulation (EU) 2017/746 (IVDR); EU Artificial Intelligence Act (EU) 2024/1689). While these may not be immediately or fully applicable to qualified novel methodologies, they do provide essential concepts and best practices that developers should consider when establishing lifecycle management strategies.

A lifecycle management plan should adopt a prospective, science-driven, and risk-based approach. Key components should include continuous validation, robust change control procedures, systematic performance monitoring, and prespecified documentation practices enabling auditing if required (e.g., during assessment of marketing authorisation applications that rely on evidence generated by the qualified methodology). Agreed lifecycle management plans will be included in published qualification opinions ensuring transparency and clarity on agreed measures.

Process

Lifecycle management requirements of qualified novel methodologies will vary significantly based on the methodology, the specific Context of Use (CoU) and the technology involved. Therefore, standardised rules for monitoring, re-validation, or fixed re-qualification intervals cannot be meaningfully established. Instead, specifically tailored lifecycle management plans will need to be proposed by applicants, agreed with the CHMP and clearly described in published qualification opinions.

Stakeholders applying a qualified methodology will need to monitor the setup and performance of the qualified methodology in line with the published specifications and the agreed lifecycle management plan. Validation studies may need to be performed if significant changes occur - such as e.g., the introduction of new imaging devices, use of wearables and smartphones with substantially different performance characteristics, introduction of new software or algorithms, or if relevant AI/ML model drift or population drift in real-world data sources are observed.

Qualification opinion holders may consider submitting the results of such studies as follow-up qualification opinion request. After assessment by the Qualification Team and discussion at SAWP, CHMP may confirm the continued validity of the methodology and issue an updated qualification opinion, highlighting the changes. Updated qualification opinions will be published on the QoNM webpage, alongside earlier versions, ensuring transparency in lifecycle management for stakeholders and the public.

Stakeholders (e.g. medicinal product developers) applying a qualified method and submitting this evidence as part of a regulatory application will need to justify that performance of the qualified method was in line with the published qualification opinion or that changes do not adversely impact on the validity of the methodology.

New Context of Use

A new qualification opinion will need to be requested if methodologies which have been qualified for specific CoUs are to be validated in a different CoU (e.g., as an outcome measure in a related but distinct medical condition, or as primary efficacy endpoint after qualification as secondary efficacy endpoint in the same medical condition previously). Reference can be made to evidence which had been submitted and assessed previously that is still applicable and relevant to support the new context of use.

Periodic informal dialogue/trialogue (QO holder, MP developers, EMA)

Qualification opinion holders have indicated that periodic informal meetings could be beneficial, possibly also involving medicinal product developers or marketing authorisation holders utilising qualified methodologies. Such meetings will provide opportunity to share experiences, address operational and methodological challenges, support lifecycle management strategies and help to identify a need to re-validate and update qualification opinions.

For example, holders of qualified patient registries might seek input on how administrative changes, adjustments in patient characteristics, or changes to the data elements collected can maintain or enhance the registry's utility within the qualified CoU. Also, registries might need to adapt their setup for registry-based studies investigating new classes of medicinal products.

EMA is amenable to organising such periodic dialogues/trialogues upon justified request. Meetings can be arranged as one-off informal interactions free of charge via the Scientific Advice Office. The discussion at the meeting will be based on a briefing document and a presentation to be provided by the qualification opinion holder. A request should be submitted at least 3 months prior to the intended scheduling of the meeting via EMA-Qualification-support@ema.europa.eu, and the briefing document and presentation should be available at least 2 weeks before the meeting.

Conclusion on life-cycle management

Regular lifecycle management activities should be documented by any stakeholder applying a qualified methodology and should be submitted as supportive information if evidence generated using a qualified methodology is submitted as part of a regulatory application (e.g. marketing authorisation application (MAA)).

Published qualification opinions will document the agreed elements of a life-cycle management plan ensuring that methodologies remain valid, reliable, scientifically robust, and adaptable to methodological and technological advancements. It is of critical importance to proactively monitor and document performance based on clearly defined and measurable criteria and manage necessary updates through prospective lifecycle management strategies. Continuous validation aligned with agreed performance standards will ensure sustained regulatory compliance and maintain confidence in the methodology’s utility throughout its lifecycle. Any significant methodological changes or updates should be clearly documented and communicated proactively to EMA to confirm ongoing acceptability.

