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Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

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[1] Main changes are in the presubmission phase.
Based on experience, the presubmission phase is important not only from the procedural help to the applicant point of view but also from a scientific point of view. Therefore it has been extended to 60 days with appointment of the Coordinator and the Qualification team one month before the start of the procedure compared to the appointment at start of procedure previously.
Also the timing of the preparatory meeting with the applicant has been moved from the beginning of the procedure (previously 5-15 days after start) into the presubmission phase, i.e. approximately 15 days before the start based on the usefulness of this timing observed in the procedures to far.[2] Main changes are the inclusion of the dates and deadlines for submission of letters of intent for qualification of novel methodologies.
[3] Main change is the inclusion of the letter of support, as an option following a qualification advice procedure.
[4] Main change is related to submission process.
[5] Hyperlink updates.

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Qualification of novel methodologies for drug development: guidance to applicants

The EMA qualification process is a new, voluntary, scientific pathway leading to either a CHMP Qualification opinion or a qualification advice on innovative methods or drug development tools:

- **CHMP qualification opinion** on the acceptability of a specific use of the proposed method (e.g. use of a novel methodology or an imaging method) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data;
- **CHMP qualification advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.

As the scientific knowledge and the intended use of a new method may change in line with the generation of additional data the EMA qualification process may encompass an ongoing interaction between the CHMP and the applicant. Prior to final adoption of a qualification opinion, the CHMP evaluation, being open to public consultation of the scientific community will ensure that CHMP shares information and is open to enlarged scientific scrutiny and discussion. The impact of the qualification on regulatory technical standard also requires that the international dimension of the scientific evaluations is accommodated for within the available confidentiality arrangements.

Legal basis

The Regulation No 726/2004 of the European Parliament and of the Council provides a legal basis for the provision of scientific advice in the frame of the development of medicinal products.

Scope

The qualification process addresses innovative drug development methods and tools. It will focus on the use of novel methodologies developed by consortia, networks, public/private partnerships, learned societies and pharmaceutical industry for a specific intended use in pharmaceuticals R&D.

The existing scientific advice/protocol assistance procedure is prospective advice related to a specific product(s), indication(s) or technology within a development programme. The existing scientific advice/protocol assistance procedure is not affected by the qualification procedure.

This guidance is without prejudice of the requirements laid down in the medical devices' legislation, and in particular in Directive 98/79/EC on in vitro diagnostic medical devices, where applicable (OJ L 331, 7.12.1998, p. 1, as last amended).

Applicant input

Qualification opinion: protocols, study reports and supportive data to establish the use of a defined novel methodology for a specific purpose in drug development.

Qualification advice: draft protocols and development plans for future studies to establish the use of a defined novel methodology for a specific purpose and any data available so far to support these plans.

Operations

A specialised group appointed by the CHMP, named "**qualification team**," led by two rapporteurs who are CHMP and/or SAWP members is in charge of the review of data and protocols, ensuring that efficient use is made of the resources available in the EMA experts' network. The procedure applicable to provide qualification advice is based on the existing Scientific Advice procedure adapted to host the activity of the Qualification team and to incorporate international collaboration. In addition, **a public consultation** will be pursued prior to a final qualification opinion to take the views of the scientific community into consideration. The public consultation of the scientific community will ensure that CHMP/SAWP shares information and is open to enlarged scientific scrutiny and discussion. The timing of the public consultation will be agreed with the applicant, who will also have the opportunity to remove any confidential information from the document to be published. The operational sustainability of the process will require the levy of appropriate assessment. The process is reviewed on a yearly basis to be adjusted to workload and the needs of parties involved. The preparatory discussion with the EMA is free of charge.

Fees

The procedure for "qualification opinion" and "qualification advice on future protocols and methods for further method development towards qualification" will be charged according to the fees described in the e*xplanatory note for fees payable to the European Medicines Agency. Please note that fees are updated on the 1st of April of each calendar year.*

Output

- CHMP qualification opinion and scientific assessment (public document).
- CHMP qualification advice on future protocols and studies to be further performed for qualification purposes (confidential document). Based on the qualification advice a letter of support may be proposed by EMA as an option, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data. This letter includes a high-level summary of the novel methodology, context of use, available data and on-going/future investigations. Letters of support will be made publicly available on the EMA website subject to sponsor's agreement. The objective of the letter of support is to encourage the efforts for data sharing and facilitate studies towards qualification for the novel methodology under evaluation.

