Webinar
How to engage with regulators EMA / FDA

6 December 2017 • 14:00 CET
Agenda

- Welcome and introduction
  Nathalie Seigneuret & Catherine Brett, IMI

- EMA activities in support of EU-funded research projects for medicines innovation
  Corinne de Vries, EMA

- The EMA’s Innovation Task Force in practice
  Falk Ehmann, EMA

- EMA’s Qualification of Novel Methodologies – assuring the generation of appropriate evidence to qualify novel development tools (from the start)
  Thorsten Vetter, EMA

- EMA’s support to SMEs in support of innovative medicines development
  Leonor Enes & Constantinos Ziogas, EMA

- Questions and answers

- Opportunities for Engagement to Support Drug Development: New and Ongoing Activities
  Ameeta Parekh, FDA

- Question and answers
How to use GoToWebinar - audio

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- Try **another country’s** phone number
- Still not working? Select **Computer audio** and dial the numbers given on your phone
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- Send a question in writing → Say which speaker(s) your question is for
Before we start…

- This webinar is being recorded and will be published on the IMI website and / or IMI YouTube channel
- Presentation slides will be published on the IMI website
Objective of the webinar

- Most IMI projects have regulatory relevance
- **Early** engagement with regulatory authorities essential to:
  - understand the potential regulatory impact of projects' results at an early stage
  - understand the impact of the regulatory system on the projects
  - maximise the impact of the projects’ outputs
- Be familiar with opportunities for regulatory interactions to initiate this engagement
- This webinar will:
  - explain the different EMA activities to support researchers
  - present practical examples on how and when IMI consortia can interact with EMA
  - understand the opportunities for engagement at FDA
  - answer any questions you may have
EMA activities in support of EU-funded research projects for medicines innovation
EMA activities in support of EU-funded research projects for medicines innovation

Presented at IMI webinar, 6 December 2017

Presented by Corinne de Vries, Head of Science & Innovation Support
Human Medicines Research & Development Support Division
Outline

- Overview of involvement with regulatory science activities past, current & foreseen
- Q&A
- Discussion: are we on the right track? Adaptations required?
Overview of processes & feedback received

- True for all requests for involvement in regulatory science activities
- IMI the most prominent
(Options for) engagement:

1. Scientific committee representation, incl
   • Input in research agenda
   • Input in mid term review
   • Input in call texts
2. Routine regulatory interaction with / without dedicated EMA contact point
   (presentations @ kick-off meetings, overview document on IMI website)
3. Winning consortia are invited to ITF
4. Ad hoc attendance of consortium meetings
5. External advisory board member (not as observer; no confidentiality agreement)
6. Consortium partner or lead
Overview of involvement with regulatory science activities past, current & foreseen
EMA engagement with IMI research agenda

- Regulatory summit: 2014, 2017
- Annual stakeholder forum
- Scientific Committee meetings & webinars
- Draft call texts: ≥3 EMA colleagues
  - 3 calls in last 12 months
Decisions on involvement made based on

In summary

- **Resource implications:**
  - ... days of AD / AST over .... years
- **Fit with EMA strategy & priorities**
- **Anticipated involvement of committees & working parties**
- **Collaboration with external stakeholders**
- **Anticipated impact for EMA and EU public health**
- **Risk of (perceived) conflict of interest**
  - Not just one or two pharma involved
- **Existing opportunities for regulatory interaction**
  - Could ITF/SA support the consortium?
EU Medicines Agencies Network Strategy to 2020
towards a system that
• is more agile
• more likely to deliver innovative medicine
• meets unmet medical needs
• fosters excellence, incl:
  • effective use of resources available across the EU
• is patient focused
• promotes better regulation
• ensures effective communication

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000292.jsp&mid=WCOb01ac05800293a4
EMAT engagement @ different stages – last 12 months

1. Competitive stage: review the proposed EMA involvement only.

2. Winning consortium:
   - full grant proposal and, if EMA participation:
     - evaluator’s panel feedback
     - anticipated EMA contribution (deliverables, ftes)
   - Ask for DoA and invite to ITF
   - present at kick-off meeting (webinar) if needed
   - EAB / consortium membership:
     - Affected managers & Executive level to agree

regulatory.science@ema.europa.eu

47 requests
6 ITF meetings had; 3 pending
5 proposals to senior management re involvement
2 EAB memberships; 2 pending
no consortium partnerships in 2018
1 Marie Curie collaboration
<table>
<thead>
<tr>
<th>Funding body</th>
<th>Acronym</th>
<th>Description</th>
<th>MLT Date</th>
<th>Summary</th>
<th>SRS Office Response</th>
<th>EMA Office contacted</th>
<th>Reasoning/ Outcome</th>
<th>MLT Feedback</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM2</td>
<td>PARADIGM</td>
<td>Patients Active in Research and Dialogues for an Improved Generation of Medicines: Adverse event and meaningful patient experience to the type of medicine</td>
<td>19/06/2017</td>
<td>Invitation to join project consortium - Stage 2</td>
<td>To be presented at MLT for discussion</td>
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<td>H2020</td>
<td>Marie Curie</td>
<td>Minded</td>
<td>19/06/2017</td>
<td>Invitation to join the Advisory Board</td>
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<td>H2020</td>
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<td>IM2</td>
<td>RUPAT(2)</td>
<td>Sarcopenia Research, Early Identification of Comorbidities and Complement Therapeutic Targets</td>
<td>21/07/2017</td>
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<td>H2020</td>
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<td>Minded</td>
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2009 - 2017 IMI projects with EMA participation
## Resource implications for EMA

