Raising Awareness of Regulatory Requirements

A guidance tool for researchers

Document prepared by EFPIA and IMI

version 1

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Contents

Introduction

Objectives of this guidance tool

Multiple new research projects are expected to generate results - such as new surrogate endpoints or biomarkers, patient reporting tools, new definition of population etc, - **that may influence regulatory decision making.**

It is therefore important to consider the potential regulatory impact of these projects at an early stage, to enable planned outputs likely to require future regulatory approval to be proactively built into the research plan.

This succinct guidance tool has been developed **to raise awareness** of the existing regulatory support measures currently available in the EU and the USA and **is intended for use by researchers who wish to have a better understanding of these opportunities.**

For IMI projects

The Call topic should indicate any potential intended impact on the regulatory practice, including potential enablers to Medicines Adaptive Pathways to Patients (MAPPs).

Unless the project has no regulatory relevance, early dialogue with regulators is encouraged. **The consortium would need to have in the workplan of their action, a strategy for seeking regulatory qualification/acceptance of project outputs where applicable.** Aspects to consider include:

- A plan for dialogue with regulatory agencies (and health technology assessment bodies if relevant) with milestones to achieve the uptake of the outputs.
- Resources allocated (e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion).

Expected outcomes & benefits of using this guidance

Clarification regarding the opportunities available for dialogue with regulators, when desired, with the aim to maximise potential impact of science generated by new research projects on the regulatory requirements.

Stimulate early dialogue with regulators to discuss best strategy/timing for qualification and/or integration of project outputs into regulatory practices.

Expected benefits:

- **Scientific and regulatory input** into the new science to be developed
- **Maximise the value of the new research outputs** (increased certainty & predictability)
- **Accepted new standards for the scientific & regulatory community** and thus translation into practical applications in drug development
- **Ultimately leads to more efficiency in the R&D** of innovative medicines for the benefit of patients
- **Opportunity for mutual learning regarding emerging science/technologies**

NOTE

The information in this guidance has been compiled to raise awareness of the various opportunities to interact with regulators in the framework of research on regulatory sciences with a potential impact on public health.
This high-level overview is intended to familiarise researchers with existing services offered by regulators. This guidance is published with the expectation that it will be updated as necessary.
It does not replace official procedures and requirements to validate or obtain formal advice from the relevant regulatory agencies.
Further information can be found on the European Medicines Agency (EMA) and Food and Drug Administration (FDA) respective websites and by contacting these agencies directly.

Questions on this guidance?

Contact the IMI Programme Office: infodesk@imi.europa.eu – the IMI scientific officer in charge of your project, the IMI regulatory contact point (nathalie.seigneuret@imi.europa.eu)

Contact the EFPIA Office. science-policy@efpia.eu

1 Guidance tool

1.1 TIPS on how to get started

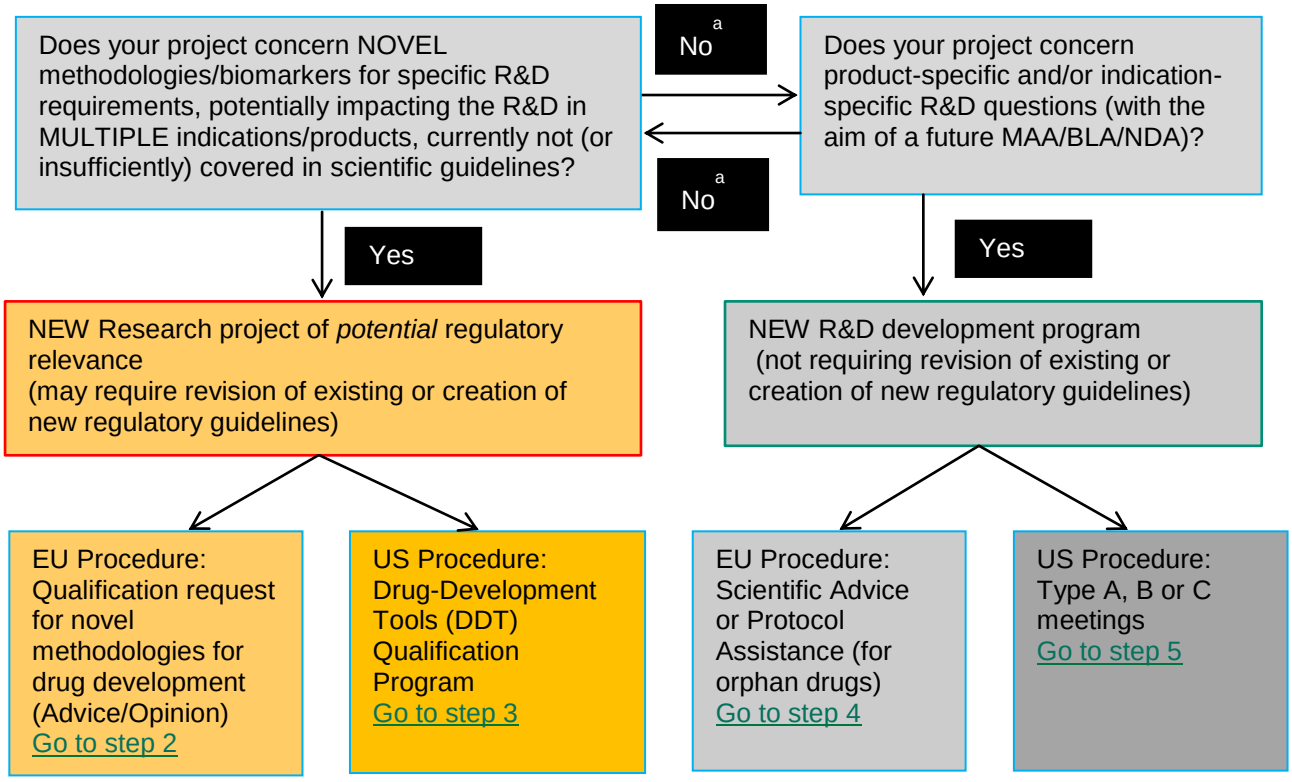
- Consider the potential regulatory relevance of the expected research output (Step 1) and define clear project objective(s).
- Consider whether (early) dialogue with regulators could inform the development of the project outputs and/or potentially speed up the regulatory acceptance process and help to define the development strategy accordingly.
- Choose the most applicable regulatory procedure to be followed as well as timing and identify the right entry channel for engaging in dialogue.
- Do not hesitate to get in contact with EMA and FDA.
- Use the hyperlinks to navigate in the various sections of the document.