Other interactions with the EMA

Briefing meetings with the pharmacogenomics working party on the development of genomic novel biomarkers can still take place (before the procedure of qualification of novel methodologies) and are encouraged at an early stage of development. Briefing meetings normally occur once on each specific approach and do not result in a document expressing the CHMP opinion on the issues discussed. The sponsor is recommended to request the new qualification procedure after the briefing meeting. Briefing meetings should not occur during the qualification procedure.

Meetings with the innovation task force are not affected by the new procedure(s).

Post advice

In the event that new scientific information relevant to the qualified novel methodology/ies becomes available after final adoption of the qualification opinion / qualification advice letter, or if the applicant wishes to, a follow-up procedure can be initialised.

The follow-up procedure will follow the same timelines as the normal qualification opinion/ qualification advice on future protocols and methods for further method development towards qualification procedure.

If needed, the applicant may request a clarification after receipt of the qualification advice letter. This is only intended to provide the applicant with the opportunity to clarify the meaning of the qualification advice on future protocols and methods for further method development towards qualification procedure that is perceived as being not clear or precise enough. Any new information will only be considered as part of the review of a follow-up request.

Involvement of non-EU regulatory agencies

Experts from non-EU regulatory agencies who have a confidentiality agreement with the EMA in place may join Qualification meetings as observers if possible. This is encouraged to increase dialogue and maximise the chance for scientific consensus. Applicants are encouraged to clarify options proactively in advance with relevant contact points at those agencies and the EMA scientific officer. Information on standing confidentiality arrangements can be found here.

Procedure

Day -60[5]

Submission

Applications should be submitted via EMA's secure online IRIS platform.

A complete draft dossier should also be submitted (see template(s) for qualification request for further information on the content of the dossier). These requests will follow general submission deadlines which are published yearly in our guidance webpage.

Please note that in order to submit an application via IRIS a research product identifier (RPI) is required to track medicines and methodologies through pre-authorisation procedures.

Companies and individuals that approach EMA for the first time with a new methodology will need to request a new RPI via e-mail to scientificadvice@ema.europa.eu.

Reports of initial informal discussion at EMA or international level shall be submitted as supportive appendices. It is not mandatory at the time of the start of the procedure to decide on the procedural route to be followed (qualification opinion or qualification advice on future protocols and methods for further method development towards qualification). This may depend on the assessment of the submitted data and can be decided during the course of the procedure between the qualification team and the applicant.

[5] Calendar days

An EMA scientific officer will be assigned to support each qualification request. This person will be the applicant's main contact person at the EMA.

An initial validation step will be performed by the EMA (scientific advice office) and there is a possibility to have an informal teleconference with the EMA scientific officer and relevant experts (see fig 1). The applicant may be asked to provide additional information/data after this interaction.

Day -30

Appointment of the rapporteurs and the qualification team

A specifically tailored qualification team reflecting the expertise needed will be appointed to each individual qualification request in order to perform, on behalf of the CHMP, the scientific and technical preparatory work.

For each request entering the qualification process the CHMP together with the SAWP will discuss the essential scientific and technical competences required and appoint two rapporteurs either from the CHMP or the SAWP who will be in charge of the procedure and a qualification team of experts based upon a proposal elaborated by the EMA scientific advice office in conjunction with the CHMP and SAWP Chairs. Resources will be derived from the CHMP, SAWP, related EMA working parties and the larger EU experts' network. This will ensure the selection of the most suitable experts as well as a close collaboration between specialists in the various technologies/methods and experts in regulatory assessment. For example, the core qualification team for a qualification process would be composed of a minimum of five members, supported by a dedicated EMA scientific officer, and will include a CHMP member, a SAWP member, and three experts identified based on:

- The technology supporting the development of the novel methodology for which the qualification process is requested (e.g., proteomics, genomics, ultrasound, MRI imaging etc.)
- The context of use of the novel methodology (e.g., non-clinical safety testing, translational research, defined therapeutic areas of relevance etc.)

The CHMP, as the owner of the process, will contribute to the discussions prior to and for the adoption of the qualification opinion.

Day -15

Preparatory meeting

Approximately 15 days before the start of the procedure a preparatory meeting between the applicant, the EMA scientific advice office will take place via teleconference. The preparatory meetings will be hosted by the scientific advice office. Members of the qualification team may join as appropriate, allowing for an informal scientific discussion.