<table>
<thead>
<tr>
<th>Consortium member</th>
<th>Advisory board member</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Work up of full grant agreement</td>
<td>11. Admin incl CDA negotiations</td>
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<tr>
<td>2. Admin related to signature of project agreement and grant agreement;</td>
<td>12. Usually 2 meetings per project year and relevant preparatory work</td>
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<tr>
<td>3. Ad hoc project meetings</td>
<td>13. Monitoring &amp; follow-up on project outcomes</td>
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<tr>
<td>4. Consortium workshops &amp; meetings/TCs</td>
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<tr>
<td>5. Preparation of periodic reports</td>
<td>14. Plus, for both, discussions if expectations are not met to the extent the EMA is placed at risk</td>
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<td>6. Budget monitoring</td>
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<td>7. Budget revisions</td>
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<td>8. Final reports</td>
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<td>9. Audits</td>
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<td>10. Follow up on IMI revision after submission of final reports</td>
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Feedback received:

- ‘paranoia’
- ‘too rigid’
- ‘who do you think you are’

versus

- ‘good! Sounds like a fair approach’
- ‘glad we have a structured approach’
- ‘good to have a range of options’
- ‘helpful to have the regulatory context explained’
- ‘useful to have everyone around the table’
- and: ‘why don’t we see more of these consortia for QA?’

In summary

- Resource implications:
  – ... days of AD / AST over .... years
- Fit with EMA strategy & priorities
- Anticipated involvement of committees & working parties
- Collaboration with external stakeholders
- Anticipated impact for EMA and EU public health
- Risk of (perceived) conflict of interest
  – Not just one or two pharma involved
- Existing opportunities for regulatory interaction
  – Could ITF/SA support the consortium?
Thank you for your attention

Further information
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Early interactions on innovation at EMA (ITF)
Early interactions on innovation at EMA (ITF)

IMI SGG webinar regarding EMA support to H2020 funded research

Presented by: Falk Ehmann, Science & Innovation Support (EMA)
Regulators became gatekeepers and enablers...

Clinical pharmacology & Therapeutics; Advance online publication 3 April 2013. doi:10.1038/clpt.2013.14 ; F Ehmann, M Papaluca Amati, T Salmonson, M Posch, S Vamvakas, R Hemmings, HG Eichler and CK Schneider
Innovation Task Force (ITF)

Multidisciplinary platform for preparatory dialogue and orientation on innovative methods, technologies and medicines
ITF objectives (ASAP):

• Assist Knowledge exchange on innovative strategies involving regulatory network

• Support drug development via early informal dialogue on
  - Scientific, legal and regulatory issues
  - Products, methodologies and technologies

• Address the impact of emerging therapies and technologies on current regulatory system

• Preparing for formal procedures
Since 2016 the ITF supports informal meetings with research consortia, e.g. IMI, HZ 2020, FP7
Multidisciplinary ITF resources (internal and external):

ITF Secretariat

- SME Office
- Orphan
- Safety & Efficacy
- Quality
- Risk Management
- Research Institutions, e.g. Karolinska, Max-Planck
- EMA Committees and Working Parties
- Academia
- EC DG, Research, SANTE, GROWTH
- Other EU bodies (ECDC, NB, Device authorities)
- Intl. Regulators (FDA, PMDA, HC, TGA)
- EU Institutions, e.g. JRC, EFSA, EDQM

- Clinical Pharmacology / Non-Clinical
- Gene-Cell-Tissue MP
- IT
- Veterinary Medicines
- Scientific Advice
- GCP
- Inspection / GMP
- Regulatory Affairs
- Biostatistics
- Paediatrics
- Legal
80% of ITF meetings (F2F or webinar → minutes) submitted by consortia, academia and SMEs

→ Assist applicants to focus on regulatory deliverables and
  • maximise impact of work planned or performed
  • ensure results are of regulatory value and standard
  • help signpost through the regulatory ‘maze’

→ Impact includes preparation and referral to
  • formal scientific advice procedure
  • Qualification of methodology (e.g. Biomarker qualification) incl. publication on EMA web-site
How to apply for informal dialogue with the network

- Complete and send ITF request form
- After initial contact prepare a briefing document with main issues to be discussed
- 1 ½ h webinar, TC or F2F
- Share minutes for review
Take home messages

- The Regulator encourages early interaction with research consortia
- Early dialogue ensures deliverables are of regulatory value and standard
- The aim is maximising impact of your work for patients

Further information


Contact us at: ITFsecretariat@ema.europa.eu

Acknowledgements: Corinne de Vries
Qualification of Novel Methodologies –
A key regulatory tool to facilitate drug development
Qualification of Novel Methodologies –
A key regulatory tool to facilitate drug development

IMI webinar, Dec 2017

Thorsten Vetter, Scientific Advice
Disclosures and Disclaimer

Nothing to disclose

Views presented are my own and should not be perceived as having been made for or on behalf of the European Medicines Agency or its Scientific Committees or Working Parties
• …on the regulatory validity and acceptability of a specific use of a proposed method in R&D context (in non-clinical and clinical studies)

• Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm

• One procedure with two outcomes:
  • Qualification Advice, OR
  • Qualification Opinion

**Long-term benefits from EMA perspective:** Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisations, improve public health

Examples of **Novel Methodologies:**

- Biomarkers (prognostic/diagnostic and predictive)
- Clinical Outcome Assessments (COA: PRO, ClinRO, ObsRO)
- Imaging Markers
- Symptom Scales
- Animal Models
- Statistical Methods
- Methodologies for pragmatic/hybrid trials, registries
Applications throughout life-cycle

**Preclinical development**
- pharmacological screening
- mechanism of action
- **predict activity/safety**
- PK/PD modelling
- toxicogenomics

**Clinical development**
- verify MoA
- **dose/exposure-response**
- proof of concept Ph2
- **enrich/stratify population**
- **surrogate endpoint**
- Early detection of safety signals

**Drug utilisation**
- optimise target population
- guide treatment regimen
• **Context of Use (CoU)** → Full, clear and concise description of the way a novel methodology is to be used and the medicine development related purpose of the use. The Context of Use is the critical reference point for the regulatory assessment of any qualification application.