1.2 Overview of regulatory support and dialogue opportunities

Step	Action
1	Based on the purpose of the research project and its potential regulatory relevance, researcher may consider availing themselves of the available interaction opportunities with EMA or FDA.
2	For early informal guidance on scientific, technical and regulatory issues arising from emerging therapies and technologies or borderline products (i.e . whether they could be considered as medicinal products), contact EMA's Innovation Task Force (itfsecretariat@ema.europa.eu).
3	For scientific questions on product independent innovative drug development methods and tools in EU, follow the EMA process for advice relative to a future 'Qualification request for novel methodologies for drug development'.
4	For scientific questions on product independent innovative drug development tools in US, follow the guidance provided under FDA's 'Drug-Development Tools (DDT) Qualification Program'.
5	For questions specifically on a product (class), and/or indication, and/or pharmaceutical or manufacturing issues within an R&D program, and expected to lead to a MAA in EU, follow the EMA process on 'Scientific Advice' or 'Protocol Assistance' (orphan drugs for rare diseases).
6	For questions specifically on a product and/or indication, within an R&D program, and expected to lead to an NDA/BLA in US, follow the FDA process on Pre-submission meetings (Type A, B or C, as applicable).
NOTE	All interaction opportunities mentioned above may be linked to procedural timetables and some may require the payment of fees. Further details are provided in the next sections of the document.

1.3 Steps

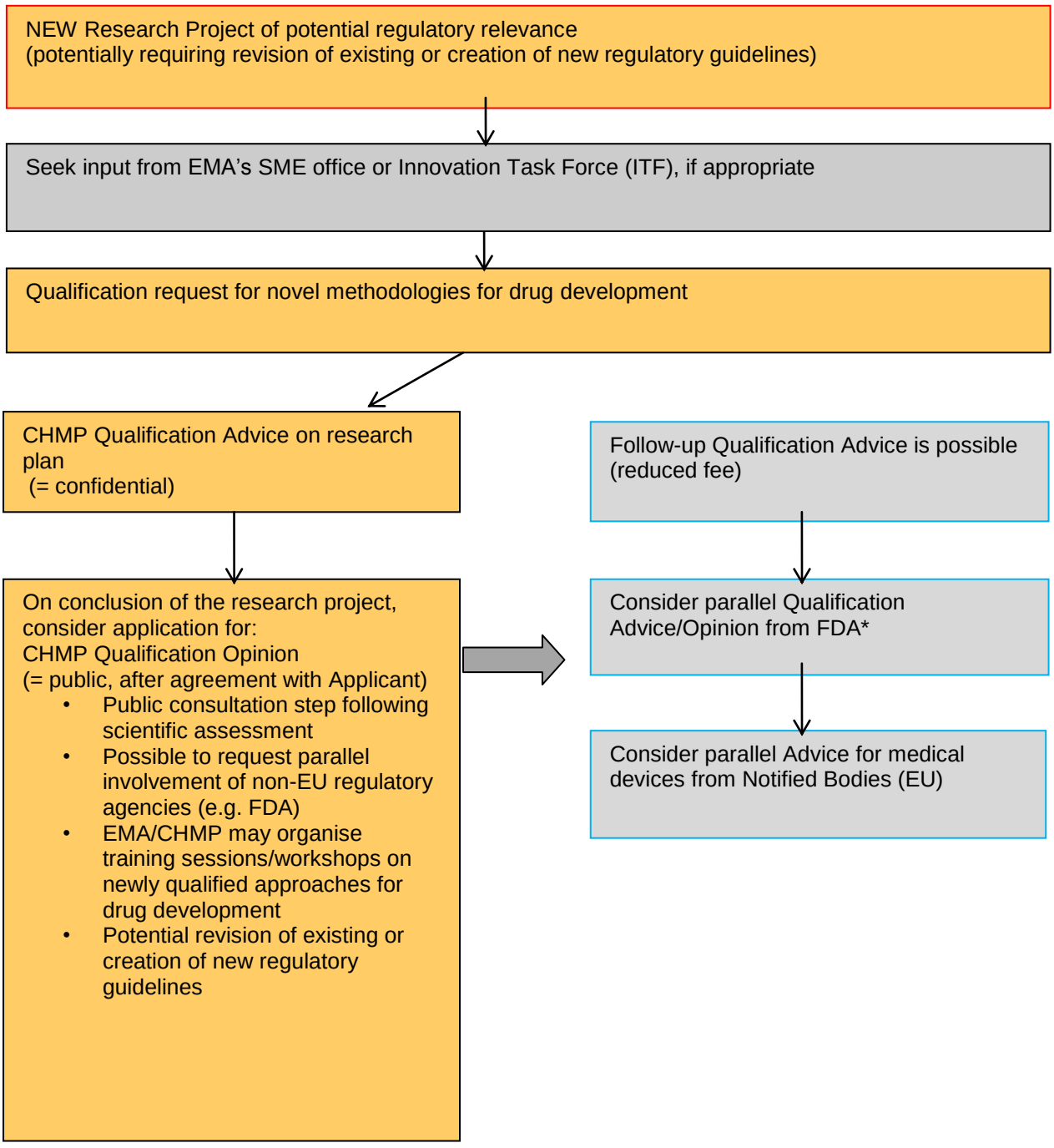
Step 1: Define the purpose of the project and consider its potential regulatory relevance at an early stage



[a] STOP in case the answer to both questions is NO; consider reaching out to EMA/FDA for clarification in case of scientific questions on your research project

Annex 1: Additional Guidance on step 1

Step 2: EU - Qualification request for novel methodologies for drug development



Annex 2: Additional Guidance on step 2

Step 3: US FDA – Drug development tools (DDT) Qualification Program

3 pathways currently exist for DDT Qualification:

- Clinical Outcome assessments

e.g. Patient Reported Outcomes (PRO), Clinician Reported Outcomes (ClinRO), Observer Reported Outcomes (ObsRO), Performance Outcomes (PerfO)