The preparatory meeting may provide preliminary feedback on whether the data set submitted is likely to be sufficient for a qualification opinion or may rather serve as a basis for a CHMP qualification advice.

Day 0

Start of the procedure.

Day 15-30

Evaluation of data and discussion with the applicants

Draft report:

The data will be primarily assessed by the qualification team experts. A first background summary and list of questions enriched by comments from qualification team members and from other experts involved in the process (e.g., working party members, FDA experts etc.) will be created by the qualification team rapporteurs. Additional expertise to enrich the discussion will be considered on a case-by-case basis (e.g., statistical, modelling & simulation). The list of questions will be sent to the applicant after the SAWP meeting at day 30.

Day 60

A discussion with the applicant (also in liaison with other national authorities, e.g. FDA) will take place with the qualification team in the framework of the SAWP meeting. Additional interactions can be organised via teleconferencing to discuss additional data submission or further analyses of data to be provided in preparation of the discussion meeting.

Note: The applicant may request a clock-stop if needed at any time point during the procedure.

Day 70-90

SAWP review:

The draft report prepared by the qualification team rapporteurs in consultation with the qualification team members and enriched by the face-to-face interactions with the applicant will be reviewed in the plenary session of the SAWP. The SAWP will be in charge of discussing the qualification team report, contributing to its scientific quality and consistency and providing input on the possible need for further studies to support the qualification request.

If needed the qualification team should indicate the need for an additional meeting with the applicant.

Considering the applicant's request, the SAWP will recommend whether the procedure will be eligible for a qualification opinion or a qualification advice:

- **Qualification advice for future studies**: The report of the qualification team may recommend adopting a qualification advice on future studies to be performed in order to generate the data

required to support the proposed context of use of the method in drug development. This outcome is envisaged for those cases where sponsors wish to start to explore a potential new development method (e.g. a candidate novel methodology) and require support from the CHMP or when the data submitted for the qualification are still preliminary and not sufficiently supportive of a qualification opinion. When the new data is generated, the applicant may request a qualification opinion. Based on the review of the preliminary qualification data submitted, the EMA may propose a letter of support for the novel methodology to encourage further studies and data sharing.

- **Qualification opinion for public consultation**. The report of the qualification team may recommend the adoption of a qualification opinion on the acceptability of the innovative method concerned for a specific intended use. The CHMP will be provided with the draft qualification opinion one month in advance of the plenary session when the discussion is scheduled. The draft qualification opinion will be amended to include the comments and the discussion at the CHMP level.

Note: If the methodology is not accepted for qualification the procedure will turn into a "qualification advice on future protocols and methods for further method development towards qualification" which will not be made public.

Day 100

CHMP adoption of qualification advice and discussion of qualification opinion:

The CHMP will discuss and adopt the qualification advice for future studies (confidential document to be sent to the applicant) or discuss the qualification opinion as appropriate.

Day 130-190

Public consultation (for qualification opinion only):

Following discussion and adoption at the plenary CHMP,

- The draft qualification opinion will be forwarded to the applicant prior to publication on the website of the EMA. The applicant has the right to remove any confidential information from the report (5 working days).
- Announcement is made on the EMA website, CHMP press release and monthly report. The draft qualification opinion and assessment report, identifying the context, the intended specific use of the new development method, and the basis for its regulatory acceptance is released for **6 weeks of public consultation**, with proactive consultation of relevant learned societies in order to ensure that the views of the wider scientific community are duly reflected in the final qualification opinion.
- Depending on the outcome of the public consultation, a workshop may be organised subsequently with participation of the qualification team and the applicant prior to finalisation of the CHMP qualification opinion.

