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**

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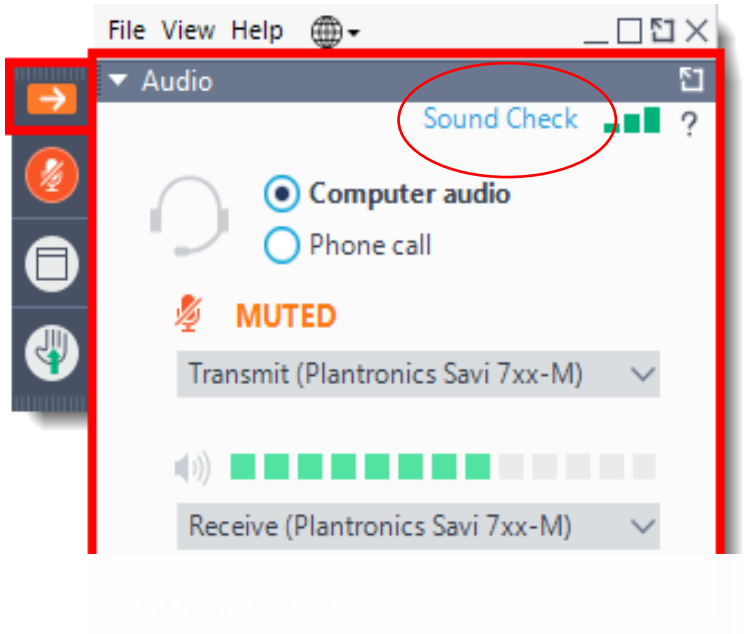

innovative medicines initiative

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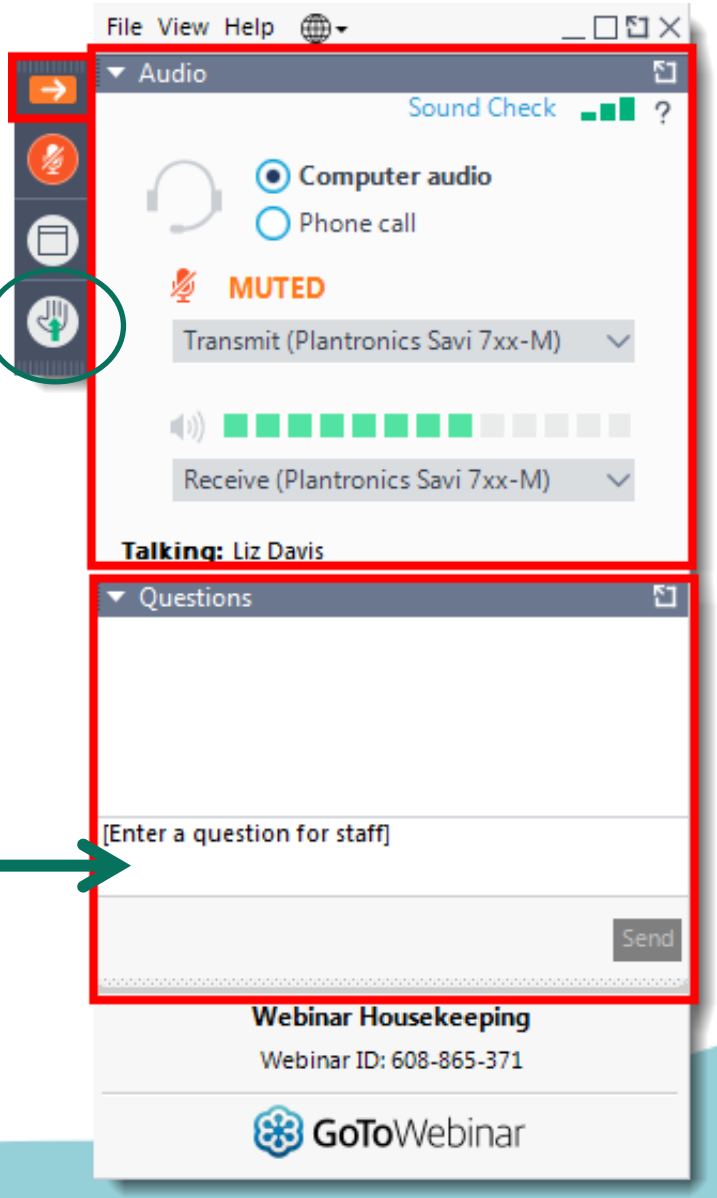

innovative medicines initiative

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

innovative medicines initiative

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

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EMA activities in support of EU-funded research projects for medicines innovation

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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?

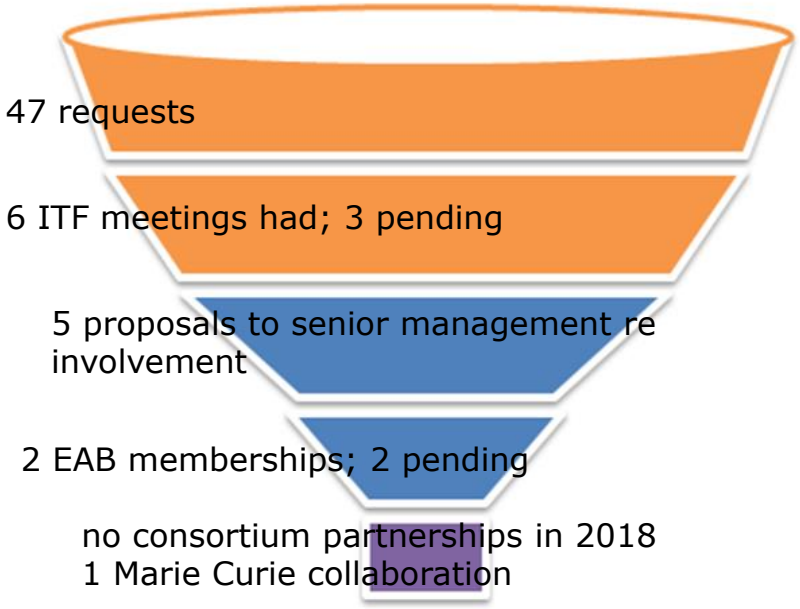
EU Medicines Agencies Network Strategy to 2020

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

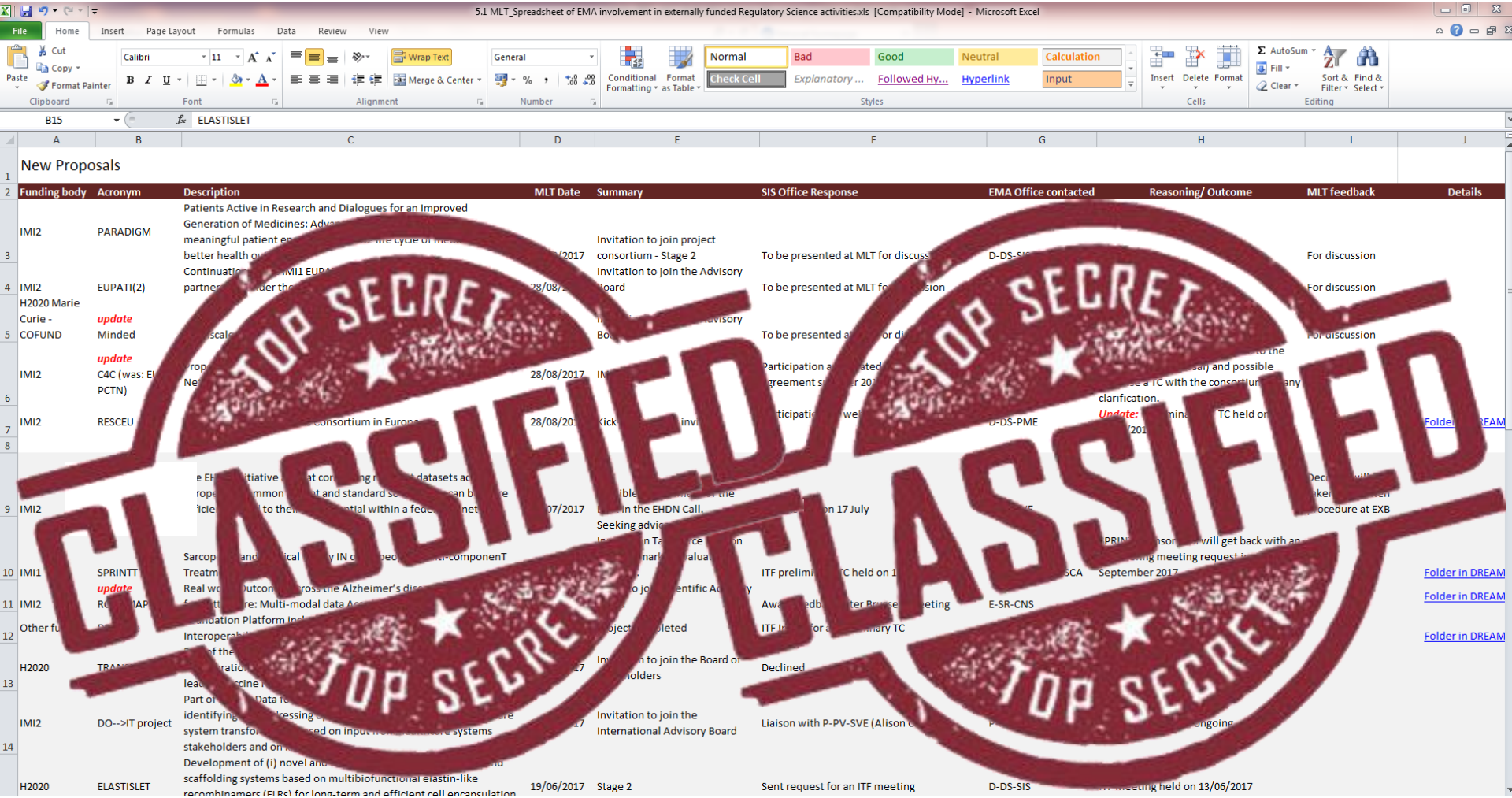
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000292.jsp&mid=WC0b01ac05800293a4