- Biomarkers

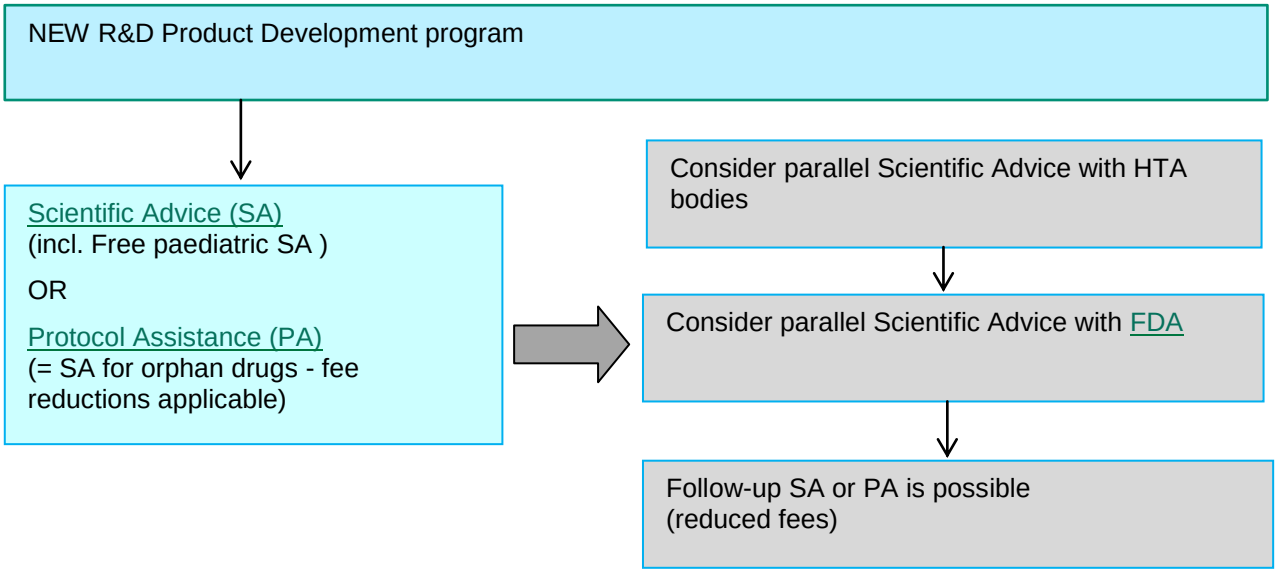
e.g. diagnostic biomarkers, prognostic biomarkers, predictive biomarkers, response biomarkers

- Animal models (Animal Rule)

e.g. Qualification of product-independent animal models under the Animal Rule (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284078.htm)

Annex 3: Additional Guidance on step 3

Step 4: EU - Scientific advice and Protocol Assistance



scientificadvice@ema.europa.eu

Annex 4: Additional Guidance on step 4

Step 5: US FDA processes - Type A, B or C meetings

For NEW drug development programs, aiming to result in a marketing authorisation, early contact with the FDA is possible through Type A, B or C meetings (dependent on the scope):

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm153222.pdf

Annex 5: Additional Guidance on step 5

2 Overview of interaction opportunities with regulators / EMA on NEW research projects

	Innovation Task Force (ITF)	Qualification procedure	Scientific advice	Protocol assistance
Scope	Development of emerging therapies and technologies, particularly by SMEs	Novel methodology for specific R&D requirements – may concern several indications or products	Specific to a product (class), and/or indication, and/or pharmaceutical/ manufacturing issue within an R&D program	Product- and indication – specific (rare diseases, EMA designated orphan medicines)
Objective	Receive informal advice and guidance	Receive Advice/Opinion on innovative drug development methods & tools for a specific intended use in the context of R&D in pharmaceuticals, when of regulatory relevance	Receive Advice on the appropriateness of test & studies in development of a medicine (i.e. quality, safety, efficacy questions) – with the aim of marketing authorisation application	Special form of scientific advice, for orphan medicines for rare diseases - with the aim of future marketing authorisation application
Assessment team	N/A ITF briefing meetings are informal and engage a multidisciplinary team of EMA and EU network experts	SAWP/CHMP Qualification Team: QT coordinator, dedicated group of multidisciplinary experts (min 4), incl. expert on 'context of intended use', technical platform, stats), Scientific Officer (EMA)	SAWP/CHMP: Scientific Coordinator, large group of multidisciplinary experts (min 28), Scientific Officer (EMA)	SAWP/CHMP: Scientific Coordinator, large group of multidisciplinary experts (min 28), including COMP members (focus on significant benefit), Scientific Officer (EMA)
Applicants	Any organisation developing innovative medicines or technology, but in particular micro, small and medium-sized enterprises (SMEs)	Consortia, networks, public/private partnerships, learned societies and pharmaceutical industry	Any organisation developing a medicinal product (Pharmaceutical company, academic group, SME, non-EEA SME client company)	Any organisation developing a medicinal product (Pharmaceutical company, academic group, SME, non-EEA SME client company)

	Qualification procedure	Scientific advice & Protocol assistance
Procedural timelines	Flexible timelines and procedures	Fixed timelines (40 or 70 days)
Type of interactions	Face-to-face meetings; applicant can raise issues for discussing during the procedure	Face-to-face meeting if requested by SAWP (generally in case of disagreement with the proposal)
Outcome of the procedure	SAWP QT assesses the data Advice (non-binding)/ Opinion (binding)	SAWP 'looks' into the data but focuses on the methodology; Advice (non-binding)
Confidentiality	Advice: Confidential (positive) Opinion: Public (after agreement with the applicant)	Always confidential until drug is approved (then included in EPAR)
Best strategic timing	Early stage (validation study design): Advice Later stage (results): Opinion	Start at Early stage, consider follow-ups throughout the lifecycle of the product
Is parallel advice with FDA possible?	Yes	Yes
Is parallel advice with HTA bodies/Notified Bodies possible?	Currently not possible but the possibility may exist in the future	Yes
Contact for general questions to EMA	http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/q_and_a/q_and_a_detail_000079.jsp&mid=WC0b01ac05800294a8	

3 Other considerations

Global development:

Whereas the focus of this guidance is on the EU/US regulatory framework, other regulations may need to be taken into account when developing novel methodologies/new development projects with a global scope.

Where relevant, appropriate regulations from these other regions are to be consulted as well as cross-regional guidelines (e.g. ICH, covering EU, US and Japan).

Reimbursement:

Pricing & reimbursement procedures are handled on a national and/or regional level. It is advised to contact the Health Technology Agencies (HTAs) and /or Notified Bodies (NBs) in EU, or equivalent institutions in other regions, early in the development process, when the future marketing of novel drugs, novel methodologies and/or accompanying medical devices is being considered.
Depending on the region, joint meetings between regulatory agencies and HTAs/NBs may be possible.

The separate HTA/NB processes are **not** covered in the current document.