Day 190

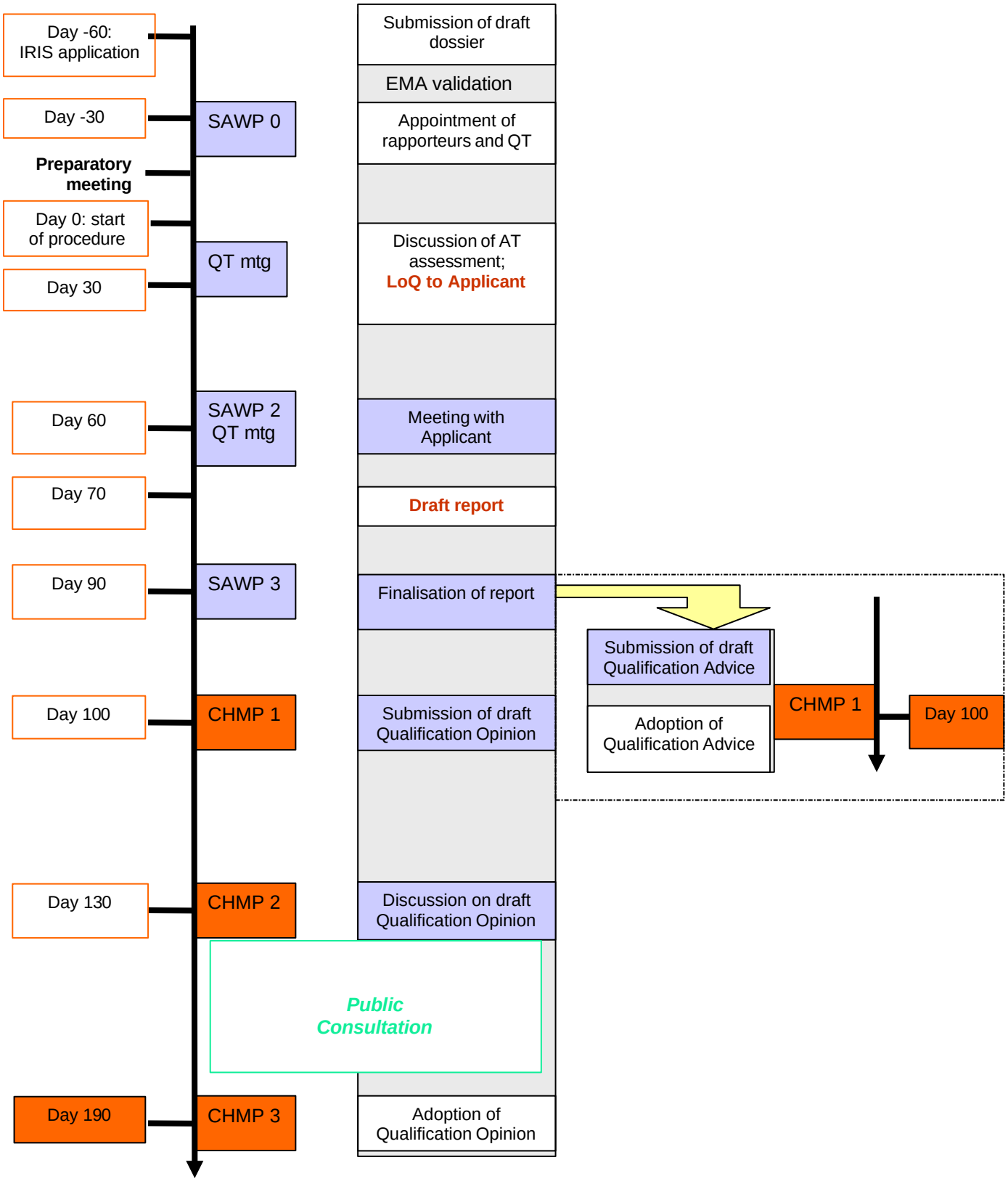
Adoption of the final CHMP qualification opinion:

The CHMP, depending on the data package submitted, the discussions, the consultation of the scientific community and the state of the art in science may conclude with a qualification opinion, whereby the CHMP considers the proposed innovative development method as an acceptable regulatory standard for the claimed use in a defined context for drug development.

Communication and training:

The final CHMP qualification opinion and the grounds for acceptance will be made publicly available on the EMA website 15 days after the final CHMP opinion. The EMA/CHMP will organise periodically training sessions/workshops on newly qualified approaches for drug development and amend relevant guidelines as appropriate.

Figure 1: Procedure for the qualification of novel methodologies and/or scientific advice on future protocols and methods for further method development towards qualification



Attachments:

- Draft proposed format for the applicants request for CHMP qualification opinion/ CHMP qualification advice for novel methodologies in the non-clinical setting.
- Draft proposed format for the applicants request for CHMP qualification opinion/ CHMP qualification advice for novel methodologies in clinical drug development.