EMA engagement @ different stages – last 12 months



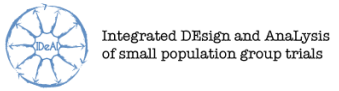
regulatory.science@ema.europa.eu

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



Funding body	Acronym	Description	MLT Date	Summary	SIS Office Response	EMA Office contacted	Reasoning/ Outcome	MLT feedback	Details
IMI2	PARADIGM	Patients Active in Research and Dialogues for an Improved Generation of Medicines: Adv... meaningful patient en... better health ou... Continuatio...	.../2017	Invitation to join project consortium - Stage 2	To be presented at MLT for discuss...	D-DS-SI...		For discussion	
IMI2	EUPATI(2)	...IMI1 EUPA... partne... ...der the...	28/08/...	Invitation to join the Advisory Board	To be presented at MLT fo... ...sion			For discussion	
H2020 Marie Curie - COFUND	*update* Minded	...scale...		...dvisory Bo...	To be presented a... ...or di...			For discussion	
IMI2	*update* C4C (was: E... PCTN)	...rop... Ne...	28/08/2017	IN...	Participation a... ...ated ...greement s... ...r 201...		...to the ...sal) and possible ...se a TC with the consortiu... ...any clarification.		
IMI2	RESCEU	...consortium in Europe	28/08/20...	Kick... ...invi...	...ticipati... ...wel...	D-DS-PME	*Update:* ...mina... TC held or... ...201...		Folder ...EAM
IMI2		...e EH... ...itiative ...at cor... ...g r... ...t datasets ac... ...rope... ...mmon ...t and standard s... ...can b... ...re ...icie... ...to the... ...tial within a fede... ...net...	...07/2017	...ible ...the ...in the EHDN Call. Seeking advic...	...on 17 July				Dec... ...ke... ...ocedure at EXB
IMI1	SPRINTT	Sarcop... ...and ...ical ...y IN o... ...pec... ...componenT Treatm...		...n Ta... ...ce ...on ...mar... ...valua...	ITF prelimi... ...TC held on 1...	...SCA	...IPRIN... ...sor... ...will get back with an ...ing meeting request i... September 2017		Folder in DREAM
IMI2	*update* RO... ...IAP...	Real wo... ...utcom... ...ross the Alzheimer's dis... ...f... ...tt... ...re: Multi-modal data A...		...o jo... ...entific Ad... ...y	Awa... ...edb... ...ter Bruge... ...eting	E-SR-CNS			Folder in DREAM
Other fu...		...ndation Platform incl... Interoperab...		...oject... ...oleted	ITF I... ...for a... ...mary TC				Folder in DREAM
H2020	TRA...	...f the... ...ratio... lea... ...cine ...	...17	In... ...n to join the Board of ...holders	Declined				
IMI2	DO-->IT project	Part of... ...Data fo... identifying... ...ressing e... system transfo... ...sed on input fr... ...re systems stakeholders and on...	...17	Invitation to join the International Advisory Board	Liaison with P-PV-SVE (Alison C...	P...	...ongoing		
H2020	ELASTISLET	Development of (i) novel and... ...nd scaffolding systems based on multibiofunctional elastin-like recombinamers (ELRs) for long-term and efficient cell encapsulation	19/06/2017	Stage 2	Sent request for an ITF meeting	D-DS-SIS	...meeting held on 13/06/2017		

2009 - 2017 IMI projects with EMA participation



Resource implications for EMA

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

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)

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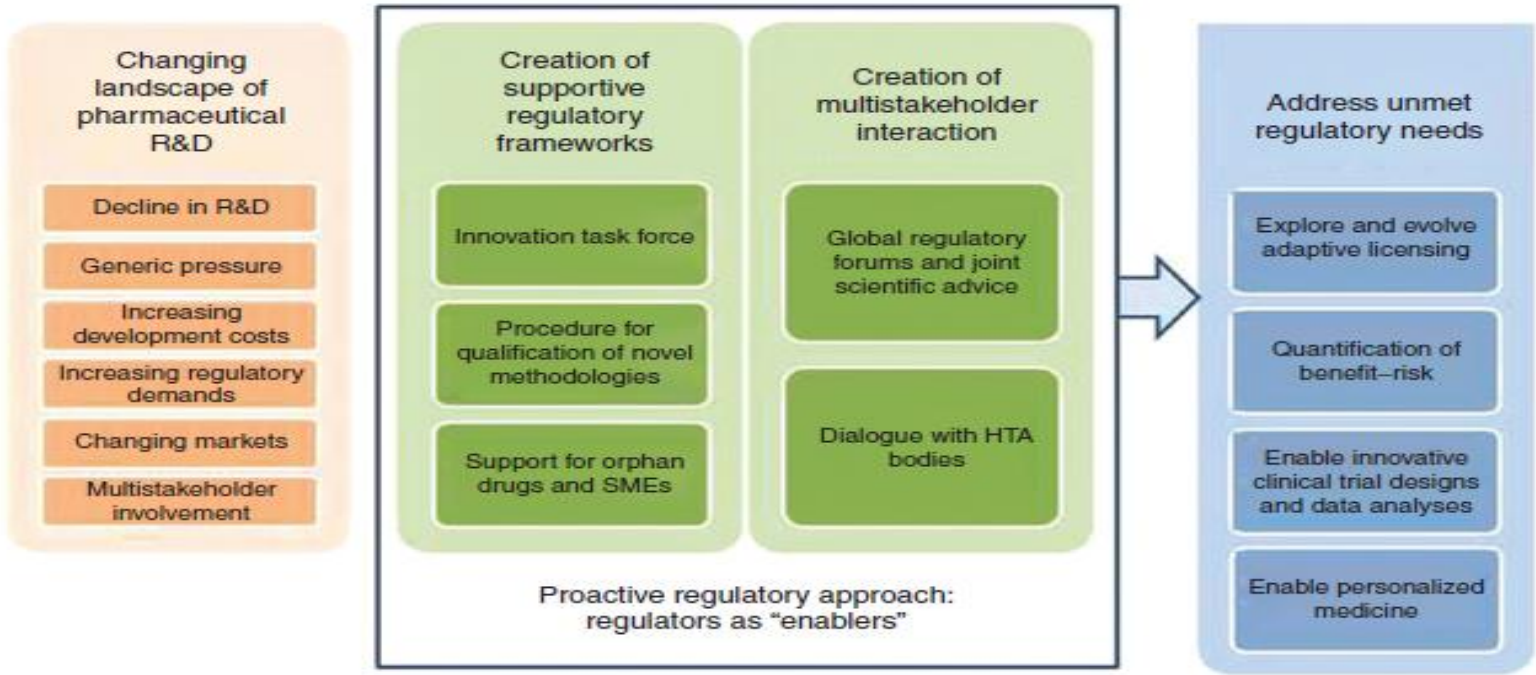
Early interactions on innovation at EMA (ITF)

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

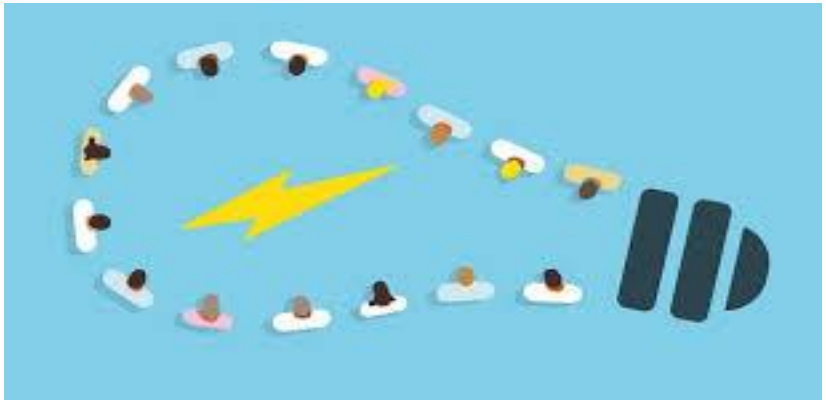
for preparatory dialogue and orientation on

innovative methods, technologies and medicines

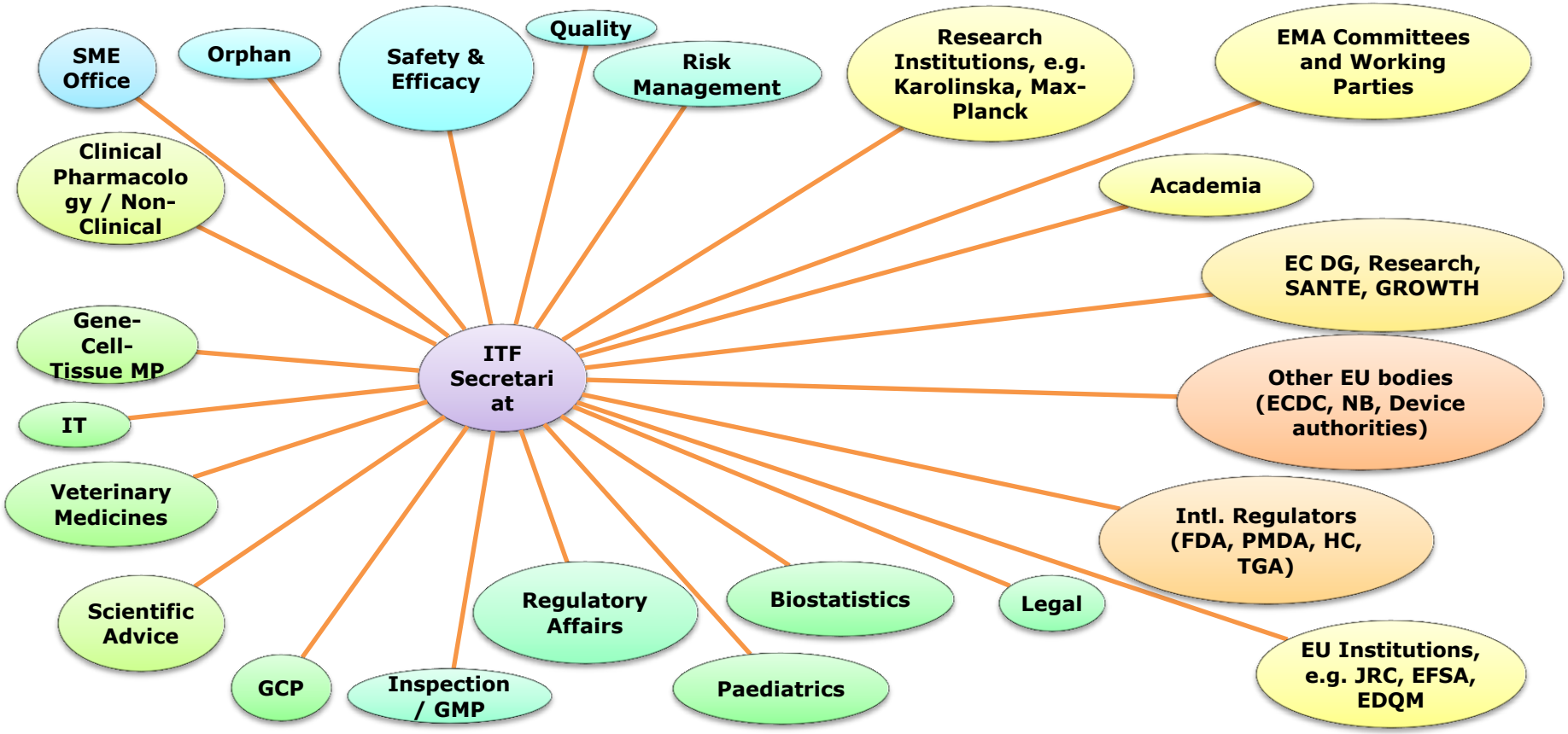
ITF objectives (ASAP):

- **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):