• **Endpoints** → Demonstration of diagnostic and prognostic performance (sensitivity and specificity), predictive value for drug response, likelihood ratios.

• **Statistical Analysis plan** → Will study design and data analysis support targeted CoU?
  - **Prospective/retrospective studies** may be appropriate depending on CoU.
  - pre-specified analysis path.
  - exploratory and confirmatory datasets needed.
  - If cross-validation approaches are considered (e.g. in small populations) these should be pre-specified and not considered post-hoc.
• **Demonstration of clinical utility**: Impact of methodology on **diagnostic thinking, patient management and clinical outcome**

• **Standard of truth/surrogate standard of truth**: Assessment of true state of a patient or true value of measurement might not exist or is invasive and/or unethical
  → Surrogate standard to be justified

• **Analytical platforms**: Technical/performance characteristics to be defined and justified, fit for purpose
**Guidance/Principles/Requirements**

**Design of qualification studies:** Diagnostic/Prognostic BMs disease states, progression, physiological changes, toxicity: **Guideline on clinical evaluation of diagnostic agents**


**Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions** (ICH E16)


**GUIDELINE ON GENOMIC SAMPLING AND MANAGEMENT OF GENOMIC DATA** (ICH E18)


**Biological matrix sampling, storage and transportation:** Reflection paper on pharmacogenomic samples, testing and data handling


**Analytical platform:** EMA guideline on bio-analytical method validation for proteomic markers


**Statistical principles for clinical trials:** Generally follow ICH Topic E9

Qualification **advice** on future protocols and methods for further development towards qualification, based on the evaluation of the **scientific rationale and on preliminary data** submitted, **confidential**

**Qualification opinion** on the acceptability of a specific use of the proposed method in a R&D context, based on the assessment of data, not product-specific. Will involve all relevant scientific groups at EMA, CHMP discussion and adoption, public consultation, publication

The procedural route is not fixed but will follow the assessment of the data

**Aims:** EMA early involvement in the design of the strategy, with commitment to evaluate data from agreed studies and to provide opinion

**Scope:** Focus on acceptability of specific use of the proposed methodology developed for a **specific intended use** in the context of pharmaceutical R&D (Context of Use)
Role of SAWP and CHMP

**Scientific Advice Working Party (SAWP) –**
Serves as primary scientific group, allows extensive networking within the Agency (Committees, other working parties and expert groups will be involved as appropriate)

**Committee for Medicinal Products for Human Use (CHMP) involvement -**

- CHMP member can be team member; peer review, discussion and adoption of final responses (Advice Letter or Qualification Opinion) by CHMP plenary
- Helpful for future CHMP interactions, also in the context of Marketing Authorisation Applications
Qualification team

2 Coordinators
(SAWP or CHMP)

Experts
multidisciplinary, min 4

context of use:
e.g. non-clinical safety
testing, translational research

technology platform
supporting the development
of the novel methodology:
e.g. genomics, proteomics,
ultrasound, MRI imaging

Adding external experts as appropriate
therapeutic areas
statistics

Project Manager
(EMA)
Timelines, Qualification Team (QT) meetings and meetings with applicant adjusted on a **case by case basis**
• **Applicants:** Consortia, Networks, Public/Private Partnerships (e.g. IMI, Critical Path Institute), Learned societies, Academia, Pharmaceutical industry

• **Fee incentives:** Same fee reductions as in scientific advice for paediatric use, orphan conditions and SMEs (small and medium-sized enterprises)

• **Qualification Advice:** Confidential

• **Qualification Opinion:** Public consultation prior to final publication ensuring scrutiny of and alignment with scientific community and external stakeholders

• Webpage for published Qualification Opinions and Letters of Support:

18 Qualification Opinion and 104 Qualification Advices finalised to end 2017
Letters of Support

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. The Agency publishes letters of support on this page, if the sponsors agree.

16 Letters of Support have been issued by end 2017
| Draft qualification opinion on plasma fibrinogen as a prognostic biomarker (drug development tool) for all-cause mortality and COPD exacerbations in COPD subjects | Prognostic marker for all-cause mortality and exacerbations in COPD patients | Prognostic biomarker | clinical |
Qualification Opinions published to date

<table>
<thead>
<tr>
<th>Opinion</th>
<th>Category</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paediatric ulcerative colitis activity index (PUCAI)</strong></td>
<td>Disease activity</td>
<td>scale</td>
</tr>
<tr>
<td><strong>Ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials</strong></td>
<td>compliance</td>
<td>Technology</td>
</tr>
<tr>
<td><strong>Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD)</strong></td>
<td>Prognostic marker</td>
<td>Prognostic biomarker</td>
</tr>
<tr>
<td><strong>Qualification of exacerbations of chronic pulmonary disease tool (EXACT), and EXACT-respiratory symptoms measure (E-RS) for evaluating treatment outcomes in clinical trials in COPD</strong></td>
<td>Treatment outcome</td>
<td>Scale – measuring tool</td>
</tr>
<tr>
<td><strong>In-vitro hollow fiber system model of tuberculosis (HFS-TB)</strong></td>
<td>Preclinical</td>
<td>In vitro disease model</td>
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### Qualification Opinions published to date