Draft proposed format for the applicants request for CHMP qualification opinion / CHMP qualification advice for novel methodologies in the non-clinical setting

This document is a high-level proposal on context, structure, and format of regulatory submission dossiers for CHMP qualification opinion or qualification advice on novel methodology(ies) intended for use in non-clinical drug development. It is not binding and sections/subheadings may be added or omitted as appropriate. The document does not address technical/methodological issues or the requirements for novel methodology qualification. The qualification request may be supported with a range of non-clinical and clinical information, such as: primary data, published articles from peer-reviewed journals, expert statements regarding the use of the novel methodology(ies) from academic bodies, medical boards that provide guidance regarding its use and the basis for such, expert summaries from regulatory bodies, or any combination of the above.

The applicant is encouraged to discuss format and content issues with the scientific advice secretariat and the assigned scientific administrator at the EMA prior to the start of the procedure. An informal teleconference or a face-to-face meeting may be organised at the request of the applicant (see guidance document).

1. Table of contents

2. Executive summary

This section should include the following areas:

- The objective(s) of your request
- The need and impact of proposed novel methodology(ies)
- Characteristics of the proposed novel methodology(ies)
- Context of Use for which a Qualification is requested
- Sources of data and major findings
- Remaining gaps and a brief overview of how these will be addressed (if applicable)
- Conclusion

3. Statement of need and impact of proposed non-clinical novel methodology(ies)

This section is expected to contain a general introduction to the novel methodology and may address the following areas:

a. The intended application of the novel methodology(ies):

This section should describe the Context of Use in which the qualification of the novel methodology(ies) is pursued.

- The intended use of the novel methodology(ies) in medicinal development and use, e.g., early signs of toxicity or efficacy, lead optimisation, candidate drug identification, first in man safety, efficacy prediction.
- How the information from measurement of this novel methodology is to be integrated in drug development and regulatory review.
- The limitations to the qualification sought, e.g., the novel methodology(ies) will be used for dose finding in first in man setting and not substitute the phase II dose selection studies etc.
- Describe the potential impact of the proposed novel methodology(ies) on current regulatory guidelines, if applicable.
- Relevance and adequacy to extrapolate the animal model/novel methodology(ies) to the clinical setting.

b. The disease/condition/experimental setting that is associated with the novel methodology(ies):

- Summarize the signs and symptoms, pathophysiology, risk factors and epidemiology, diagnosis, established therapy, and prognosis of the condition. Focus on factors that contribute to improved medicinal development or treatment outcome e.g. early diagnosis, risk prediction, detection of drug related adverse effects, determination of therapeutic response and optimization of therapy.

c. Currently available tools:

- Describe the utility and limitations of currently available non-clinical methods/parameters that are used for the intended application(s) of the proposed novel methodology(ies) and the added benefit of the proposed novel methodology(ies).
- Describe and justify the reference standard for the intended application of the exploratory novel methodology. The reference standard should optimally provide a true value of the variable being assessed by the exploratory novel methodology in the relevant setting, and thereby validate the exploratory novel methodology and define its diagnostic/predictive performance.

d. Characteristics of the proposed novel methodology(ies):

- Elaborate on the scientific rationale for the proposed novel methodology(ies), i.e. biological, pharmacological and (patho)physiological background.
- Briefly summarise the technical aspects of the proposed biomaker(s) (a detailed description should be included in section 4. Methodology and Results), including: technology platform, analytical validation and biological qualification.

4. Methodology and results

This section is intended to provide a detailed overview and critical analysis/interpretation of the novel methodology(ies) development programme (including relevant clinical data if applicable). Detailed protocols/reports of individual studies, meta-analysis and/or analysis combining data from multiple studies should be provided in the appendices. The data set (raw data) should be provided on request and submitted electronically in a format agreed with the agency during the review. The overview may include:

a. Methods

- Experimental approach: design of the studies, selection of the animal models, definition of the reference standards and positive and negative controls.
- Briefly describe the analytical/technological platform(s) used for novel methodology(ies) quantification. More information should be made available in the appendices.
- Statistical plan for analytical/technological assay validation and biological qualification.

b. Results

- Brief summary of design and results of individual studies (in tabular and/or synopsis format).
- Analytical/technological assay validation [i.e. repeatability (intra-run precision), intermediate precision (intra-lab precision), reproducibility (inter-lab precision)].
- Biological qualification: intra and inter-animal variability, difference between species or strains, descriptive statistics or/and ROC curves or/and any other statistical methodology towards qualification.

c. Describe remaining gaps and how these will be addressed. Include detailed protocol(s) of planned studies in the appendices (if applicable).

d. Evidence from published literature. It is recommended to perform a systematic review following a predetermined search protocol and analysis plan. Consider issues such as search strategy, selection of studies, data collection, data analysis, presentation of results including the use of meta-analysis, and evaluation of consistency and robustness of the analysis.