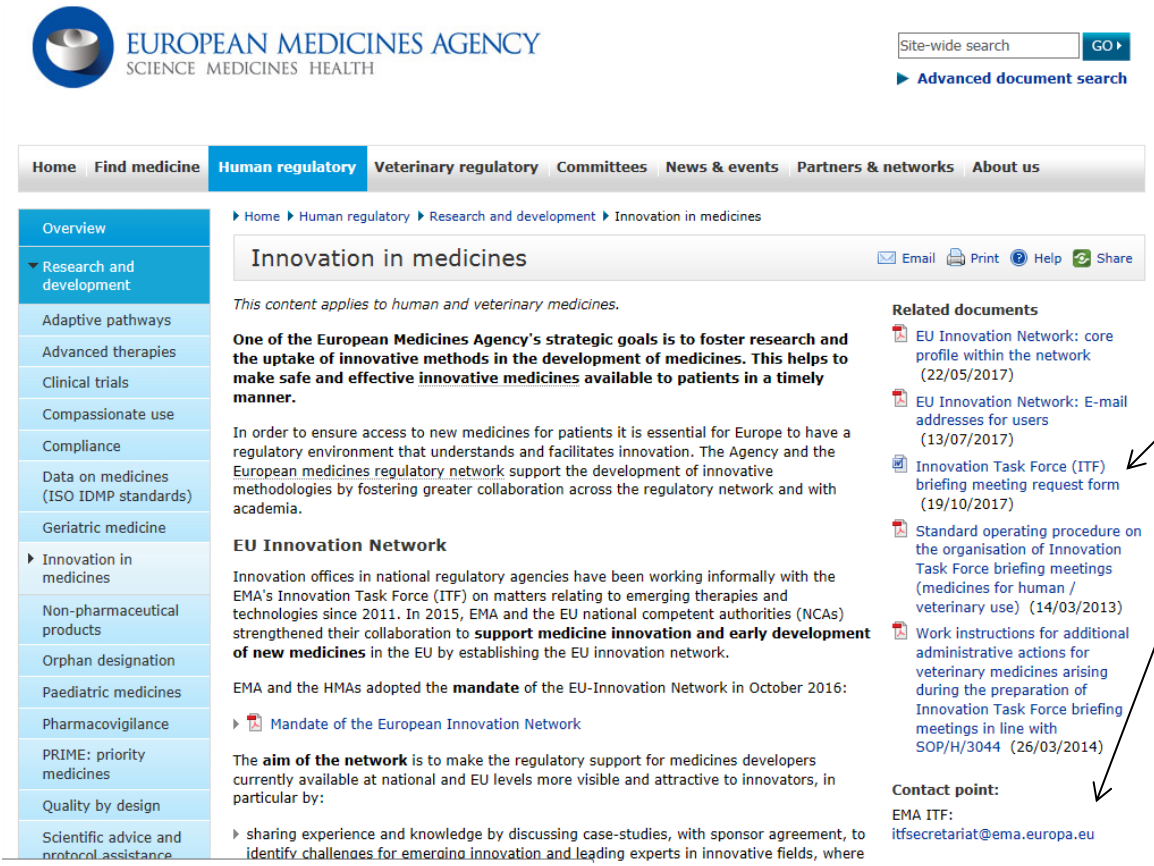
80% of ITF meetings (F2F or webinar → minutes**)** submitted by **consortia, academia and SMEs**

→ **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



- 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

See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9

Contact us at: ITFsecretariat@ema.europa.eu

Acknowledgements: Corinne de Vries

Qualification of Novel Methodologies – A key regulatory tool to facilitate drug development

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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

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10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

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

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

Qualification of Novel Methodologies

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

Design of qualification studies: Diagnostic/Prognostic BMs disease states, -progression, physiological changes, toxicity: **Guideline on clinical evaluation of diagnostic agents**
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003580.pdf

Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions (ICH E16)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003863.pdf

GUIDELINE ON GENOMIC SAMPLING AND MANAGEMENT OF GENOMIC DATA (ICH E18)
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E18_Step2.pdf

Biological matrix sampling, storage and transportation: Reflection paper on pharmacogenomic samples, testing and data handling
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003864.pdf

Analytical platform: EMA guideline on bio-analytical method validation for proteomic markers
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

Statistical principles for clinical trials: Generally follow ICH Topic E9
http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf

Qualification of novel methodologies

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

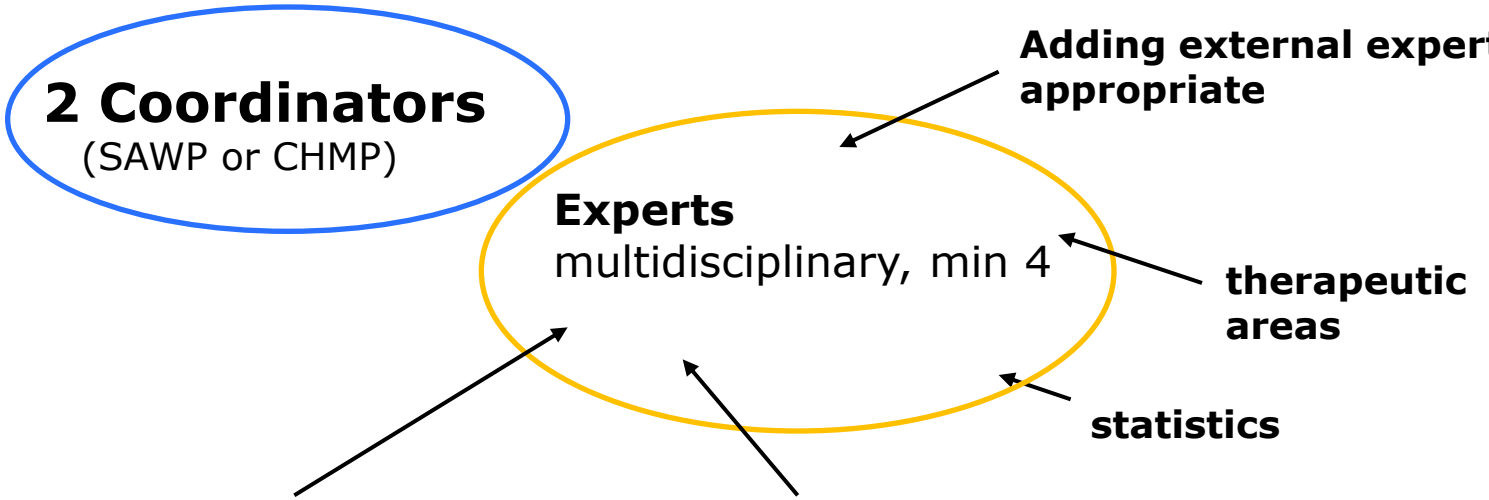
Scientific Advice Working Party (SAWP) –

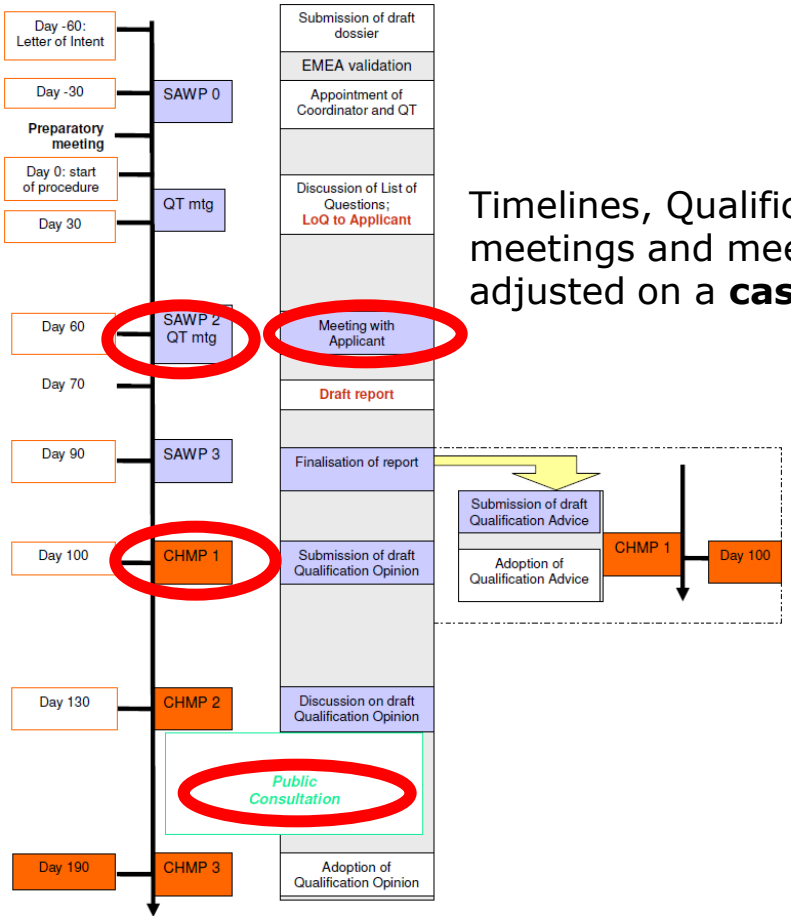
Serves as primary scientific group, allows extensive networking within the Agency (Committees, other working parties and expert groups will be involved as appropriate)