Annexes: Additional guidance

Annex 1 - Additional guidance on step 1: Define the purpose of the project and consider its potential regulatory relevance

Examples of new research with potential regulatory impact

- New manufacturing controls & processes, new analytical methods
- New biomarkers (e.g diagnostic, prognostic, predictive, response), new drug targets
- New non-clinical models (e.g *in vitro*, animal models, *in silico*)
- New *in-vitro* & *in-vivo* models of drug-induced toxicities
- New PK/PD models (or PB/PK/TK/PD models)
- New modelling & simulation tools
- New clinical tools & methodologies (e.g. imaging, diagnostic assays)
- New approaches for clinical trials – innovative design, analysis & process (e.g. autism, schizophrenia)
- New disease definitions (e.g. severe asthma)
- New clinical endpoints
- New clinical outcome assessments (e.g. patient- reported outcomes)

Examples of new science that may influence regulatory guidance

- The CHMP Qualification opinions can be found on EMA website: http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

  Example of such opinions:

  - EMA Qualification Opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's Disease
  - EMA Qualification Opinion on low hyppocampal volume (atrophy) by MRI for use in clinical trials for regulatory purpose - in pre-dementia stage of Alzheimer's disease
  - EMA Qualification Opinion on MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

- FDA Qualified Biomarkers (e.g Clinical biomarkers: Plasma fibrinogen as a prognostic enrichment biomarker for patient selection in COPD, Galactomannan as a clinical biomarker to classify patients having invasive aspergillosis; Preclinical biomarkers:seven BMs of drug-induced nephrotoxicity in rats, Non-clinical qualification of urine BMs of nephrotoxicity, Non-clinical qualification of circulating cardiac troponins T and I as BMs of cardiac morphologic damage): http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

How to consider if new research projects are of potential regulatory relevance?

New research projects are considered to be of potential regulatory relevance:

- When the research project has a broad scope, potentially covering multiple indications and/or products

- When the intended use of the science will change the way medicines are developped and used as well as add benefit compared to current standards
- When the science is NEW and could result in new (or revised) scientific guidelines to facilitate innovative drug development
- When the research topic is not, or is insufficiently covered by the available scientific guidelines (EMA, FDA, ICH – see further)
- When the science and the approach address an unmet public health need

Consider whether (early) dialogue with regulators could improve the project outputs or potentially speed up the regulatory acceptance process and help to define the development strategy accordingly.

Choose the most applicable regulatory procedure to be followed as well as timing and identify the right entry channel for engaging in dialogue (e.g. seek early advice and/or full qualification of the innovative drug development method and tool from EMA and/or FDA. In the EU, get help from the SME office or ITF, when assistance is needed, as applicable).

Additional information: Scientific guidelines

EU scientific guidelines

The EMA's CHMP prepares scientific guidelines in consultation with regulatory authorities in the EU Member States, to help applicants prepare marketing authorisation applications for human medicines.

Guidelines provide a basis for practical harmonisation of how the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy specified in the Community directives.

Scientific guidelines exist in different areas: Quality, Biologicals, Non-Clinical (incl. Pharmacology), Clinical efficacy and safety, Multidisciplinary (incl. cell therapy, vaccines, nanomedicines) and Statistics.

EMA: All scientific guidelines:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb

EMA Special topics: methodologies & statistics:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000353.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac05800baedd

Other scientific guidelines to consider

FDA: all FDA guidance: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm

ICH: all ICH guidelines: http://www.ich.org/

- Efficacy guidelines: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
- Safety guidelines: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html
- ICH – process of harmonisation (new topics or existing guidance): http://www.ich.org/about/process-of-harmonisation.html

Back to step 1

Annex 2 - Additional guidance on step 2: EU Qualification request for novel methodologies for drug development

SME office

The European Medicines Agency (EMA) launched a micro-, small- and medium-sized enterprise (SME) office in 2005 to address the particular needs of smaller companies. It provides support in navigating the pharmaceutical regulatory landscape:

- Regulatory, administrative and procedural assistance
- SME User guide
- Newsletter and Workshops

Fee incentives for SMEs:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000059.jsp&mid=WC0b01ac05800240cc

Contact: sme@ema.europa.eu, Tel: +44 (0)20 3660 8787, Fax + 44 (0)20 3660 5550.

Innovative Task Force (ITF)

The Innovation Task Force (ITF) is a multidisciplinary group that includes scientific, regulatory and legal competences, set up to ensure Agency-wide coordination in the areas of interest and to provide a forum for early dialogue with applicants.

The ITF briefing meetings provide guidance on regulatory, technical and scientific issues arising from innovative medicines development, new technologies and borderline products. The scientific discussions are led by experts from the Agency scientific network, working parties and committees. The meetings are free of charge and are intended to facilitate the informal exchange of information and the provision of guidance early in the development process.

Areas of ITF engagement have included nanomedicines, pharmacogenomics, synthetic biology, biomaterials, modelling and simulation and m-Health.

Contact: itfsecretariat@ema.europa.eu

Links: General ITF site:
http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9

and **Organisation of ITF meetings**
http://www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC500002943.pdf

EMA Qualification of novel methodologies for drug development

The EMA offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development of pharmaceuticals.

Scope: novel methodology, novel imaging methods, novel biomarkers, new statistics (e.g. quantitative model-based tools for drug development). The EMA qualification process is a 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, use of a biomarker…) in *a research and development (R&D) context* (non-clinical or clinical studies), based on the assessment of submitted data; public
- **CHMP Qualification Advice** on future protocols and methods for further method development *towards qualification (Opinion)*, based on the evaluation of the scientific rationale and on preliminary data submitted; confidential

- It is not mandatory at the time of start of the procedure to decide on the procedural route to be followed. 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.

Aim: SAWP/CHMP early involvement in design of strategy, with commitment to evaluate data from agreed studies and to provide an Opinion.

Comparison between EU process on 'Qualification method for novel technologies' and US process on 'DDT Qualification'. See table under Annex 3.