<table>
<thead>
<tr>
<th>Description</th>
<th>Type of Study</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase-II dose-finding studies under model uncertainty</td>
<td>Dose finding</td>
<td>Modelling technique</td>
</tr>
<tr>
<td>A novel data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer’s disease</td>
<td>Disease activity</td>
<td>Progression biomarker</td>
</tr>
<tr>
<td>Alzheimer’s disease novel methodologies / biomarkers for the use of cerebrospinal-fluid amyloid beta 1-42 and t-tau and/or positron-emission-tomography amyloid imaging (positive / negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer’s disease</td>
<td>Disease staging</td>
<td>Disease biomarker</td>
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<tr>
<td>Low hippocampal volume (atrophy) by magnetic-resonance imaging for use in clinical trials for regulatory purpose in predementia stage of Alzheimer’s disease</td>
<td>Disease staging</td>
<td>Disease biomarker</td>
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<tr>
<td>Novel methodologies in the predementia stage of Alzheimer’s disease: cerebrospinal-fluid-related biomarkers for drugs affecting amyloid burden</td>
<td>Disease staging</td>
<td>Disease biomarker</td>
</tr>
<tr>
<td>Alzheimer’s disease novel methodologies / biomarkers for BMS-708163</td>
<td>Disease staging</td>
<td>Disease biomarker</td>
</tr>
<tr>
<td>Final conclusions on the pilot joint European Medicines Agency / Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers</td>
<td>Drug toxicity</td>
<td>Prognostic biomarker</td>
</tr>
<tr>
<td>ILSI / HESI submission of novel renal biomarkers for toxicity</td>
<td>Drug toxicity</td>
<td>Prognostic biomarker</td>
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</table>
• Encouraged by both Agencies
• Voluntary, at request of sponsor
• Discussion between FDA-EMA and tripartite meeting with sponsor
• Alignment of procedural flow between agencies is important: preparatory interactions with both agencies should start early
• Each Agency will issue separate responses to sponsor’s questions in line with their usual procedures

→ Increased dialogue between Agencies and sponsor from early stages of development
→ Exchange views, share expertise
→ Optimise and facilitate global development, meeting both agencies requirements
• The Qualification exercise is complex and requires collaboration between interested parties – mostly PPP’s. Efficient communication between Collaborators is key
• Danger to embark on overly ambitious and complex projects which may not be in line with project funding horizon
• Late initiation of regulatory interaction to discuss the collated existing evidence, perform gap analysis, develop qualification strategy and agree on evidentiary requirements for regulatory Qualification based on a clear CoU is a common challenge
• Feasibility considerations should inform (and limit) the number of targeted CoU’s: e.g. for safety markers:
  - Time point to detect robust safety signal
  - Discrimination of the histopathologic mechanism of organ injury (e.g. necrosis, apoptosis, immune activation)
  - Differentiation of likelihood of progression/regression/adaptation with ongoing exposure;
• Key: Adequate, well characterised study populations for **exploratory studies/learning datasets**; once these analyses have identified clear candidate markers with appropriate characterisation of **thresholds** and **time course**, these will need to be **confirmed**, ideally prospectively; alternatively a well characterised independent biobank of samples from patients who have experienced the target organ toxicity and its various clinical outcomes may be used for confirmation; SAP/methodology should be pre-specified and agreed a priori

• qualification will depend on appropriate study designs (adequate well-defined target population, definition of a success criterion with regard to clinical utility of the marker, rationale for sample size, methodology for internal and external validation of the statistical prediction model, adjustment for other covariates such as subject characteristics, time point of marker measurement, drug exposure) in which predictive/classification rules are established and validated in order to assess the clinical utility of the marker (panel)

• EMA Qualification Advice provides platform to agree on these considerations early
• Qualification is not a trivial exercise
• **Regulatory requirements are case dependent and require dialogue**
• **Many Stakeholders** (e.g. Regulators, Learned Societies, Patients, Notified Bodies)
• **Many Scientific Disciplines** (Analytical Scientists, Pharmacologists, Toxicologists, Modellers, Clinicians, Statisticians)
• **EMA Qualification procedure** is a platform for **dialogue**:
  • Identifying and agreeing evidentiary requirements to support CoU
  • **Cooperation of international regulators** facilitates adequate study designs
  • Vision: speed up/optimise drug development and utilisation, improve public health
Thank you

Further information

Thorsten Vetter

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An overview of EMA initiatives supporting SMEs
An overview of EMA initiatives supporting SMEs

SME info day „Supporting innovative medicines' development and early access“
17 November 2017, EMA

Presented by: Leonor Enes
SME Office, Corporate Stakeholders Department, Stakeholders & Communication Division
1. SME Regulation
2. What the SME Office does
3. SME action plan
4. Recommendations for SMEs
SME Regulation

COMMISSION REGULATION (EC) No 2049/2005 of 15 December 2005

**Aim:** to promote innovation and the development of new medicines for human and veterinary use by SMEs

SME Office launch in December 2005

- A single contact point
- Assistance to SMEs
  - Regulatory, administrative and procedural support
- Facilitates communication
  - With SMEs in veterinary and human pharma sector
- Coordinating & networking
  - Working closely with EU, SME partners and stakeholders
What the SME Office does

- Assignment of SME status
- Regulatory Assistance & SME briefing meetings
- Fee Incentives
- Translation Assistance