9. Glossary

- **AI system:** a machine-based system that is designed to operate with varying levels of autonomy and that may exhibit adaptiveness after deployment, and that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments (Regulation (EU) 2024/1689, Article 3(1))
- **AI Act:** European Union regulation (EU 2024/1689) governing the development and use of artificial intelligence technologies EU AI Act Explorer
- **Applicant:** Individual or organisation submitting a request for qualification advice or opinion to the EMA. EMA Scientific Advice
- **Biomarker:** a defined and measurable characteristic that indicates normal biological processes, disease processes, or responses to an exposure/intervention (e.g., a therapy). Typical types include molecular, histologic, radiographic, or physiologic measures (BEST glossary)
- **CHMP (Committee for Medicinal Products for Human Use):** EMA committee responsible for assessing and approving medicines for human use in the EU. Adopts qualification opinions for Novel Methodologies, CHMP
- **CoU**: Context of Use, description of the methodology and its specific role and scope to answer the scientific question of interest, see chapter 7 for detail
- **DHT (Digital Health Technology):** Systems that use computing platforms, connectivity, software, and sensors for healthcare and related uses. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device, or as part of combination medicinal products. They may also be used to develop or study medicinal products.
- **EMANS (European Medicines Agencies Network Strategy):** A strategic plan guiding the work of the European medicines regulatory network. EMANS to 2028
- **EMRN (European Medicines Regulatory Network):** A network of regulatory authorities and experts across the EU collaborating on medicines regulation.
- **GDPR (General Data Protection Regulation):** EU regulation (2016/679) governing data protection and privacy for individuals. GDPR Text
- **IRIS (Integrated Regulatory Information System):** EMA's secure online platform for submitting and managing regulatory requests. EMA IRIS
- **ISO 13485:** International standard for quality management systems for medical devices. ISO 13485
- **ISO 14971:** International standard for risk management in medical devices. ISO 14971
- **IVDR (In Vitro Diagnostics Medical Device Regulation):** EU regulation (2017/746) governing in vitro diagnostic medical devices. IVDR text
- **Letter of Support:** A public statement from EMA recognizing a promising methodology that cannot yet be qualified, supporting collaboration and data sharing for future qualification. EMA Qualification of Novel Methodologies
- **Lifecycle Management:** The ongoing process of monitoring, documenting, updating, and ensuring the continued validity of a qualified methodology. To be described and agreed on a case-by-case basis in published qualification opinions

- **MCID (Minimal Clinically Important Difference):** The smallest change in a treatment outcome that patients perceive as beneficial or healthcare professionals consider relevant for treatment decisions
- **MDR (Medical Device Regulation):** EU regulation (2017/745) governing medical devices. MDR text
- **ML (Machine Learning):** A computational/AI technique by which a system infers patterns, models, or decision logic from input data using methods such as supervised learning, unsupervised learning, reinforcement learning, or deep learning, and uses the resulting model(s) to generate outputs (predictions, recommendations, decisions, content) for new inputs.
- **NAMs**: New approach methodologies, refer to novel methodologies that are compliant with the so-called 3Rs principles for the ethical use of animals in medicine testing across the European Union (EU). '3Rs' stands for replacement, reduction and refinement of animal use.
- **Outcome Measure:** specific measurable variable or instrument (e.g., scale, test, assessment) used to quantify an endpoint for a stated estimand, including its scoring and interpretation, prespecified in a protocol and statistical analysis plan
- **Patient-Reported Outcome (PRO):** Any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s) EMA HrQoL guidance
- **Performance Characteristic:** A measurable property that describes how a methodology or device functions. ICH Q2(R2) Validation
- **Real-World Data (RWD):** Data collected from routine clinical practice, outside of controlled clinical trials. EMA Data Quality Framework
- **Real-World Evidence (RWE):** Evidence derived from the analysis of real-world data. EMA Reflection Paper on RWE
- **Registry-Based Study:** A study that uses data from patient registries to answer research questions. EMA Registry-Based Studies Guidance
- **Research Product Identifier (RPI):** A unique identifier required for submitting a request to EMA. RPI guidance (see p.29)
- **SAWP (Scientific Advice Working Party):** EMA working party that provides scientific advice and hosts the Qualification of Novel Methodologies procedure. SAWP
- **SME (Small and Medium-sized Enterprise):** A business category defined by the EU, often eligible for special regulatory support and fee incentives. EMA SME Office
- **Surrogate endpoint:** An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself but has been demonstrated to predict clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