Link:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

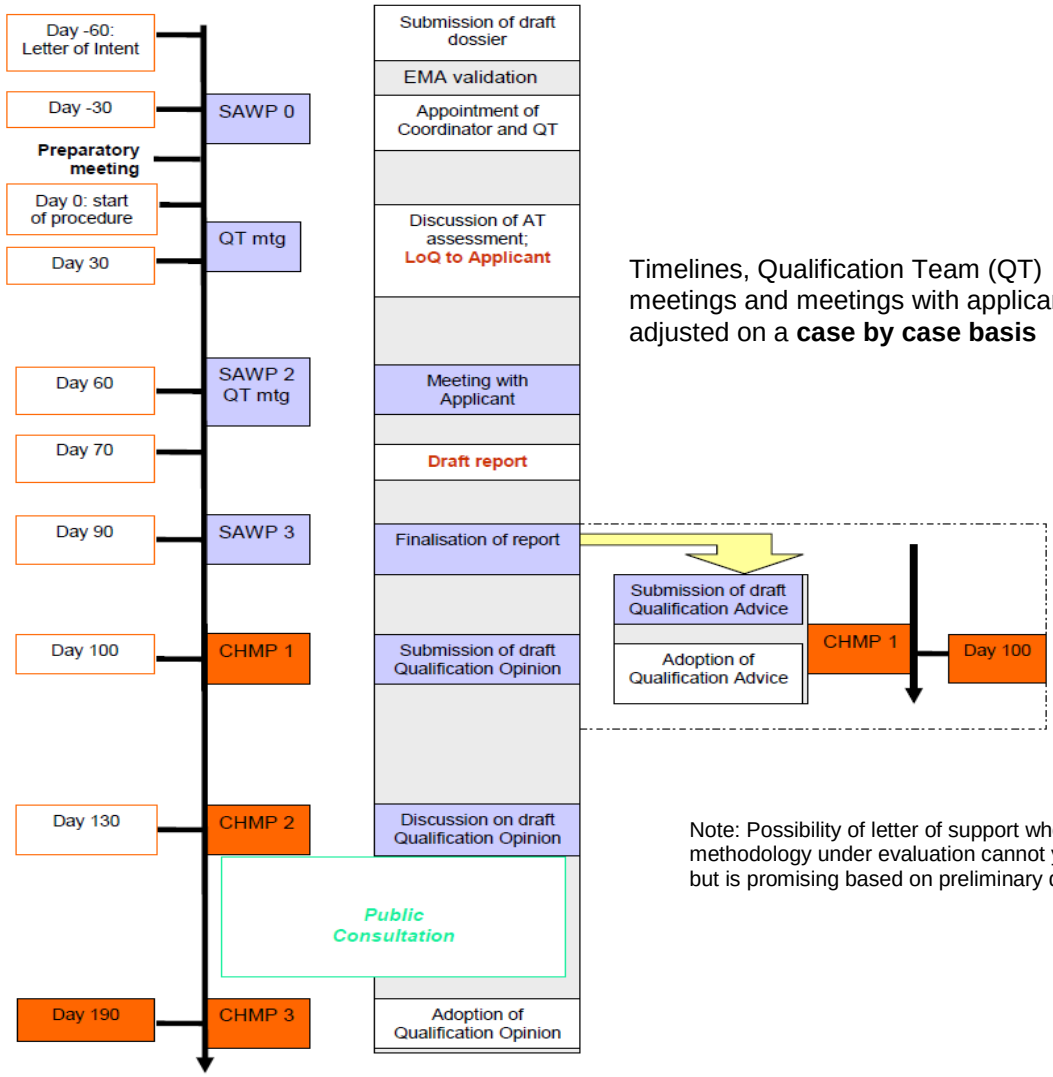
Guidance for applicants:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

NOTE: As per the data requirements, analytical/technological validation and clinical validation of the novel methodology is to be submitted for assessment.

Fees: as for Scientific Advice.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000327.jsp

Contact: qualification@ema.europa.eu

Procedural timelines



Timelines, Qualification Team (QT) meetings and meetings with applicant adjusted on a **case by case basis**

Note: Possibility of letter of support when the novel methodology under evaluation cannot yet be qualified but is promising based on preliminary data

- Day -60: Intention to submit [letter + draft dossier]
- Day -30: Appointment of the Coordinator and the Qualification team
- Day -15: Preparatory meeting
- Day 0: Start of the procedure.
- Day 15-30: Evaluation of data
- Day 30: The list of questions is sent to the applicant
- 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.
- Day 70-90: SAWP review of draft Qualification team report and recommendation for Qualification Advice or Qualification Opinion
- Day 100: CHMP adoption of Qualification Advice or discussion of Qualification Opinion, as appropriate

If Qualification Opinion:

- Day 130-190: Public consultation (for Qualification Opinion only)
- Day 190: CHMP adoption of Qualification Opinion

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.

EMA/FDA Parallel Qualification advice

To facilitate parallel submissions of applications for drug biomarker qualification or clinical outcome assessment to EMA and FDA, the two agencies launched a joint letter of intent (LOI) in December 2014.

The joint LOI allows the two agencies to share scientific perspectives and advice. The agencies are also able to provide the same response to submitters.

With the joint LOI, the agencies intend to reduce the time taken by applicants to prepare LOIs. However, applicants do not have to submit jointly to EMA and the FDA - they can send EMA or FDA-specific LOIs separately if they wish. Some sections of the LOI are specific for EMA or the FDA. See the template for details.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0#section11

Letters of Support

Based on qualification advice, the Agency may propose a letter of support as an option, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data.
Letters of support aim to encourage data-sharing and to facilitate studies aimed at eventual qualification for the novel methodology under evaluation.

These letters include a high-level summary of the novel methodology, context of use, available data, and on-going and future investigations. If the sponsors agree, the Agency publishes letters of support on this page:
http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0

Medical devices and In-vitro Diagnostics (including companion diagnostics)

The regulatory framework for medical devices is currently described in three main Directives:

- Council Directive 90/385/EEC on active implantable medical devices (AIMDD),
- Council Directive 93/42/EEC on medical devices (MDD), and
- Directive 98/79/EC of the European Parliament and of the Council on *in vitro* diagnostic medical devices (IVDD).

The medical device directives are currently under revision: http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision/index_en.htm

- Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices (26.09.2012):

  http://ec.europa.eu/growth/sectors/medical devices_old/documents/revision/files/revision_docs/proposal_2012_542_en.pdf
- Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on *in vitro* diagnostic medical devices (26.09.2012):

  http://ec.europa.eu/growth/sectors/medical-devices_old/documents/revision/files/revision_docs/proposal_2012_541_en.pdf

Back to step 2

Annex 3 - Additional Guidance on step 3: US FDA – Drug development tools (DDT) Qualification Program

- DDT Qualification Program created by CDER (Center for Drug Evaluation & Research)
- Part of the FDA's Critical Path Initiative
- Framework for development and regulatory acceptance for use in drug development programs
- CDER guides submitters and rigorously evaluates the submission: for use in the regulatory process in a specific context of use
- Qualified DDT: drug developers can use in qualified context (e.g. IND, NDA, BLA) without re-review for suitability of the DDT use.

Regulatory definitions

DDTs are methods, materials, or measures that aid drug development.