- Training and Awareness
- Partnering & Networking *SME Register*
- Reporting
01 Assignment of SME status
Commission Recommendation 2003/361/EC

1. Submission
2. Review
3. Qualification
4. Renewal
Registered SMEs

- From 28 countries across EU
- Top 5 countries: UK (17%), Germany (13%), France (9%), Italy (6%) and Spain (5%)
- 41% micro, 34% small, 25% medium
- Majority human (78%), 4% vet, 5% human/vet & 13% service providers
- Information on registered companies available in the SME public register
Administrative, regulatory and procedural queries are addressed by email, phone or in a briefing meeting.
Regulatory assistance to SMEs (2/3)

Tailored to SMEs

Direct administrative and procedural assistance

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<td>135</td>
<td>130</td>
<td>163</td>
<td>141</td>
<td>174</td>
</tr>
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158 Reg. Ass. cut off date 16/11/2017
02 SME briefing meetings (3/3)

- Provides a platform for early dialogue with SME to discuss regulatory strategy of medicinal product development and navigate the range of procedures and incentives available

- Multidisciplinary group, co-operation with other EMA offices (scientific advice, paediatrics, orphans, regulatory affairs, etc)

- Open to medicinal products for human and veterinary use

- Free of charge

- SME request to SME Office with background on the product on the product development

- Can be face to face or via TC

- 2005 - 2015: 65
- 2016: 13
- 2017 (Jan - Nov): 15
03 SME fee incentives (1/2)

- Fee reductions and exemptions for scientific advice, scientific services, inspections & establishment of maximum residue limits
- Deferrals of the fee payable for an application for marketing authorisation or related inspection
- Conditional fee exemption
- Fee reductions and exemptions for post-authorisation procedures and pharmacovigilance activities
- Waiver of the MedDRA licensing fee for micro and small companies

*Full details on all fees and fee reductions are available in:* [Explanatory note on general fees payable to the European Medicines Agency](https://ema.europa.eu/en/) and [Explanatory note on pharmacovigilance fees payable to the European Medicines Agency](https://ema.europa.eu/en/)
Conditional fee exemption (SMEs)

- Applicant request to SME Office with supporting document and justification
- Review of compliance with SA

1. Negative opinion or withdrawal
2. SA received and followed
3. MAA fee waived
04 Translation assistance

- Assistance with translations of the product information and opinion annexes, in the event of a CxMP positive opinion

- No cost to SME applicant
05 Training & awareness for SMEs

Info days
regulatory training course tailored for SMEs

Newsletters
Circulated quarterly; published on the EMA Website.

Announcements
Information sent by email to SMEs and stakeholders

SME User Guide
Updated regularly

Provide training & ease the access to regulatory information
**SME Register**

Set up in consultation with SME stakeholders aiming:

- to increase information available to SMEs and their stakeholders
- to facilitate and promote interaction, partnering and networking between SMEs
- to provide a source of information for EU institutions, agencies and Member States
07 Reporting

SME Office annual report 2016

Overview of SME activities: platforms to advance innovative developments and regulatory strategies and SMEs experience with human and veterinary marketing authorisation applications

EMA SME 10 year report
Marketing authorisations

SME Applicants – MAA outcome by year for Human Medicines (2006-2016)
Outlines a series of objectives and actions grouped by theme, which were identified in the EMA 10-year report and the SME survey.

4 key areas including 16 actions

1. **Awareness of EMA’s SME initiative:** engagement with incubators, universities and investors.

2. **Training and education**

3. **Support the development of innovative medicines:** maximising the use of regulatory tools to support the development of and access to medicines and enhancing cooperation with EU partners on projects subject to EU funding.

4. **Engagement with SMEs, EU partners and stakeholders:** EU Innovation Network, EU initiatives supporting SMEs and start-ups and interacting with international regulatory authorities.
Recommendations for SMEs

- Consult available guidance (procedural and scientific) and SME User Guide
- European Public Assessment Reports are useful source of information
- Regulatory assistance/briefing meeting with SME Office
- Informal dialogue through Innovation Task Force
- Early Scientific Advice (multidisciplinary)
- Eligibility to PRIME scheme
- Build timelines for paediatric investigation plan (PIP) and modification/compliance check, as appropriate
- Early pre-submission dialogue in run up to MAA filing
- Consider policy 70 on clinical data publication
- Take advantage of the various opportunities to enter in a dialogue with EMA
Take home messages

The SME initiative offers a broader range of incentives to SMEs

The EMA remains committed to fostering an environment which provides incentives to SMEs: awareness of the EMA SME initiative, training and education, supporting innovative medicines’ developments, and further engaging with SMEs, partners and stakeholders

Further information

See: supporting SMEs
Contact us at: sme@ema.europa.eu
SME helpline 8787
Questions
Questions?

Raise your hand if you want to ask a question orally.

Send a question in writing.