10. Regulatory guidance/sources/documents to consider

- ICH Q2(R2) Validation of analytical procedures
- ICH Q10 Pharmaceutical quality system
- ICH Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management
- ICH Q14 Analytical procedure development

- ICH M10 on bioanalytical method validation – Step 5
- ICH E18 Guideline on genomic sampling and management of genomic data
- Guideline on computerised systems and electronic data in clinical trials
- Guideline on clinical evaluation of diagnostic agents, including Annex 1
- Harmonisation and update of the clinical aspects in the authorised conditions of use for radiopharmaceuticals and other diagnostic medicinal products - Scientific guideline
- ICH E15 Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories - Scientific guideline
- ICH E16 Genomic biomarkers related to drug response: context, structure and format of qualification submissions - Scientific guideline
- Guideline on registry-based studies
- Data Quality Framework for EU medicines regulation
- Draft of Data Quality Framework for EU medicines regulation application to real-world data
- Catalogue of RWD sources
- HMA-EMA Catalogues of real-world data sources and studies
- EMA Patient Registries webpage with multiple resources
- EU AI Act
- Reflection Paper on the use of artificial intelligence in the lifecycle of medicines
- Regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products - Scientific guideline
- The Use of Patient Reported Outcome (PRO) measures in oncology studies
- ICH E9 statistical principles for clinical trials
- ICH M15 Guideline on general principles for model-informed drug development Step 5
- Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence
- ICH M14 – Guideline on non-interventional studies that utilise real-world data for safety assessment of medicines
- Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches
- General Data Protection Regulation (GDPR) – Regulation EU 2016/679
- ISO 13485:2016 - Medical devices - Quality management systems
- ISO 14971:2019 - Medical devices - Application of risk management to medical devices
- IEC 62304:2006 - Medical device software - Software life cycle processes

11. QoNM related publications

- Insights from the European Medicines Agency on digital health technology derived endpoints
  Jadoenathmisier KD, Gardarsdottir H, Mol PGM, Pasmooij AMG.

  Drug Discov Today. 2025 Jun;30(6):104388. doi: 10.1016/j.drudis.2025.104388. Epub 2025 May 26. PMID: 40436264, Free article

- Regulatory considerations for developing remote measurement technologies for Alzheimer's disease research
  Erdemli G, Grammatikopoulou M, Wagner B, Vairavan S, Curcic J, Aarsland D, Wittenberg G, Nikolopoulos S, Muurling M, Froehlich H, de Boer C, Shanbhag NM, Nies VJM, Coello N, Gove D, Diaz A, Foy S, Dartee W, Brem AK.

  NPJ Digit Med. 2024 Sep 4;7(1):232. doi: 10.1038/s41746-024-01211-8.

  PMID: 39232033 Free PMC article

- Evidentiary basis of the first regulatory qualification of a digital primary efficacy endpoint.

  Servais L, Strijbos P, Poleur M, Mirea A, Butoianu N, Sansone VA, Vuillerot C, Schara-Schmidt U, Scoto M, Seferian AM, Previtali SC, Tulinius M, Nascimento A, Furlong P, Singh T, Dreghici RD, Goemans N, Mercuri E, Straub V, Ormazabal MG, Braid J, Muntoni F, Tricot A, Annoussamy M, Eggenspieler D.Sci Rep. 2024 Nov 29;14(1):29681. doi: 10.1038/s41598-024-80177-9.PMID: 39613806 Free PMC article

- Big Multiple Sclerosis Data network: an international registry research network.

  Glaser A, Butzkueven H, van der Walt A, Gray O, Spelman T, Zhu C, Trojano M, Iaffaldano P, Battaglia MA, Lucisano G, Vukusic S, Vukusic I, Casey R, Horakova D, Drahota J, Magyari M, Joensen H, Pontieri L, Elberling F, Klyve P, Mouresan EF, Forsberg L, Hillert J.J Neurol. 2024 Jun;271(6):3616-3624. doi: 10.1007/s00415-024-12303-6. Epub 2024 Apr 1.PMID: 38561543 Free PMC article.

- Regulatory Qualification of a Cross-Disease Digital Measure: Benefits and Challenges from the Perspective of IMI Consortium IDEA-FAST.

  Nobbs D, Piwko W, Bull C, Cormack F, Ahmaniemi T, Holst SC, Chatterjee M, Maetzler W, Avey S, Ng WF; IDEA-FAST Consortium.Digit Biomark. 2023 Sep 19;7(1):132-138. doi: 10.1159/000533189. eCollection 2023 Jan-Dec.PMID: 37901363 Free PMC article.