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

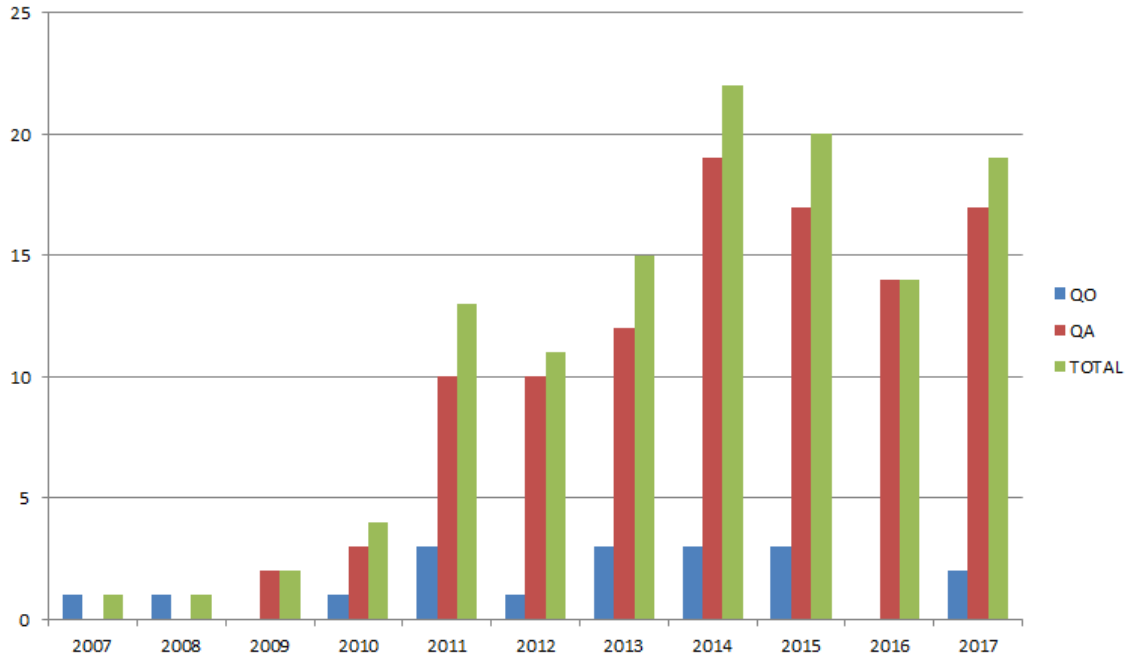




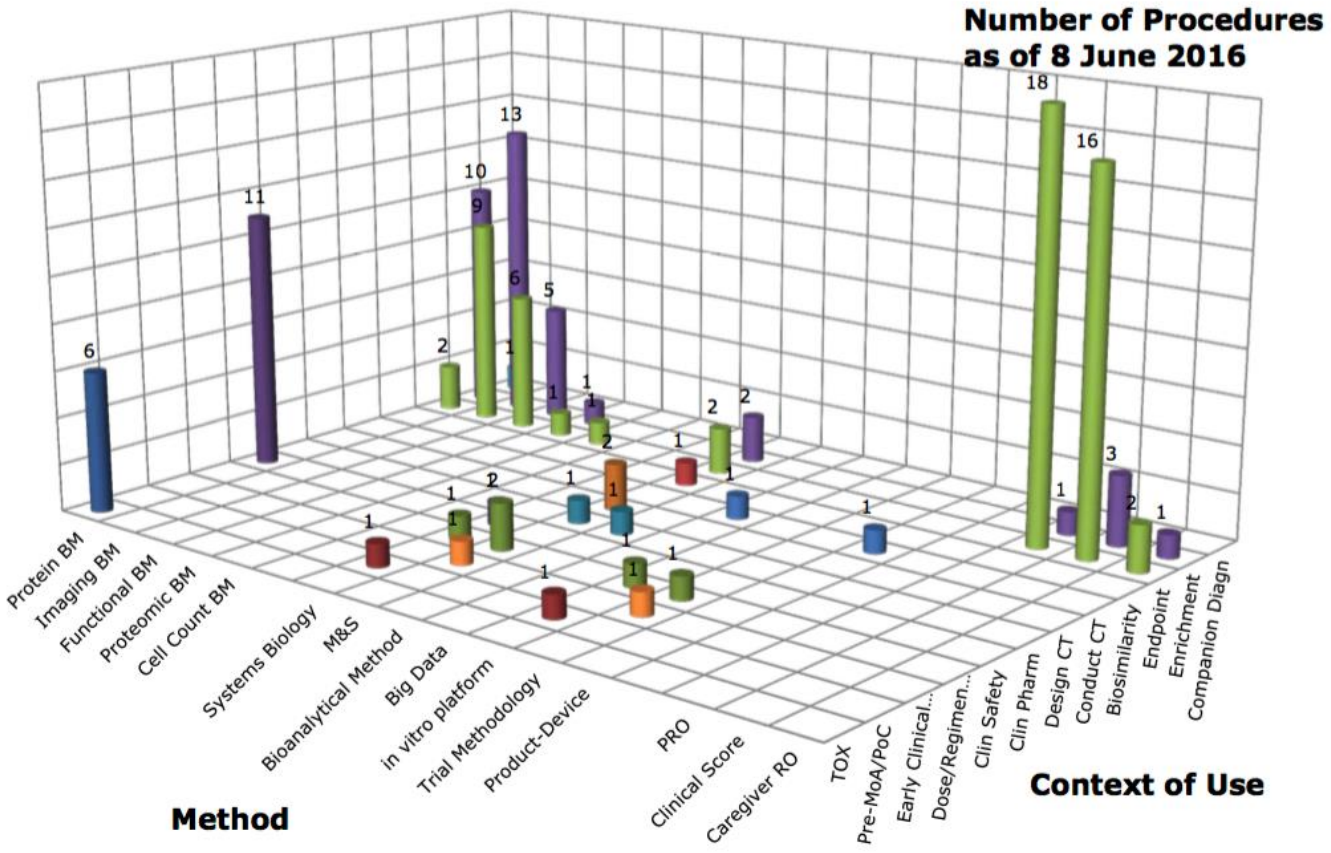
Timelines, Qualification Team (QT) meetings and meetings with applicant adjusted on a **case by case basis**

- **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:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0#section3



18 Qualification Opinion and 104 Qualification Advices finalised to end 2017


Number of Procedures
as of 8 June 2016
Protein BM
Imaging BM
Functional BM
Proteomic BM
Cell Count BM
Systems Biology
M&S
Bioanalytical Method
Big Data
in vitro platform
Trial Methodology
Product-Device
PRO
Clinical Score
Caregiver RO
TOX
Pre-MoA/PoC
Early Clinical...
Dose/Regimen...
Clin Safety
Clin Pharm
Design CT
Conduct CT
Biosimilarity
Endpoint
Enrichment
Companion Diagn
Method
Context of Use

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.

Letters of support

Document(s)	Language	Status	First published
Letter of support for glutamate dehydrogenase, a biomarker of hepatocellular liver injury	(English only)		28/11/2017
Letter of support for drug-induced vascular injury (DIVI) biomarker	(English only)		09/11/2017
Letter of support for drug-induced renal tubular injury biomarker(s)	(English only)		12/01/2017

16 Letters of Support have been issued by end 2017

Qualification Opinions published to date

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

• Paediatric ulcerative colitis activity index (PUCAI)	Disease activity	scale	clinical
• Ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials	compliance	Technology	clinical
• Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD)	Prognostic marker	Prognostic biomarker	clinical
• 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	Treatment outcome	Scale – measuring tool	clinical
• In-vitro hollow fiber system model of tuberculosis (HFS-TB)	Preclinical development	In vitro disease model	Preclinical – drug activity

Qualification Opinions published to date

• MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase-II dose-finding studies under model uncertainty	Dose finding	Modelling technique	clinical
• A novel data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease	Disease activity	Progression biomarker	clinical
• 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	Disease staging	Disease biomarker	clinical
• Low hippocampal volume (atrophy) by magnetic-resonance imaging for use in clinical trials for regulatory purpose in predementia stage of Alzheimer's disease	Disease staging	Disease biomarker	clinical

Qualification Opinions published to date

• Novel methodologies in the predementia stage of Alzheimer's disease: cerebrospinal-fluid-related biomarkers for drugs affecting amyloid burden	Disease staging	Disease biomarker	clinical
• Alzheimer's disease novel methodologies / biomarkers for BMS-708163	Disease staging	Disease biomarker	clinical
• Final conclusions on the pilot joint European Medicines Agency / Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers	Drug toxicity	Prognostic biomarker	clinical
• ILSI / HESI submission of novel renal biomarkers for toxicity	Drug toxicity	Prognostic biomarker	clinical

FDA-EMA parallel Qualification ADVICE

- 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 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

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An overview of EMA initiatives supporting SMEs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

2 SME action plan

3 Recommendations for SMEs

4

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

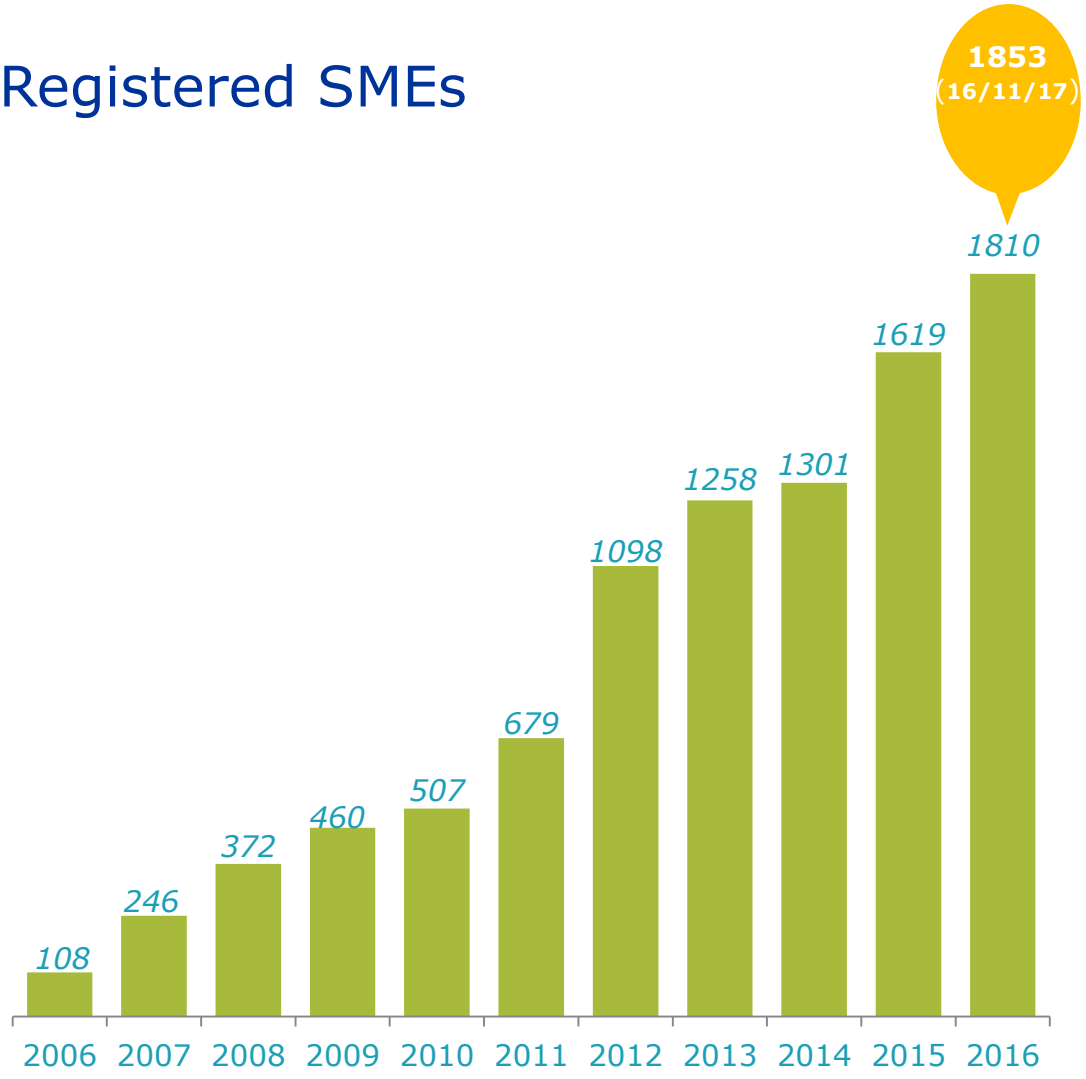
- Assignment of SME status
- Regulatory Assistance & SME briefing meetings
- Fee Incentives
- Translation Assistance
- Training and Awareness
- Partnering & Networking *SME Register*
- Reporting