After the webinar, send any questions to the **IMI Programme Office**

infodesk@imi.europa.eu
Opportunities for Engagement to Support Drug Development
New and Ongoing Activities
Opportunities for Engagement to Support Drug Development

New and Ongoing Activities

Ameeta Parekh, Ph.D.
Senior Advisor for Scientific Collaborations
Center for Drug Evaluation and Research (CDER)
US Food and Drug Administration

December 6, 2017
Outline

• Opportunities for innovation in drug development

• Approaches to address drug development challenges

• Drug Development Tools and Qualification

• Strategies for regulatory engagement
21st Century Cures Act - An Opportunity

- Enacted December 13, 2016

- Increasingly places FDA as an active participant in drug development

- Requires expanded efforts to enhance drug development:
  - Novel innovative trial designs
  - Real world evidence (RWE)
  - Patient-focused drug development
  - Drug development tools (DDT) qualification
Opportunities for Innovation

Streamlined clinical trials
New sources of evidence
Enhanced response predictors
Improved endpoints
Better evaluation tools

Efforts to address these challenges have been ongoing through stakeholder collaborations.
The 21st Century Cures Act (Cures Act): A proactive stance to modernize medical product development

www.fda.gov
Addressing Drug Development Challenges: Master Protocols

- Challenges with standard approaches to clinical trials and need for complex adaptive and innovative trial designs

- **Master Protocol (MP):** One overarching protocol designed to answer multiple questions

- **Features of Master Protocols (examples):**
  - Multiple treatments
  - Multiple companies
  - Shared control arm
  - Adaptive designs
  - Seamless trial design
  - Bayesian approach

MP efforts: broaden design options to address complex clinical trial issues


*Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both*
Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.
Addressing Drug Development Challenges: Complex Innovative Trial Designs

Assist sponsors in incorporating complex adaptive and other novel trial designs into clinical protocols to facilitate more efficient drug development

- Publish draft guidance on complex adaptive (including Bayesian adaptive) trial designs
- Convene a public meeting to discuss various complex adaptive, Bayesian, and other novel clinical trial designs
- Develop a pilot program for highly innovative trial designs which require simulations to determine operating characteristics
- Develop staff capacity to support the review of these designs
RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real world data (RWD).

RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices.
Addressing Drug Development Challenges: Real World Evidence (RWE)

**Cannot** completely replace controlled clinical trials for efficacy and safety of new drugs

**Can** augment and increase effectiveness of clinical research  
**Can** support new indications for existing drugs  
**Can** show how a drug works in populations not included in clinical trials  
**Can** show how a drug works relative to another drug not in the study  
**Can** support post-approval requirements

Real World Evidence Transcript: Janet Woodcock, CDER FDA  
[https://www.fda.gov/Drugs/ScienceResearch/ucm583448.htm](https://www.fda.gov/Drugs/ScienceResearch/ucm583448.htm)
Addressing Drug Development Challenges: Patient Focused Drug Development (PFDD)

Systematic approach to gather patient perspective on disease burden and treatment options

2013-2017: > 20 meetings focused on specific disease areas

Incorporate patient perspective in drug development and review

Develop clinical outcome assessment (COA) tools

Qualify COA tools for use in drug development

Professional Affairs and Stakeholder Engagement (PASE) Staff
CDERPASE@fda.hhs.gov
https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm385522.htm

Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017
https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm347317.htm
Addressing Drug Development Challenges: Model Informed Drug Development

Modeling and simulation (M&S) refers to using models – physical, mathematical, or otherwise logical representation of a system, entity, phenomenon, or process – as a basis for simulations – methods for implementing a model (either statically or) over time – to develop data as a basis for managerial or technical decision making.

<table>
<thead>
<tr>
<th>Process/Disease</th>
<th>Objective</th>
<th>Application</th>
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<tbody>
<tr>
<td>Formulation change for modified release dosage forms</td>
<td>Conduct in-vitro in-vivo correlations (IVIVC)</td>
<td>Waive bioequivalence studies</td>
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<tr>
<td>Alzheimer's Disease</td>
<td>Develop disease progression models</td>
<td>Inform trial design</td>
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<tr>
<td>Partial Onset Seizures</td>
<td>Compare exposure and response between adult and pediatric patients</td>
<td>Waive pediatric efficacy studies (&gt;4 yr) for adult-approved products</td>
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Addressing Drug Development Challenges: Drug Development Tools (DDTs)

DDTs: methods, materials, or measures that have the potential to facilitate drug development.

Examples:

- a biomarker used for clinical trial enrichment
- a COA used to evaluate treatment benefit
- or a disease specific animal model used for efficacy testing under the Animal Rule

DDTs are integrated in drug development through individual Investigational New Drug/New Drug Application/Biologics License Application (IND/NDA/BLA) submissions, scientific community consensus, or the biomarker qualification pathway


www.fda.gov
Update on the Biomarker Qualification Program: What is new?

• Some new important features, but much continuity with the earlier BQP

• Formalizes a process defined by three phases:
  – Letter of Intent (LOI)
  – Qualification Plan (QP)
  – Full Qualification Package (FQP)

• Requires setting and implementing “reasonable timeframes” for the FDA review of each submission type

• Transparency provision: tools in development, stage of development, and FDA determinations
Biomarker Qualification Program: Updated Website

Information for BQ requestors

Biomarkers at CDER

BQP education and training

List of qualified biomarkers

Current BQ submissions

BQP submission FAQs

Submission resources by stage

Biomarker Guidances and reference materials

Biomarkers used as outcomes

BQ case studies

Videos and podcasts on FDA’s BQP


www.fda.gov
Biomarker Qualification Program: Videos and Podcasts

About FDA’s Biomarker Qualification Program

Making Biomarker Development Successful

What Are Biomarkers and Why Are They Important?

What Do You Need to Consider When Qualifying a Biomarker?

Biomarker Terminology: Speaking the Same Language

How Biomarkers Can Improve the Drug Development Process

Pathways for Using Biomarkers In Drug Development

What Does Biomarker Qualification Do (and Not Do)?