DDT Qualification is a conclusion that within the stated context of use, the results of assessment with a DDT can be relied upon to have specific interpretation and application in drug development and regulatory review.

Context of use describes the way the DDT is to be used and the purpose of the use. A complete context of use should describe fully the circumstances under which the DDT is qualified and the boundaries within which the available data adequately support use of the DDT.

Letter of support is issued to a submitter that briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation. This letter does not connote qualification of a biomarker. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate development of promising biomarkers (for further information see:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm412833.htm)
http://www.fda.gov/drugs/developmentapprovalprocess/ucm434382.htm

Mission and Objectives

- Qualify and make DDTs publicly available:
  - Specific context of use
  - Facilitate drug development
  - Facilitate review of regulatory applications
- Provide a framework for scientific collaboration: facilitate DDT development
- Integrate qualified DDTs in regulatory review
- Development of DDTs for unmet needs contexts of use
- Formation of collaborative groups to undertake DDT programs:
  - Increase the efficiency
  - Lessen individual resource burden
  - Innovation in drug development

Pathways for DDT Qualification

3 pathways for DDT Qualification:

- Clinical Outcome assessments

  e.g. Patient Reported Outcomes (PRO), Clinician Reported Outcomes (ClinRO), Observer Reported Outcomes (ObsRO), Performance Outcomes (PerfO)

- Biomarkers

  e.g. diagnostic biomarkers, prognostic biomarkers, predictive biomarkers, response biomarkers

- Animal models (Animal Rule)

  e.g. Qualification of product-independent animal models under the Animal Rule

US-DDT: Contacts

For further information please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

- **Contact FDA (general):** http://www.fda.gov/aboutfda/contactfda/default.htm
- **Clinical Outcome Assessment Qualification Program Study Endpoints and Labeling Development (SEALD)—Study Endpoints Team**
  Email: SEALD.ENDPOINTS@fda.hhs.gov
  Phone: (001)-301-796-0900
- **Biomarker Qualification Program**
  Marianne Noone
  Email: marianne.noone@fda.hhs.gov
  Phone: (001)-301- 796-7495
- **Animal Model Qualification Program**
  Email: AnimalModelQualification@fda.hhs.gov
  Phone: (001)-301-796-2210

Back to step 3

Comparison Qualification process (EU) vs DDT process (FDA)

	EMA	FDA
Procedure	3 stages of Qualification Process : • Presubmission • Consultation and advice by the secretariat • Review by the Scientific Advice Working party	3 stages of Qualification Process : • Initiation • Consultation and Advice • Review
Scope	Examples of novel methodologies for which there are formal Qualification programs: • Biomarkers • Preclinical models • Clinical Outcome Assessments • Modelling & statistical methods • Any other novel methodology, e.g. imaging Although scope is not formally restricted	Drug Development Tools for which there are formal Qualification programs: • Biomarkers • Clinical Outcome Assessments (patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes and Performance Outcomes (PerfO)) • Animal Models for use under the FDA Animal Rule
Definition of "qualification" **and "context of use"**	• **Qualification is a public opinion by EMA** about the specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context. • **Context of use:** specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context. Or in the clinical use of medicinal products.	• **Qualification is a conclusion** that within the stated CoU, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review • **Context of use** describes the way the DDT is to be used and the purpose of the use. A complete context of use should describe fully the circumstances under which the DDT is qualified and the boundaries within which the available data adequately support use of the DDT
Who can apply	**Applicant** = person, group, organisation or consortium; is responsible for the fees and initiates the process	**Submitter** = person, group, organisation (including the federal government), or consortium that takes responsibility for and initiates a DDT qualification proposal using described procedures
When to submit	As early as possible to obtain prospective advice	As early as possible to obtain prospective advice
How to submit/contact	• Initiation request to EMA: contact via email: Qualification • EMA-initiated invitation to submit a Letter of Intent: Electronic submission accompanied by paper cover letter to Central Document Room (see EMA Website for address)	• Initiation request to FDA: contact via email • FDA-initiated invitation to submit a Letter of Intent: Electronic submission accompanied by paper cover letter to Central Document Room (see FDA Website for address) • Contact information for the three Qualification Programs is available on FDA Website *

	EMA	FDA
Documentation	• **Letter of intent-** brief description of drug development tool, intended use of drug development tool (proposed context of use), and brief data overview supporting use of drug development tool in the proposed context of use **For parallel EMA/FDA advice:** joint Letter of intent template • **Initial Briefing Package-** Questions and applicant position: more comprehensive information and discussion describing existing knowledge, known knowledge gaps, and overview of plan to address the gaps. May include detailed statistical analysis plans and protocol outlines • **Full Qualification Package**- A comprehensive submission with complete and detailed description of the studies and analyses providing the evidence to justify qualification of the BM/Method for the intended context of use. Submission of primary data from studies will, in most cases, be expected • **Letter of Support** For those promising biomarkers/methods which are not yet ready for qualification, a Letter of Support may be issued to submitters who have assembled this information about promising biomarkers/methods to encourage further their development.	• **Initiation request-** cover letter with contact information and name of drug development tool **For parallel EMA/FDA advice:** joint Letter of intent template • **Letter of intent-** brief description of drug development tool, intended use of drug development tool (proposed context of use), and brief data overview supporting use of drug development tool in the proposed context of use • **Initial Briefing Package-** more comprehensive information and discussion describing existing knowledge, known knowledge gaps, and overview of plan to address the gaps. May include detailed statistical analysis plans and protocol outlines • **Subsequent Briefing Packages** to continue consultation and advice as warranted • **Full Qualification Package-** A comprehensive submission with complete and detailed description of the studies and analyses providing the evidence to justify qualification of the DDT for the intended context of use. Submission of primary data from studies will, in most cases, be expected • **Letter of Support** For those promising biomarkers which are not yet ready for qualification, a Letter of Support may be issued to submitters who have assembled this information about promising biomarkers to encourage further their development.
Output of the procedure	Qualification recommendations are issued as official EMA guidance, once an innovative development methods has been qualified for a specific intended use to support a MAA.	Qualification recommendations are issued as official FDA guidance. Once a drug development tool (DDT) has been qualified for a specific context of use in drug development, it can be used to produce analytically valid measurements that can be relied on to have a specific use and interpretable meaning. The DDT can be used by drug developers for the qualified context in IND, NDA and BLA submissions without the relevant CDER review group reconsidering and reconfirming the suitability of the DDT. Drug developers can use qualified DDTs, but are not required to do so.