- Patient-reported, observer-reported and performance outcomes in qualification procedures at the European Medicines Agency 2013-2018.

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- How Much Evidence Is Enough? Research Sponsor Experiences Seeking Regulatory Acceptance of Digital Health Technology-Derived Endpoints.

  Perry B, Kehoe L, Swezey T, Le Masne Q, Goldhahn J, Staley A, Corneli A.Digit Biomark. 2023 Jun 8;7(1):45-53. doi: 10.1159/000529878. eCollection 2023 Jan-Dec.PMID: 37404865 Free PMC article.

- NAFLD and NASH biomarker qualification in the LITMUS consortium - Lessons learned.

Rasmussen DGK, Anstee QM, Torstenson R, Golding B, Patterson SD, Brass C, Thakker P, Harrison S, Billin AN, Schuppan D, Dufour JF, Andersson A, Wigley I, Shumbayawonda E, Dennis A, Schoelch C, Ratziu V, Yunis C, Bossuyt P, Karsdal MA.J Hepatol. 2023 Apr;78(4):852-865. doi: 10.1016/j.jhep.2022.11.028. Epub 2022 Dec 14.PMID: 36526000 Free article.

- Consortium-based approach to receiving an EMA qualification opinion on the use of islet autoantibodies as enrichment biomarkers in type 1 diabetes clinical studies.

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- Biomarkers in Medicines Development-From Discovery to Regulatory Qualification and Beyond.

  Hendrikse NM, Llinares Garcia J, Vetter T, Humphreys AJ, Ehmann F.Front Med (Lausanne). 2022 Apr 26;9:878942. doi: 10.3389/fmed.2022.878942. eCollection 2022.PMID: 35559349 Free PMC article.

- Leveraging Real-World Data for EMA Qualification of a Model-Based Biomarker Tool to Optimize Type-1 Diabetes Prevention Studies.

  Podichetty JT, Lang P, O'Doherty IM, David SE, Muse RN, Karpen SR, Song LS, Romero K, Burton JK; Type-1 Diabetes Consortium (T1DC).Clin Pharmacol Ther. 2022 May;111(5):1133-1141. doi: 10.1002/cpt.2559. Epub 2022 Mar 11.PMID: 35276013 Free PMC article.

- Biomarker Qualification at the European Medicines Agency: A Review of Biomarker Qualification Procedures From 2008 to 2020.

  Bakker E, Hendrikse NM, Ehmann F, van der Meer DS, Llinares Garcia J, Vetter T, Starokozhko V, Mol PGM.Clin Pharmacol Ther. 2022 Jul;112(1):69-80. doi: 10.1002/cpt.2554. Epub 2022 Mar 5.PMID: 35137949 Free PMC article.

- The Qualification of an Enrichment Biomarker for Clinical Trials Targeting Early Stages of Parkinson's Disease.

  Stephenson D, Hill D, Cedarbaum JM, Tome M, Vamvakas S, Romero K, Conrado DJ, Dexter DT, Seibyl J, Jennings D, Nicholas T, Matthews D, Xie Z, Imam S, Maguire P, Russell D, Gordon MF, Stebbins GT, Somer E, Gallagher J, Roach A, Basseches P, Grosset D, Marek K; Critical Path for Parkinson's Consortium.J Parkinsons Dis. 2019;9(3):553-563. doi: 10.3233/JPD-191648.PMID: 31306141 Free PMC article.

- Molecular Neuroimaging of the Dopamine Transporter as a Patient Enrichment Biomarker for Clinical Trials for Early Parkinson's Disease.

  Romero K, Conrado D, Burton J, Nicholas T, Sinha V, Macha S, Ahamadi M, Cedarbaum J, Seibyl J, Marek K, Basseches P, Hill D, Somer E, Gallagher J, Dexter DT, Roach A, Stephenson D; Critical Path for Parkinson's (CPP) Consortium; Parkinson's Progression Markers Initiative (PPMI).Clin Transl Sci. 2019 May;12(3):240-246. doi: 10.1111/cts.12619. Epub 2019 Mar 18.PMID: 30706986 Free PMC article.

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- Strategic Regulatory Evaluation and Endorsement of the Hollow Fiber Tuberculosis System as a Novel Drug Development Tool.

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