Opportunities to Engage With the FDA About Qualification During Biomarker Development

The Biomarker Qualification Process: A Roadmap for Requestors

The Role of Consortia in Biomarker Development and Qualification

Collaboration is Needed

Enhance regulatory decision making
Nominating opportunities presented by science
Improve patient care
Expedite medical product development process
Patient Informed drug development

Adapted from figure supplied courtesy of RM Long, NIH. S Buckman, S-M Huang, S Murphy, Clin Pharmacol & Ther, 81(2): 141-144, Feb 2007

www.fda.gov
How do you engage with the regulators?
Engagement Opportunities at CDER

Independent of Specific Drug Development Program
- Tools, Methods, Approaches, Standards

PFDD
- Understand Patient Experience

Critical Path Innovation Meetings (CPIM)
- Discuss and Receive Feedback on Methodology or Technology

CDER

Specific Drug Development Program
- IND/NDA/BLA

DDT Qualification Program
- Biomarkers, COA, Animal Models

Consortia
- Foster Scientific Collaborations to Encourage the Development of Tools, Methods, Approaches, Standards

Technology Transfer
- Research Collaboration

www.fda.gov
CPIM provides an opportunity for stakeholders to communicate directly with FDA subject matter experts and have an open scientific discussion and exchange of ideas with a common goal of improving efficiency and success in drug development.
Critical Path Innovation Meeting (CPIM)

- **Product independent** and not a meeting about a specific approval pathway

- **Scope** includes emerging technologies, natural history study designs, innovative approaches to clinical trial designs and analysis

- **Outcomes** include CDER perspective on role of innovation in drug development; potential next steps

- **Nonbinding meeting** to discuss innovative strategies that address challenges in drug development
CPIM Resources

Critical Path Innovation Meetings
A consortium is a collaborative group managed by a convening or coordinating organization involving multiple stakeholder organizations including at least one non-profit or 501(c)(3) organization and at least one for profit organization.
Consortia Engagement at CDER

Why are consortia established?

A consortium can be established upon emergence and identification of a public health need, and when addressing the need is beyond the capability of any one stakeholder.

Why is CDER involved with consortia?

CDER is engaged to foster scientific collaborations to support and encourage the development of new tools to facilitate innovation in medical product development. CDER and stakeholders leverage expertise and resources to conduct mutually beneficial activities in a pre-competitive domain.

How does CDER benefit from consortia engagement?

CDER staff engage in a consortium to address specific regulatory science needs; CDER staff can keep the focus of the consortium activities on addressing the regulatory science deliverable, and the products of the partnerships are shared in public domain for a wider uptake.
Institute of Safe Medication Practices (ISMP), Product Quality Research Institute (PQRI); ILSI Health and Environmental Sciences Institute – Reproductive Toxicology (HESI-ReproTox); ILSI Health and Environmental Sciences Institute – Cardiac Safety Consortium (HESI-CSC); the National Institute for Pharmaceutical Technology and Education (NIPTE); Cardiac Safety Research Committee (CSRC); Biomarker Consortium (BC); Predictive Safety Testing Consortium (PSTC); International Serious Adverse Events Consortium (iSAEC); Clinical Trials Transformation Initiative (CTTI); Coalition Against Major Disease Consortium (CAMD); Global Language of Business (GS-1); CDC Protect Initiative; International Pharmaceutical Company Supply Chain Initiative (RX360); Critical Path to TB Drug Regimens (CPTR) Consortium; Patient Reported Outcomes (PRO) Consortium; Polycystic Kidney Disease Outcomes (PKD) Consortium; National Institute for Pharmaceutical Technology and Education (NIPTE); Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (ACTTION); Electronic Patient Reported Outcomes (ePRO); Multiple Sclerosis Outcome Assessments Consortium (MSOAC); Kidney Health Initiative (KHI); Coalition For Accelerating Standards and Therapies (CFAST); Innovation in Medical Evidence Development and Surveillance (IMEDS) Program; Accelerating Medicines Partnership (AMP); International Neonatal Consortium (INC); Duchenne-Regulatory Science Consortium (D-RSC); Pediatric Trials Consortium (PTC); Critical Path for Parkinson’s Consortium (CPP); Alcohol Clinical Trials Initiative (ACTIVE); Type 1 Diabetes Consortium (T1D); Pharmaceutical Users Software Exchange (PhUSE); Transplant Therapeutics Consortium (TTC), National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL); Children’s Registry for Advancement of Therapeutics (CREATE)
Consortia Deliverables: Examples

REVIEW
The Role of Public–Private Partnerships in Catalyzing the Critical Path

Kimberly E. Maxfield1,*, Shashandri Buckman-Garner2 and Ameeta Parekh3

INTRODUCTION
The US Food and Drug Administration (FDA’s Critical Path Initiative (CPI) was launched in 2004 and aimed at accelerating the stagnating product development pipeline. Subsequently, the Critical Path Opportunities List (CPOI) identified specific priorities to facilitate the CPI vision. Since then, the FDA’s Center for Drug Evaluation and Research (CDER) has directed considerable efforts to achieve the goals of CPI and CPOI. Collaborations with Public–Private Partnerships (PPPs) helped address several CPOI priorities to yield meaningful results to benefit public health.

THE CRITICAL PATH
In 2004, the US Food and Drug Administration (FDA) acknowledged a growing gap between the rate of basic science discovery and the translation of these discoveries into the development of medical products. To address this gap, the FDA instituted the Critical Path Initiative (CPI), which called for increased efforts to catalyze innovation in product development through the launch of several initiatives. These efforts aim to modernize product quality and manufacturing standards, develop novel approaches to assess safety and effectiveness, build nonclinical and in silico predictive models, and develop novel clinical trials and analyses methodologies. When taken together, these tools, standards, and approaches aim to assess safety, efficacy, quality, and performance of FDA-regulated products (collectively termed regulatory science). These efforts strive to streamline medical product development and accelerate the translation of scientific discovery into commercial products.