5. Conclusions

Summarize the key findings from all your evidence sources and how they fulfil the objectives of the novel methodology qualification request. If applicable, describe the limitations of currently available data (gap analysis) and discuss/justify how the proposed development plan will support a qualification.

6. References and appendices

Provide the protocols and reports of individual studies, meta-analyses, and systematic literature reviews performed. Provide PDF files of cited published articles, and any other applicable supportive documentation. If requested please submit the data set (raw data) for the analysis.

Draft proposed format of the applicants request for CHMP qualification opinion / CHMP qualification advice for novel methodologies in clinical drug development

This document is a high-level proposal on context, structure, and format of regulatory submission dossiers for CHMP qualification opinion or qualification advice on novel methodology(ies) intended for use in clinical drug development. It is not binding and sections/subheadings may be added or omitted as appropriate. The document does not address technical/methodological issues or the requirements for novel methodology qualification. The qualification request may be supported with a range of nonclinical and clinical information, such as: primary data, published articles from peer-reviewed journals, expert statements regarding the use of the novel methodology(ies) from academic bodies, medical boards that provide guidance regarding its use and the basis for such, expert summaries from regulatory bodies, or any combination of the above.

The applicant is encouraged to discuss format and content issues with the scientific advice secretariat and the assigned scientific administrator at the EMA prior to the start of the procedure. An informal teleconference or a face to face meeting may be organised (see guidance document).

1. Table of contents

2. Executive summary

This section may include the following areas:

- The objective(s) of the request
- The need for and impact of the proposed novel methodology(ies) in clinical drug development

- Characteristics of the proposed novel methodology(ies)
- Context of Use for which a Qualification is requested
- Sources of data and major findings
- Remaining gaps and a brief overview of how these will be addressed (if applicable)
- Conclusion

3. Statement of the need for and impact of the proposed novel methodologies in clinical drug development

This section is expected to contain a general introduction to the novel methodology and may address the following areas:

a. The intended application(s) of the proposed novel methodology(ies) in clinical drug development.

This section should describe the Context of Use in which the qualification of the novel methodology(ies) is pursued:

- The intended use of the novel methodology in clinical trials of drug efficacy and safety, e.g.,
  - diagnose patients with the disease/condition for inclusion into clinical trials
  - predict outcome (risk assessment) for patient selection or subgroup analysis/stratification
  - selection of therapy
  - determine therapeutic response
  - surrogate for clinical endpoint
  - determine mechanism of effect (therapeutic effect/drug toxicity)
  - dose selection/optimization
  - detect drug related adverse effects
    - early indicator/predictor of toxicity/adverse reactions
    - management of toxicity/adverse reactions
- How the information from measurement of this novel methodology is to be integrated in drug development and regulatory review.
- The limitations to the qualification sought, e.g., that the application is not intended to assess the outcome of therapy, not intended to assess impact of interventions on cost etc.
- Describe potential impact of the proposed novel methodology(ies) on current regulatory guidelines, if applicable.

b. The disease/condition/experimental setting in which the novel methodology(ies) will be applied:

- Summarize the signs and symptoms, pathophysiology, risk factors and epidemiology, diagnosis, established therapy, and prognosis of the disease/condition in relevant populations where the novel methodology(ies) will be used. Focus on factors that contribute to improved treatment outcome e.g. early diagnosis, risk prediction, detection of drug related adverse effects, determination of therapeutic response and optimization of therapy.

c. Currently available tools in patient care and clinical drug development:

- Describe the utility and limitations of currently available clinical and laboratory tools that are used for the intended application of the exploratory novel methodology(ies) in patient care (clinical practice) and in clinical drug development.
- Describe and justify the reference standard for the intended application of the exploratory novel methodology in clinical trials. The reference standard should optimally provide a true value of the variable being assessed by the exploratory novel methodology in the relevant clinical setting, and thereby validate the exploratory novel methodology and define its diagnostic performance.

d. Characteristics of the proposed novel methodology:

- Elaborate on the scientific rationale for the proposed novel methodology(ies) (i.e. biological, pharmacological and (patho)physiological background).
- Briefly summarise the technical aspects of the proposed biomaker(ies) (a detailed description should be included in section 4. Methodology and Results), including: technology platform, analytical validation, and clinical validation/utility.