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

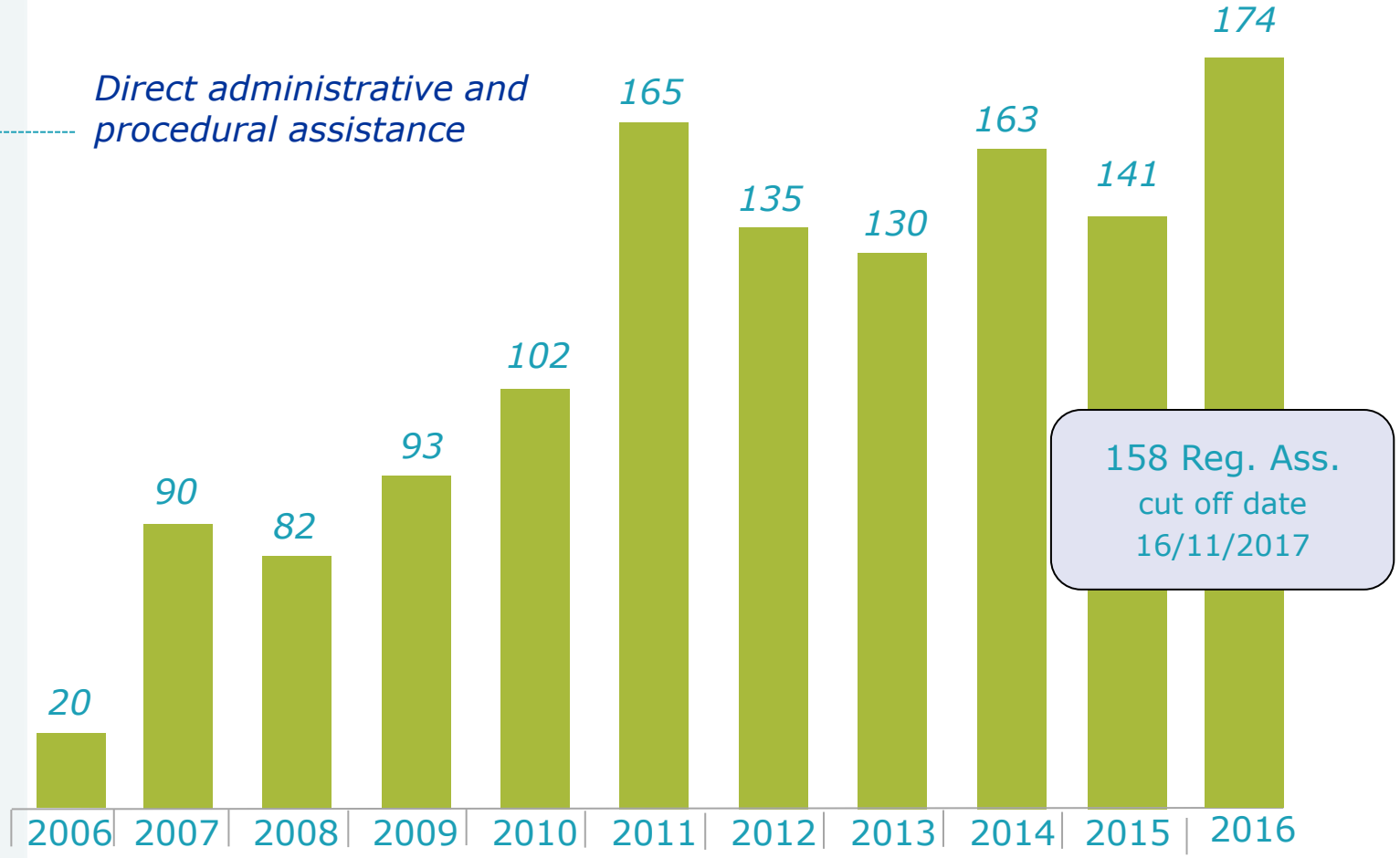
02 Regulatory assistance & SME briefing meetings (1/3)

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



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 and Explanatory note on pharmacovigilance fees payable to the European Medicines Agency

03 SME fee incentives (2/2)

Conditional fee exemption (SMEs)

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

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

Provide training
&
ease the access to regulatory information

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

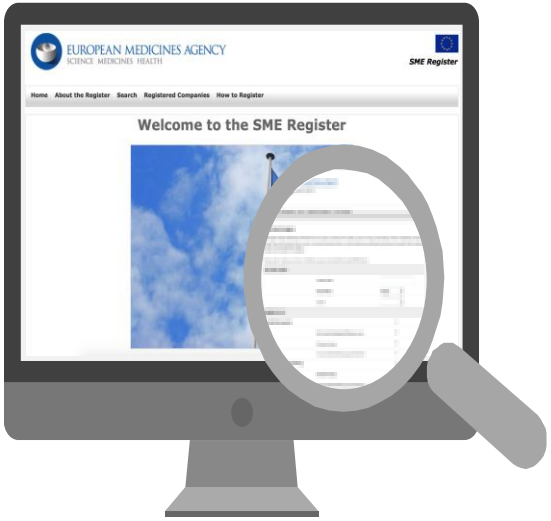
SME User Guide
Updated regularly

06 Partnering & networking

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

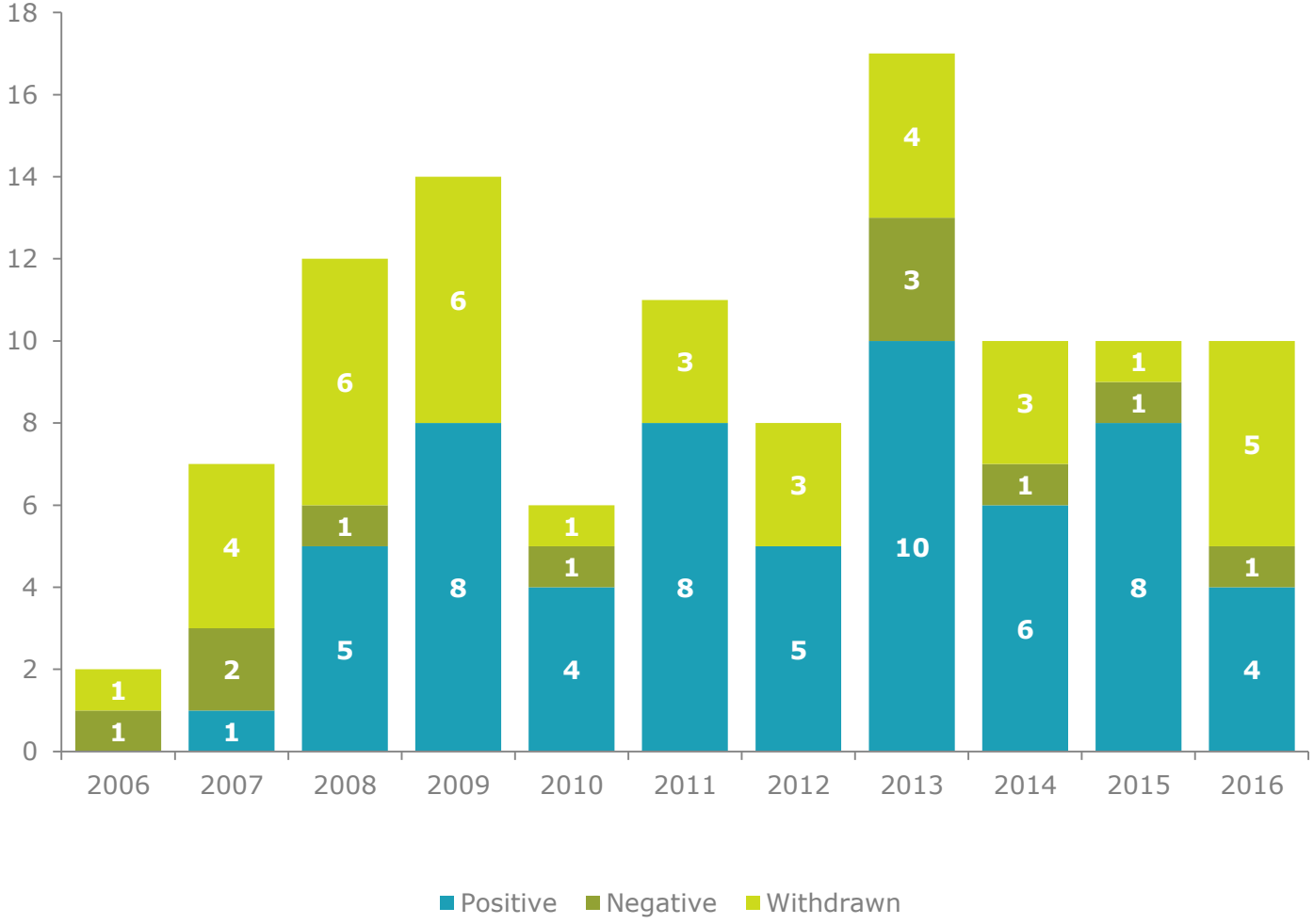
SME Office annual report 2016

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)



SME action plan (2017-2020)