The CPI further emphasized that a joint effort between the research community, industry, and FDA scientists was essential to realize the CPI vision. To this end, the FDA convened both external stakeholders and FDA scientists to identify research priorities that could guide the FDA in bringing focus to specific unmet public health needs. This effort...

Clin Transl Sci (2017) 10, 431-442; 2017 ASCPT
Process for Requesting CDER Staff Engagement with a Consortium

Consortia conveners request CDER engagement and CDER makes a determination if it is appropriate for CDER to participate in the activity.

For CDER staff to engage with consortia, see our Manual of Policies and Procedures available on our website.

Technology Transfer Program

At CDER, the Technology Transfer refers to the process of transferring materials, data, equipment, expertise, intellectual property and scientific findings from one organization to another for the purpose of further development and commercialization.

This is implemented through Collaborative Research Agreements.

Information Resource:
https://www.fda.gov/AboutFDA/business/ucm119486.htm
CDER’s Janet Woodcock on Consortia –

“Facilitating collaborative partnerships among government, academia, industry, and patients groups is arguably the most important role that CDER plays in supporting advancement of drug development and regulation”

http://www.nature.com/nrd/journal/v13/n11/full/nrd4435.html
Questions
Questions?

Raise your hand if you want to ask a question orally

Send a question in writing

After the webinar, send any questions to the IMI Programme Office
infodesk@imi.europa.eu
TAKE HOME MESSAGE

- Use the opportunities for interaction with Regulators

- Plan the interaction in your workplan

- Remember start early!
FDA back-up slides
FIND CONSORTIA

http://consortiapedia.fastercures.org/
Predictive Safety Testing Consortium (PSTC)

CDER Biomarker Qualification Program
Validation of a biomarker for a specific context of use

1st regulatory biomarker qualification:
7 biomarkers for preclinical prediction of drug-induced kidney injury

A roadmap for biomarker qualification
David G Warnock & Carl C Peck
A collaborative effort between pharmaceutical companies, regulatory agencies and academia to qualify biomarkers for kidney toxicity provides a model for investigating and identifying reliable safety markers for preclinical applications.

Critical Path to Tuberculosis Drug Regimens (CPTR)

2012 FDA Approval of Bedaquiline

Incorporated into draft FDA guidance

Accurate testing sputum in resource-poor areas

Critical Path to Tuberculosis Drug Regimens (CPTR)
Coalition Against Major Diseases (CAMD)

Academia → Data Sharing → Not-for-Profit → Pharma → Regulatory Agencies

Quantitative Disease Progression Model
To inform dose selection, patient inclusion, sample size estimates, study duration

FDA established ‘fit-for-purpose’ initiative for regulatory acceptance of dynamic tools

The Biomarkers Consortium (BC)

Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis (I-SPY-2)

- Phase II adaptive design master protocol in breast cancer
- Evaluated 12 therapies
- Across 10 molecular biomarkers
Advancing Regulatory Science

...developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products

...advance regulatory science to speed innovation, improve regulatory decision-making, and get products to people in need. ..... FDA works with diverse partners to protect and promote the health of our nation and the global community.

www.fda.gov
Commissioner’s Blog on *In Silico* Tools Innovation Initiative

- Use of in silico tools in clinical trials for improving drug development and making regulation more efficient

- M&S to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms

- Creation of natural history databases to support model-based drug development (e.g. Parkinson’s disease, Huntington’s disease, Alzheimer’s disease, and muscular dystrophy)

- An important objective of modeling and simulation is to better evaluate the behavior of new treatments in rare disease populations that are inherently hard to study due to their small size.

PPP Convener: A non-U.S. Government, nonprofit organization and coordinator of the PPP or consortium. The PPP Convener is responsible for submitting a request for CDER staff participation in a PPP or consortium activity and for providing certain assurances to CDER regarding the proposed activity.

Public-Private Partnership (PPP): For the purposes of this MAPP, a PPP or a consortium is an on-going collaborative group managed by a convening or coordinating organization involving multiple stakeholder organizations including at least one nonprofit or 501(c)(3) organization (e.g., academia, government, or foundation) and at least one for-profit organization (e.g., pharmaceutical, biotechnology, or medical device company). A PPP may involve multiple committees and working groups.

Precompetitive Domain: For the purposes of this MAPP, the precompetitive domain includes activities, including research, aimed at bridging knowledge gaps in discovery, clinical research, and medical product development. Such activities are neither proprietary in nature nor product specific, and therefore do not present a greater advantage to one stakeholder over another. In the precompetitive domain, all stakeholders benefit from added knowledge, tools, and data to enhance the efficiency of product development and the regulatory process.

Not-For-Profit: An organization, such as a professional society, academic institution, or science based foundation, which may serve as a third party convener of the collaborative activities (e.g., government, academia, science-based foundations, professional societies and patient advocacy groups).
ROLE OF CONSORTIA IN THE DEVELOPMENT AND QUALIFICATION OF BIOMARKERS

• Consortia provide a neutral collaborative environment for partnering, sharing, and leveraging the resources for biomarker development and qualification

• Consortia can help facilitate workshops, scientific discussions, gather input from scientific community, and to streamline advances in regulatory science

• A consortium setting can provide an opportunity for scientific staff engagement to discuss current thinking on biomarkers and other regulatory science efforts.

• CDER is involved in several PPPs to promote development of research tools, platforms, clinical databases, and predictive models to advance knowledge of diseases and safety profiles of drugs. Project results generated by these PPPs are made broadly available to the public to benefit public health.

Example: Qualification of kidney safety biomarkers