4. Methodology and results

This section is intended to provide a detailed overview and critical analysis/interpretation of the novel methodology development programme (including relevant non-clinical data). Detailed protocols/reports of individual studies, meta-analysis and/or analysis combining data from multiple studies should be provided in the appendices. The data set (raw data) should be provided on request and submitted electronically in a format agreed with the agency during the review. The overview may include:

a. Methods

- Include a description of the overall approach to the novel methodology development programme, including critical study design, methodology decisions, patient selection, endpoints, statistical analyses, and justification of chosen reference standard.
- Description and characterization of the technology platform, including availability of testing kits or apparatus in patient care and clinical trial settings.

b. Results

- Brief summary of design and results of individual studies (in tabular and/or synopsis format)
- Analytical/technological validation addressing parameters such as accuracy, precision, selectivity, sensitivity, reproducibility, and stability. Discuss sample requirements, cut-off values, controls and calibrators and assay conditions.
- Comparison and analysis/interpretation of results across studies with focus on the clinical validation and utility:
  - Clinical sensitivity and specificity, ROC curve, PPV, NPV etc.
  - Justify chosen diagnostic cut-off(s) and describe how and when (prospectively, retrospectively etc.) they were selected in relation to pivotal studies.
  - Patient populations (prevalence of the condition being tested for, enrichment) and endpoints.
  - Potential impact of various intrinsic and extrinsic factors on expected test performance, e.g. gender, age, ethnicity, smoking habits, clinical practice etc.
  - If applicable describe and discuss test performance when the novel methodology is used in prophylaxis studies vs. treatment studies, and in populations with proven, probable or possible disease/condition.
  - Whether the proposed novel methodology(ies) have been evaluated in relevant patient populations (reflecting those likely to be enrolled in clinical trials where the novel methodology will be used).

c. Describe remaining gaps and how these will be addressed. Include detailed protocol(s) of planned studies in the appendices (if applicable).

d. Evidence from published literature. It is recommended to perform a systematic review following a predetermined search protocol and analysis plan (such as the scientifically sound search strategies published by The Cochrane Collaboration (www.cochrane.org). Consider issues such as search strategy, selection of studies, data collection, data analysis, presentation of results including the use of meta-analysis, and evaluation of consistency and robustness of the analysis.

5. Conclusions

Summarize key findings from all evidence sources and how they fulfil the objectives of the novel methodology qualification request. If applicable, describe the limitations of currently available data (gap analysis) and discuss/justify how the proposed development plan will support a qualification.

6. References and appendices

Provide the protocols and reports of individual studies, meta-analyses, and systematic literature reviews performed. Provide PDF files of cited published articles, and any other applicable supportive documentation. If requested, please submit the dataset (raw data) for the analysis.

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[i] At the time of submission of the Qualification request the following documents have to be provided:

- Questions and applicant's position (word format)
- Detailed table of contents
- Background information e.g.:
    - Product profile
    - Investigators' brochure
    - Relevant study protocols or draft study protocols or study outlines
    - Bibliographical data (references)
    - Content or previous requests received
    - Relevant guidelines (other than CHMP guidance documents)
    - Contract agreement if the request is submitted by a consultant/CRO on behalf of the company

[ii] Please note that EMA fees are payable net of all bank charges, withholding taxes and any other deduction imposed on the customer by legislation of the country of residence.
Only the applicant will be invoiced, but the invoice can be sent to a different address. If a consultant is dealing with the Qualification request on behalf of the applicant, nevertheless the payment will be claimed to the applicant.
If purchase order is not yet available at this stage, it will have to be provided at the time of submission of the Scientific advice request.

[iii] If the applicant has an **SME status**, at the time of submission please provide the fee waiver confirmation document from the EMA SME office. **Failure to do so will incur a validation of the request without SME fee reduction and an invoice of the full amount will be sent by our account department.**