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

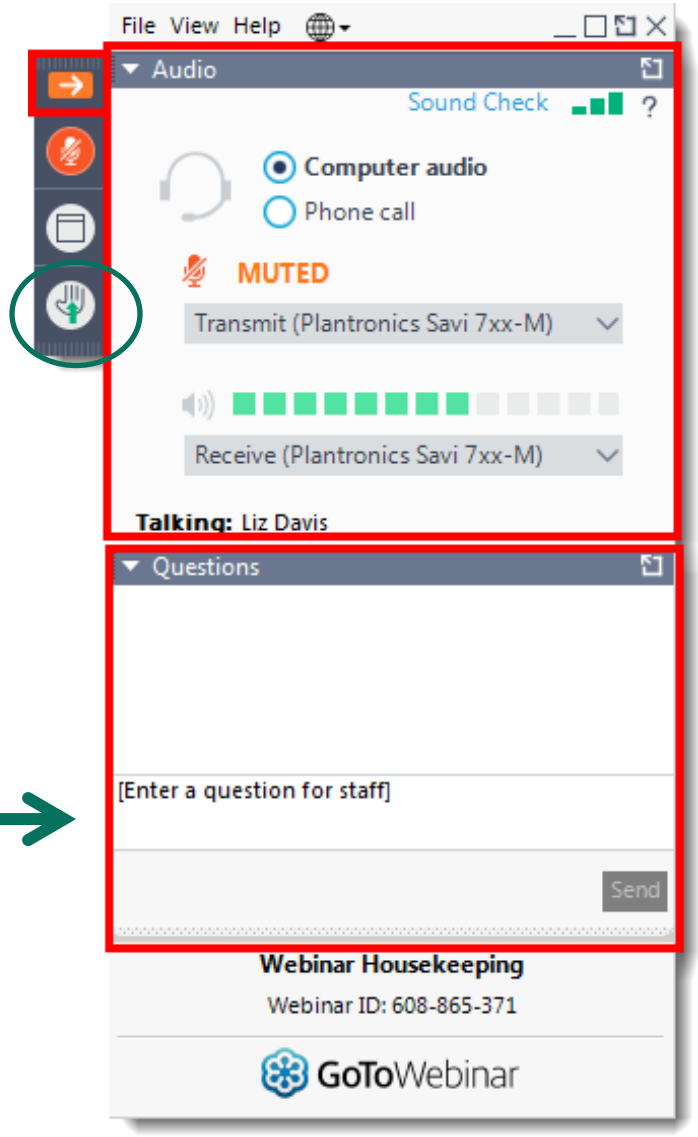
Contact us at: sme@ema.europa.eu

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

innovative medicines initiative

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

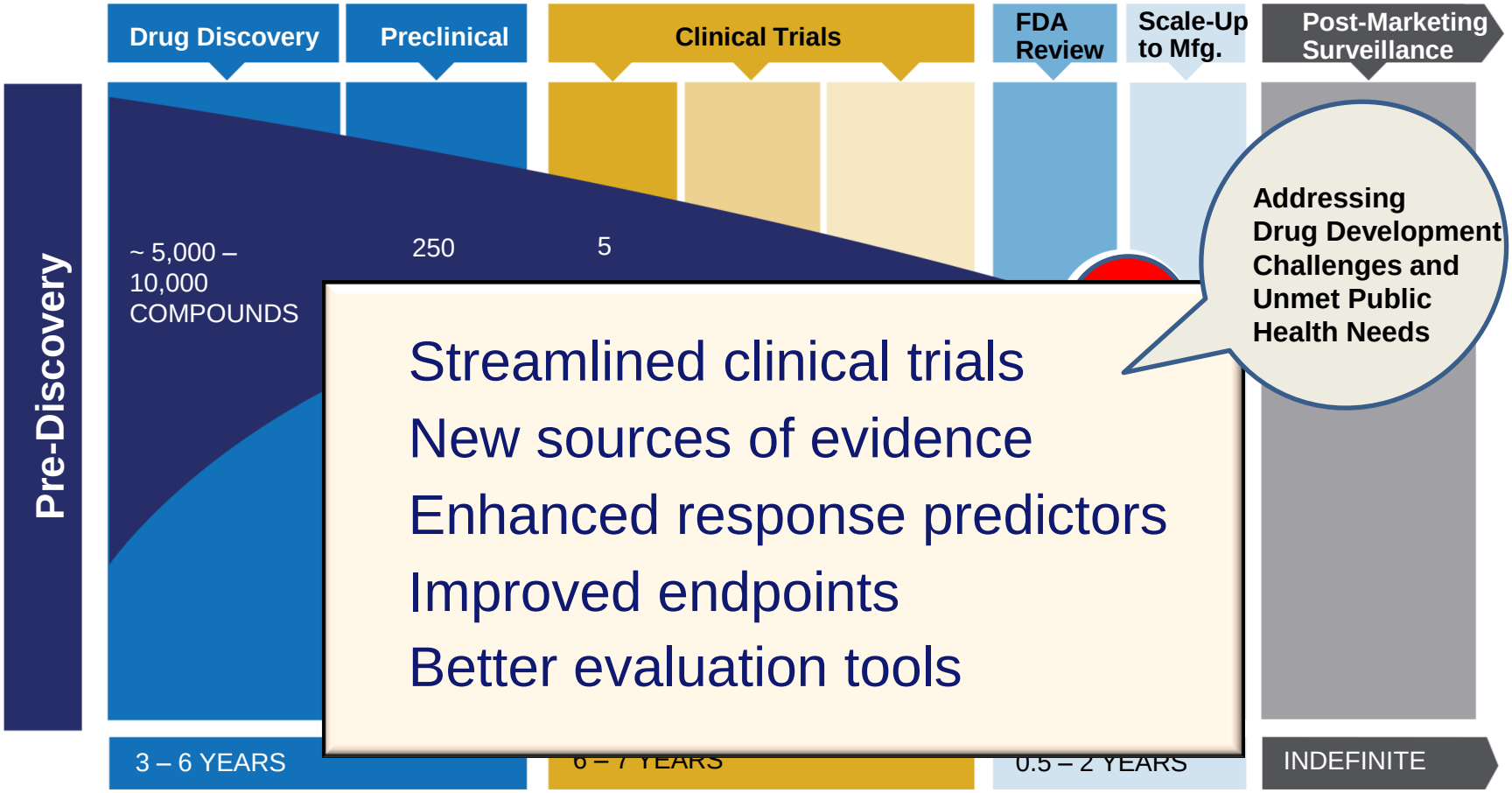
Outline

- 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



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

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

Dr. Woodcock , DIA Global Forum Podcast:
http://www.globalforum-online.org/Nov2017/index.html?page=28&_ga=2.30688056.626922387.1510946833-1209126081.1469475623

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both
Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.
N Engl J Med 2017; 377:62-70July 6, 2017DOI: 10.1056/NEJMra1510062

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

Addressing Drug Development Challenges: Real World Evidence (RWE)

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

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**.

Process/Disease	Objective	Application
Formulation change for modified release dosage forms	Conduct in-vitro in-vivo correlations (IVIVC)	Waive bioequivalence studies
Alzheimer's Disease	Develop disease progression models	Inform trial design
Partial Onset Seizures	Compare exposure and response between adult and pediatric patients	Waive pediatric efficacy studies (>4 yr) for adult-approved products

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**

Drug Development Tools Qualification Programs:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

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

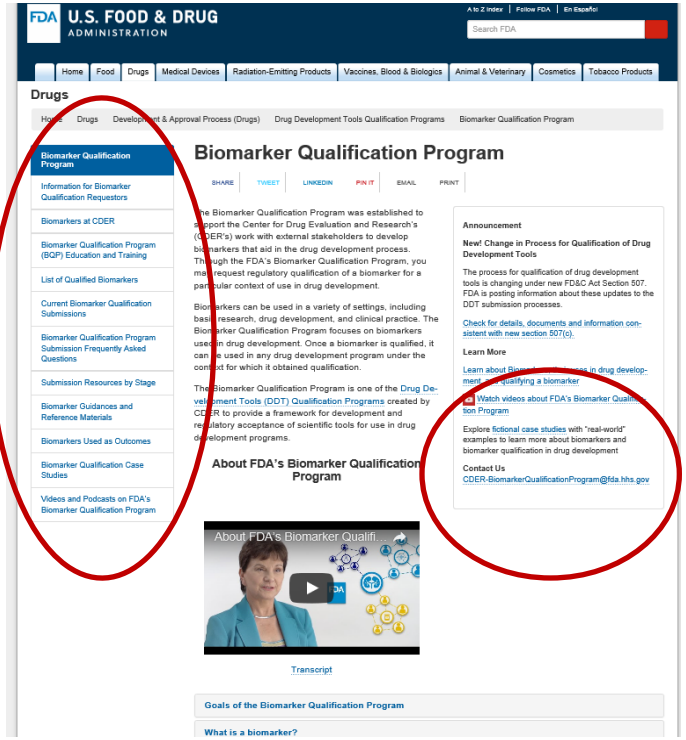
Submission resources by stage

Biomarker Guidances and reference materials

Biomarkers used as outcomes

BQ case studies

Videos and podcasts on FDA's BQP



https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm

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

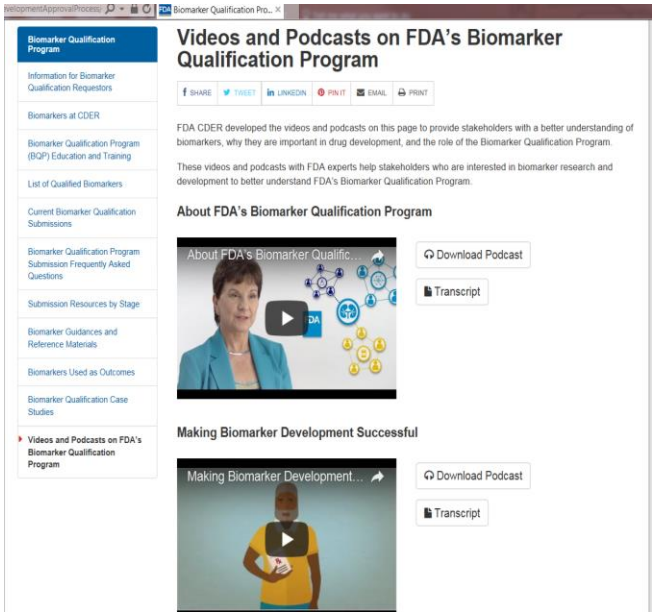
Pathways for Using Biomarkers In Drug Development

What Does Biomarker Qualification Do (and Not Do)?

Opportunities to Engage With the FDA About Qualification During Biomarker Development

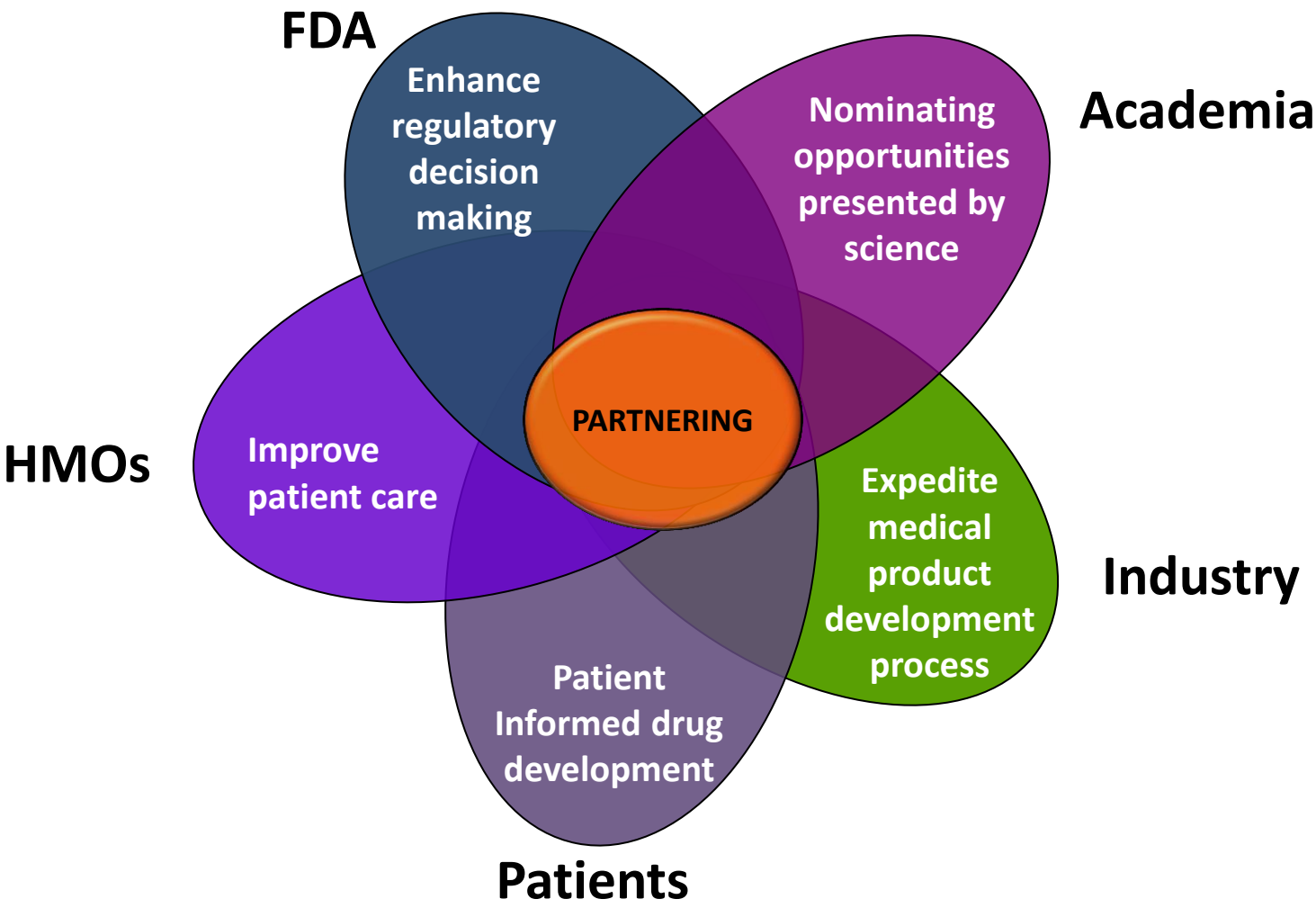
The Biomarker Qualification Process: A Roadmap for Requestors