	EMA	FDA
Confidential/public	• **Initiation, Consultation and Qualification Advice,** Confidential • **Qualification Opinion Recommendation:** at the latest public at MAA and after consultation with the Applicant • **Letter of Support**: Public upon applicant agreement	• **Initiation, Consultation and Advice, and Review Stages:** Confidential • **Qualification Recommendation:** Public • **Executive Summary:** Public • **Redacted Discipline-**Specific Reviews: Public • **Letter of Support:** Public
Fees	Same fee reductions as in scientific advice for paediatric (free), orphan conditions and SMEs (small and medium-sized enterprises (10%)).	None
Length of procedure	Qualification Advice: 100 days Qualification opinion: 190 (dependent upon complexity of submission)	Not defined (dependent upon complexity of submission)
Follow-up	Follow-up Qualification Advice: 100 days Qualification opinion: 190 (dependent upon complexity of submission	Following the Initial Briefing Package submission, additional briefing documents may be submitted to FDA for advice as needed until there is sufficient information available to initiate formal review. Once a qualification recommendation has been made publicly available, the qualification recommendation may be revised as new scientific evidence becomes available

Annex 4 - Additional Guidance on step 4: EU - Scientific advice and Protocol Assistance

New R&D product development programs via Scientific Advice or Protocol Assistance.

Scientific questions on specific products, indications, technology within a development program will qualify for Scientific Advice or Protocol Assistance.

It is anticipated that it is the Applicant's aim to file a **marketing authorization application (MAA)** in EU as a result of the development program, via a **Centralised Procedure*** or other procedure, as applicable (http://www.ema.europa.eu/ema/).

It is **strongly recommended** to request SA/PA in case of a new development program as this will **facilitate the acceptance** of the MAA by the regulators. This can be done at **early stages** of the development.

SA and PA - the difference:

- **Scientific Advice** (SA) is when the EMA gives advice to a company on the appropriate tests and studies in the development of a medicines. This is designated to facilitate the development and availability of high-quality, effective and acceptable safe medicines for the benefits of patients.
- **Protocol Assistance** (PA) is a special form of scientific advice for companies developing designated orphan medicines for rare diseases. A COMP coordinator provides link to COMP to address demonstration of significant benefit.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9

Requests for SA/PA: scientificadvice@ema.europa.eube

EU - Legal basis and scope of Scientific Advice (SA)

Scientific Advice (Article 57 (1.n) of Regulation (EC) No 726/2004) may be requested for all medicinal products for use in humans, (as defined in Directive 2001/83 (as amended)), irrespective of the medicinal product's eligibility for the centralised procedure, including advice on the design of studies and trials to support quality, safety and efficacy of a medicinal product at all stages of the product lifecycle.

EU - Legal basis and scope of Protocol Assistance (PA)

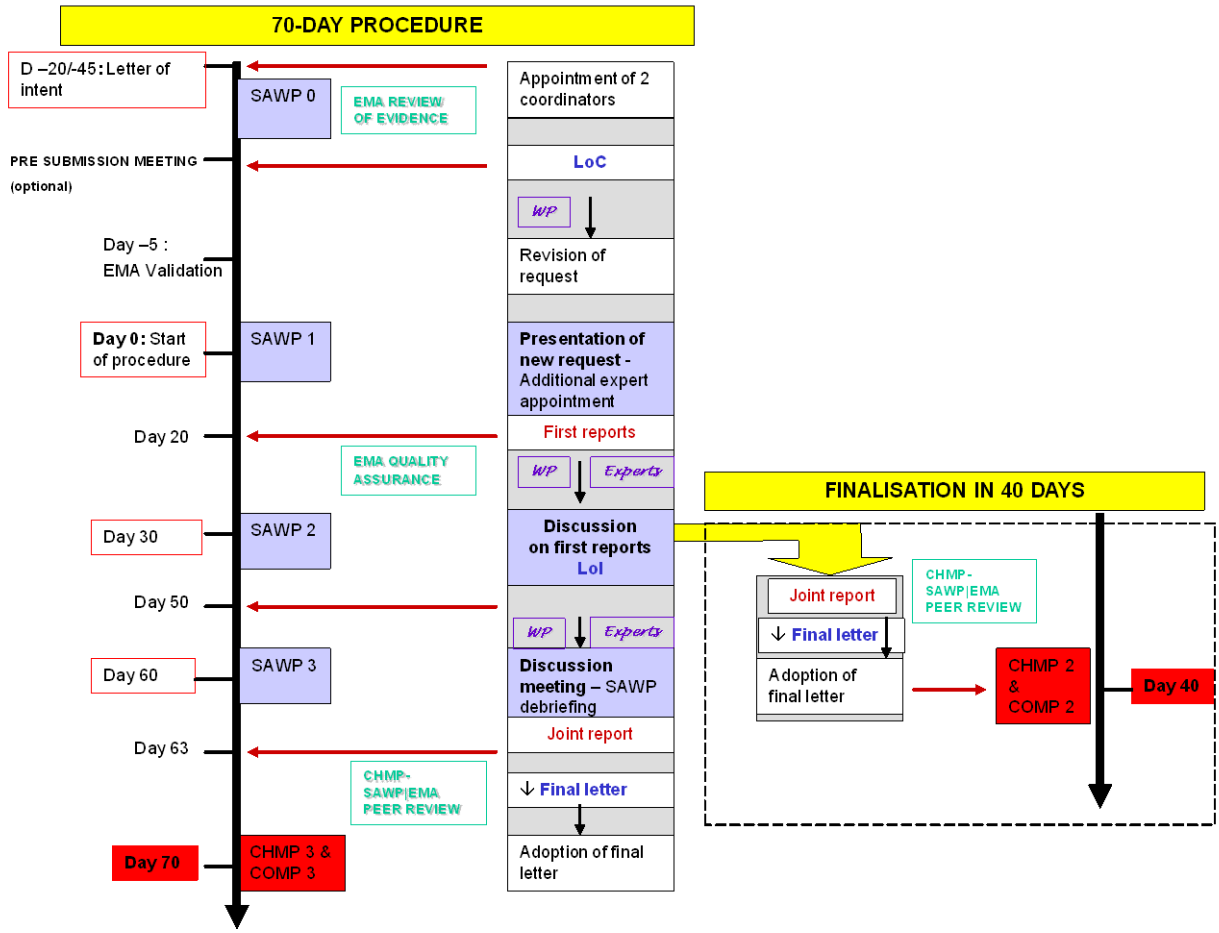
Since the pharmaceutical industry has little interest, under normal market conditions, in developing and marketing medicines intended for small numbers of patients, the EU offers a range of **incentives** to encourage the development of these medicines.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp&mid=WC0b01ac058002d4eb

After having received the European Commission decision on the designation of Orphan Drug status (based on the opinion of the Committee for Orphan Medicinal Products (COMP)), the sponsor of an orphan medicinal product is entitled to request Protocol Assistance prior to the submission of an application for Marketing Authorisation.

The procedure for provision of Protocol Assistance will follow mainly the procedure for provision of Scientific Advice, with focus on generation of clinical data for confirmation of orphan status at MA (significant benefit).

EU - Overview procedure SA & PA



Parallel Scientific Advice with FDA

Consider requesting parallel Scientific Advice with FDA; in order to avoid delays, Applicants should liaise with both Agencies to ensure they both agree to parallel Scientific Advice:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf

Parallel Scientific Advice with HTA bodies

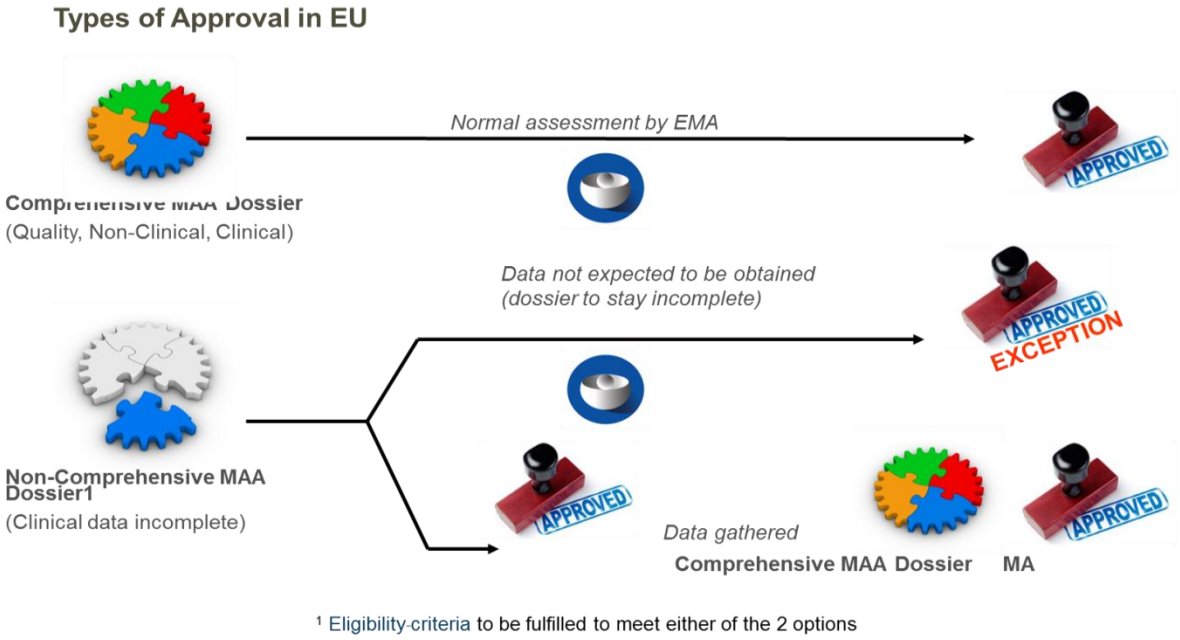
Consider requesting parallel Scientific Advice with HTA bodies.:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000476.jsp&mid=WC0b01ac0580236a57

EU regulatory framework for marketing authorisation applications

- Marketing Authorisation Application (MAA)

No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004 (article 6 of Directive 2001/83/EC)

- Historically authorisation was granted in each MS, under a **national** procedure
- 1993: Regulation (EEC) No 2309/93 establishing the **centralised procedure**



[1] Eligibility criteria to be fulfilled to meet either of the 2 options

Fees payable to EMA

The EMA charges fees for the services it provides. Fee reductions and incentives are available for micro-, small- and medium-sized enterprises (SMEs), designated orphan medicines, multiple applications on usage patent grounds and other classes of application. More information is available on the website.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000327.jsp

Back to step 4

Annex 5 - Additional Guidance on step 5: US FDA processes on new drug development programs

In general, FDA processes can be followed before, after or in parallel with the EMA processes.

For new drug development programs, aimed to result in a marketing authorisation, early contact with the FDA is possible through Type A, B or C meetings (dependent on the scope):
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm153222.pdf

A Type A meeting is a meeting needed to help an otherwise stalled product development program proceed.

Examples of a Type A meeting include:

- Dispute resolution meetings as described in 21 CFR 10.75, 312.48, and 314.103 and in the guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*3
- Meetings to discuss clinical holds in which a response to hold issues has been submitted, but the FDA and the sponsor or applicant agree that the development is stalled and a new path forward should be discussed
- Special protocol assessment meetings that are requested by sponsors or applicants after receipt of FDA evaluation of protocols under the special protocol assessment procedures as described in the guidance for industry *Special Protocol Assessment*

Type B meetings are as follows:

- Pre-investigational new drug application (pre-IND) meetings (21 CFR 312.82)
- Certain end-of-phase 1 meetings (21 CFR 312.82)
- End-of-phase 2 and pre-phase 3 meetings (21 CFR 312.47)
- Pre-new drug application/biologics license application meetings (21 CFR 312.47)

A Type C meeting is any meeting other than a Type A or Type B meeting between CBER or CDER and a sponsor or applicant regarding the development and review of a product.

Back to step 5

List of abbreviations and useful links

List of abbreviations

BLA: Biologics License Application

CDER: Center for Drug Evaluation and Research

CHMP: Committee for Human Medicinal Products

COMP: Committee for Orphan Medicinal Products

DDT: Drug Development Tools

HTA: Health Technology assessment

ITF: Innovation Task Force

LOI: Letter of intent

MAA: Marketing Authorisation Application

MS: Member State

NB: Notified Bodies

NDA: New Drug Application

ObsRO: Observed Reported Outcomes

PA: Protocol Assistance

PRO: Patient Reported Outcomes

SA: Scientific Advice

SAWP: Scientific Advice Working Party

SME: Small and Medium Sized Enterprises

Useful links

IMI website - section containing presentations on IMI projects related to regulatory mechanisms:
http://www.imi.europa.eu/content/documents#regulators

IMI/EMA/FDA Webinar of May 2013 on Regulatory Acceptance Mechanisms:
https://www.youtube.com/watch?v=0sBpPm6wOhA