The Role of Consortia in Biomarker Development and Qualification



https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm558083.htm

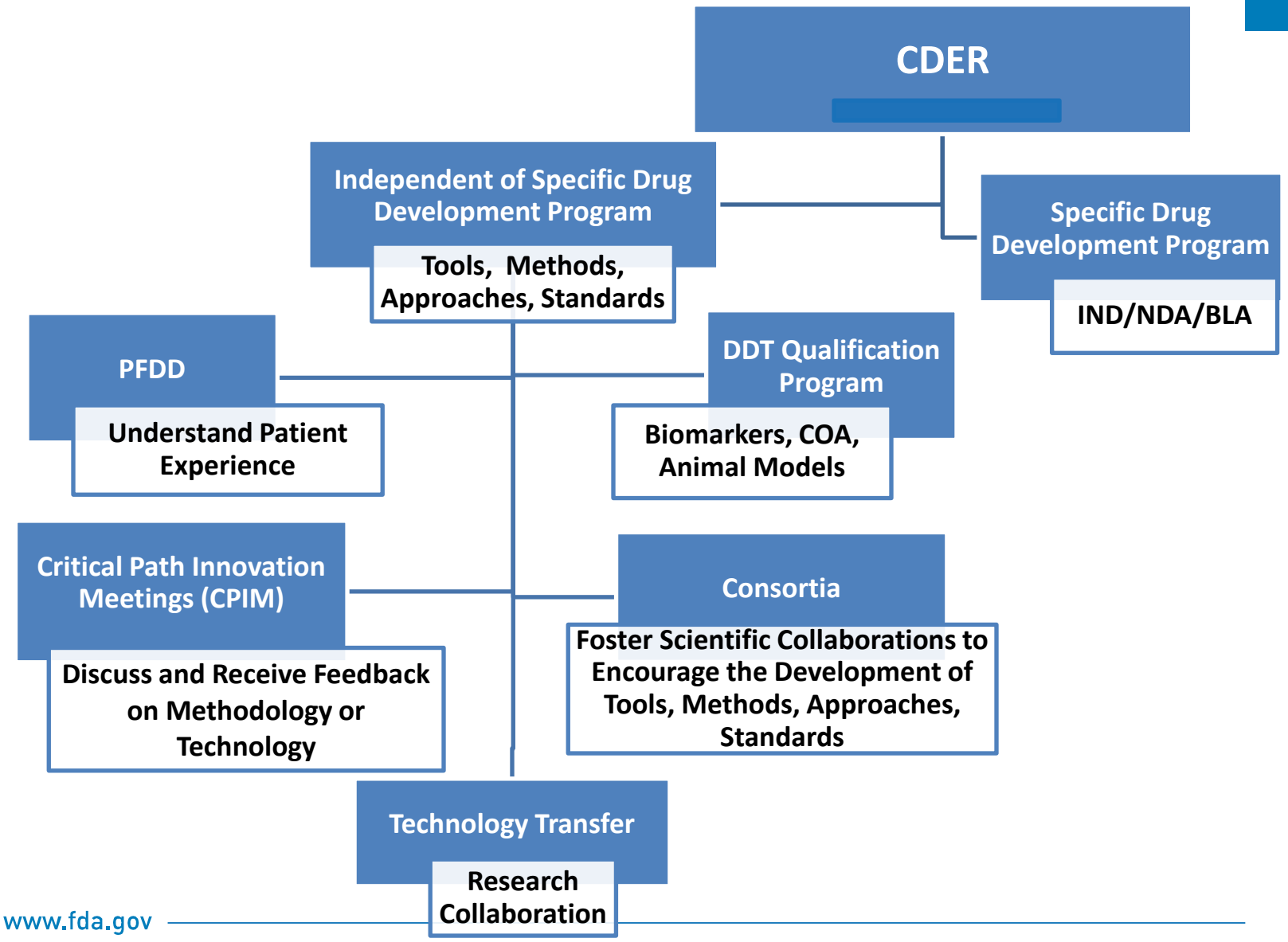
Collaboration is Needed



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

How do you engage with the regulators?

Engagement Opportunities at CDER



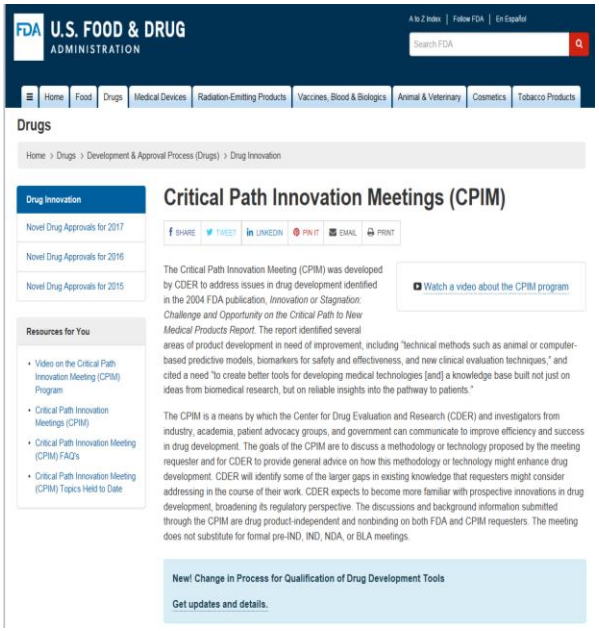
Critical Path Innovation Meeting (CPIM)

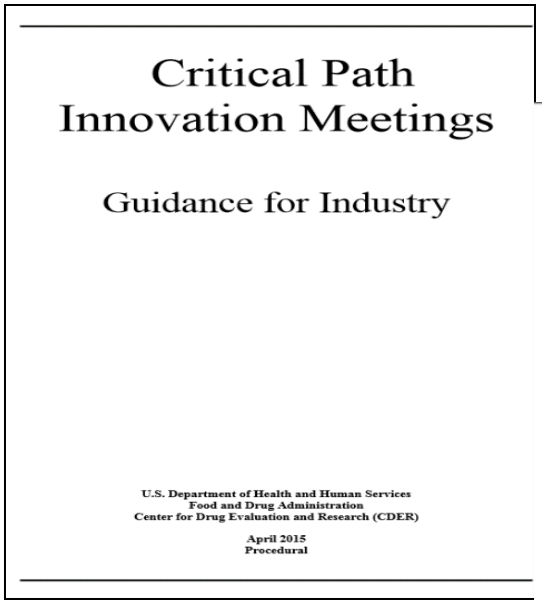
CPIM provides an opportunity for stakeholders to communicate directly with FDA subject matter experts and have an open scientific discussion and exchange of ideas with a common goal of improving efficiency and success in drug development

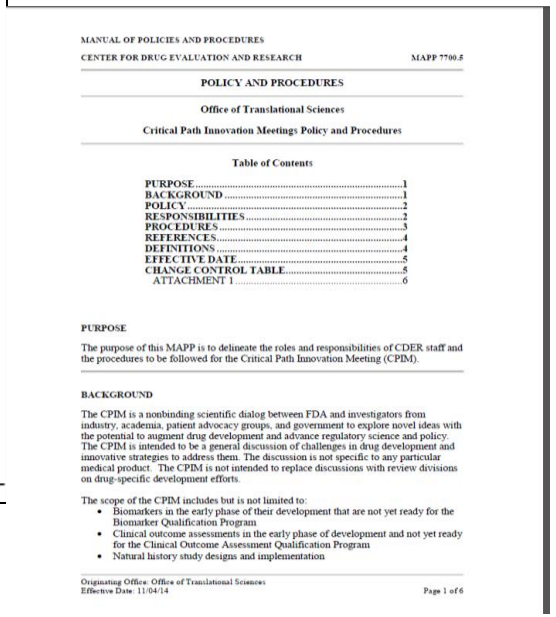
Critical Path Innovation Meeting (CPIM)

- **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



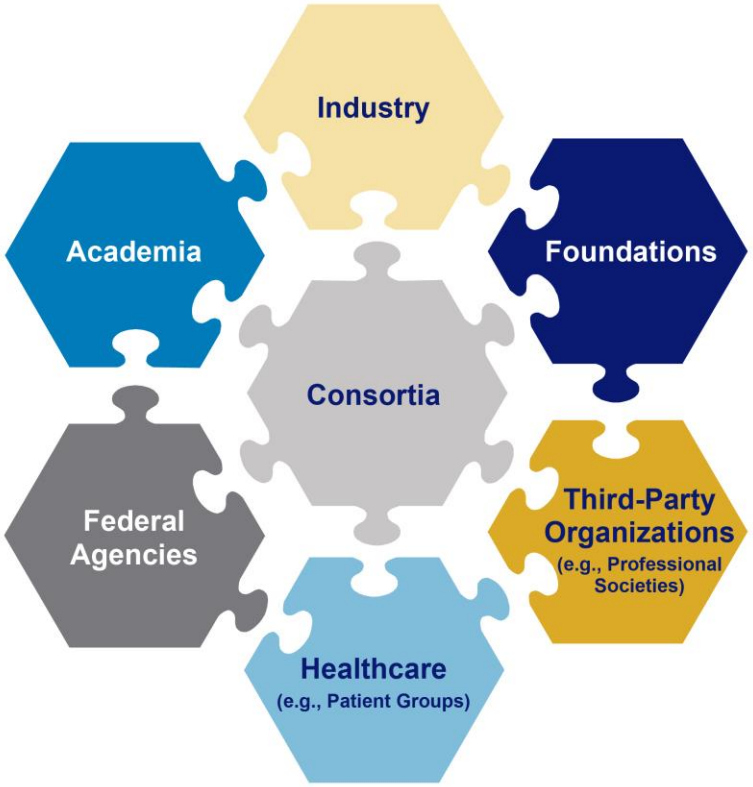




Critical Path Innovation Meetings
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

Consortia

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.



MAPP 4100.2 CDER Staff Participation in PPPs and Consortia

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM532571.pdf

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**.

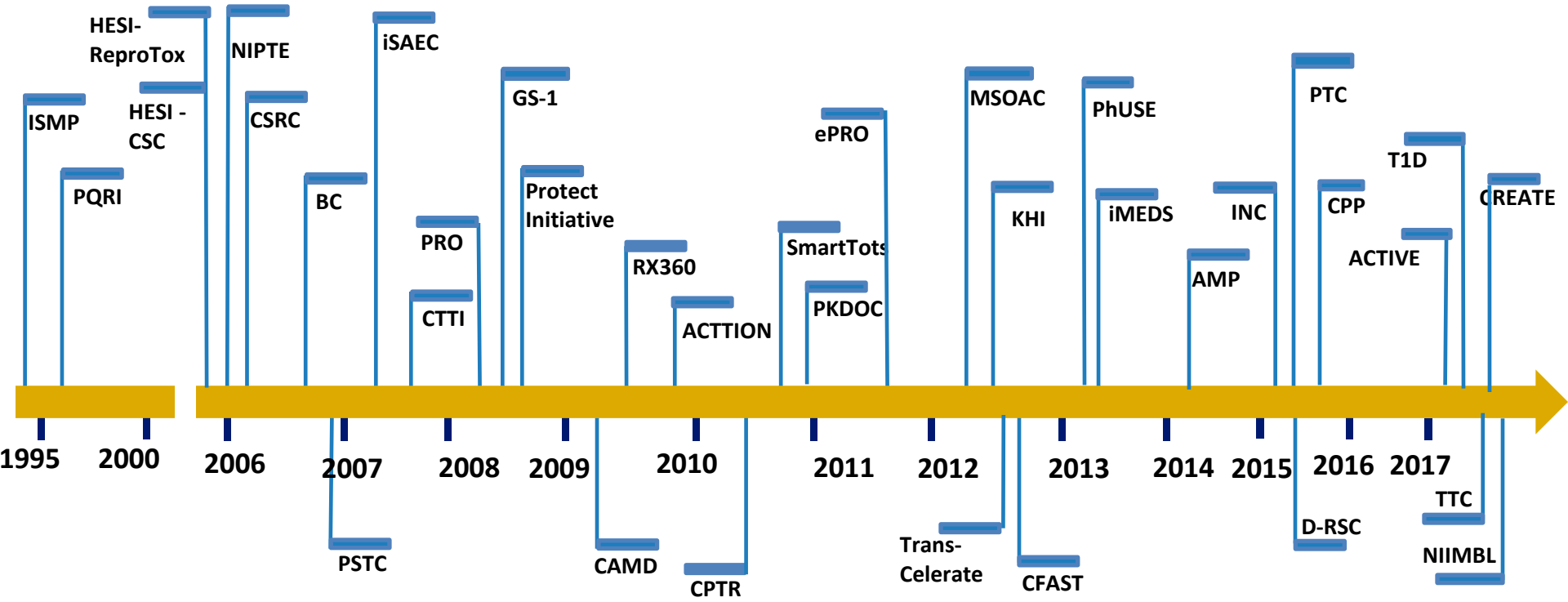
Why is CDER involved with consortia?

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.

Consortia with CDER Engagement



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

Citation: Clin Transl Sci (2017) 10, 431–442; doi:10.1111/cts.12488

REVIEW

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

Kimberly E. Maxfield[1,*], ShaAvhrée Buckman-Garner[2] and Ameeta Parekh[2]

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, in 2006, the Critical Path Opportunities List (CPOL) identified specific priorities to facilitate the CPI vision. Since then, the FDA's Center for Drug Evaluation and Research directed considerable efforts to achieve the goals of CPI and CPOL. Collaborations with Public–Private Partnerships (PPPs) helped address several CPOL 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.[1] 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.[1] To this end, the FDA convened both external stakeholders and FDA scientists to identify research priorities that could guide the FDA to bring focus to specific unmet public health needs. This effort

Topic 2: Streamlining clinical trials;
Topic 3: Harnessing bioinformatics;
Topic 4: Moving manufacturing into the 21st century;
Topic 5: Developing products to address urgent public health needs;
Topic 6: At-risk populations: Pediatrics.

Each of these topics includes a range of specific "opportunities" outlining unmet research area needs, for a total of 76. These opportunities range from broad regulatory science development efforts to targeted research that would address specific gaps in public health in a variety of therapeutic areas, and altogether, aim to advance drug development along the critical path.[2]

Following the publications of CPI and CPOL, the FDA's Centers including the Center for Drug Evaluation and Research (CDER) sought to collaborate with academic institutions, industry, patients groups, nonprofit institutions, foundations, and government agencies to foster the development of tools, standards, and approaches to enhance drug development.[1,3] Several Public–Private Partnerships (PPPs) have formed over the past decade and helped inform the modernization of CDER's regulatory processes and drug development efforts. This article highlights some key deliverables from PPP efforts aimed at the CPI's and CPOL's vision.

PPPs AND CDER ENGAGEMENT

PPPs and precompetitive research

A PPP is a collaboration between multiple stakeholder organizations, including at least one nonprofit or 501(c)(3) organization, to achieve a shared goal that is beyond the capability of any one stakeholder. In drug development, a PPP may be established upon emergence and identification of a public health regulatory or drug development need and can include global collaborations that engage international government entities, academia, industry, patient advocacy groups, nonprofit institutions, and professional organizations. Once established, the PPP members conduct "precompetitive research," whereby stakeholders, who may

Clin Transl Sci (2017) 10, 431-442; 2017 ASCPT
http://onlinelibrary.wiley.com/doi/10.1111/cts.12488/epdf

Process for Requesting CDER Staff Engagement with a Consortium

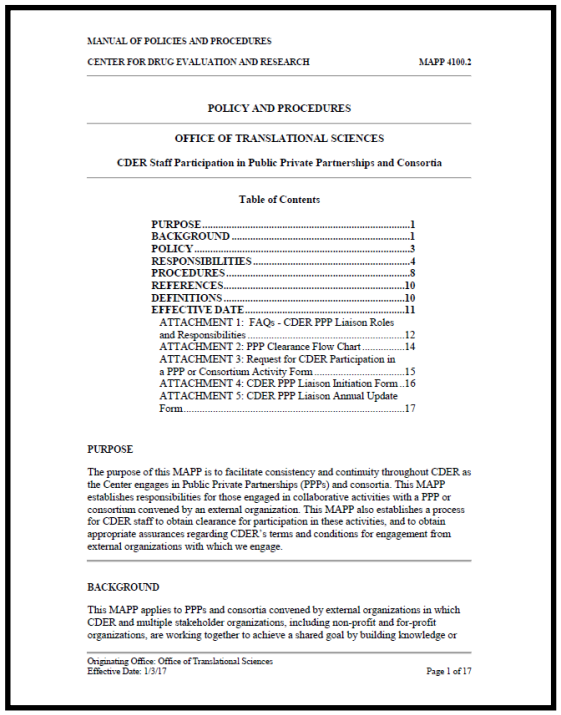
MAPP 4100.2

CDER Staff Participation in Public Private Partnerships (PPP) and Consortia.

Consortia convener requests 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.

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM532571.pdf



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 4100.2

POLICY AND PROCEDURES

OFFICE OF TRANSLATIONAL SCIENCES

CDER Staff Participation in Public Private Partnerships and Consortia

Table of Contents

PURPOSE

The purpose of this MAPP is to facilitate consistency and continuity throughout CDER as the Center engages in Public Private Partnerships (PPPs) and consortia. This MAPP establishes responsibilities for those engaged in collaborative activities with a PPP or consortium convened by an external organization. This MAPP also establishes a process for CDER staff to obtain clearance for participation in these activities, and to obtain appropriate assurances regarding CDER's terms and conditions for engagement from external organizations with which we engage.

BACKGROUND

This MAPP applies to PPPs and consortia convened by external organizations in which CDER and multiple stakeholder organizations, including non-profit and for-profit organizations, are working together to achieve a shared goal by building knowledge or

Originating Office: Office of Translational Sciences
Effective Date: 1/3/17 Page 1 of 17

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

Janet Woodcock

Director, Center for Drug Evaluation and Research,
U.S. Food and Drug Administration

CDER's Janet Woodcock on Consortia –

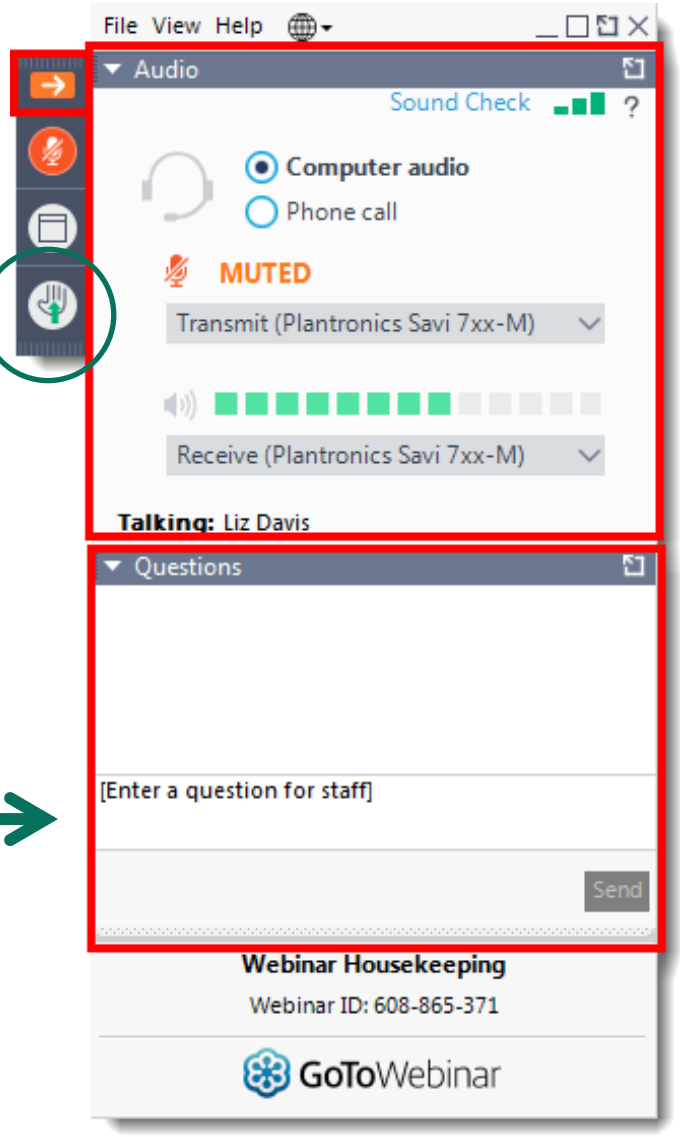
"Facilitating collaborative partnerships among government, academia, industry, and patients groups is arguably the most important role that CDER plays in supporting advancement of drug development and regulation"

J Woodcock. Nature Review Drug Discoveries. 2014 Nov;13(11):783-4.
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

innovative medicines initiative

TAKE HOME MESSAGE

- Use the opportunities for interaction with Regulators

http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

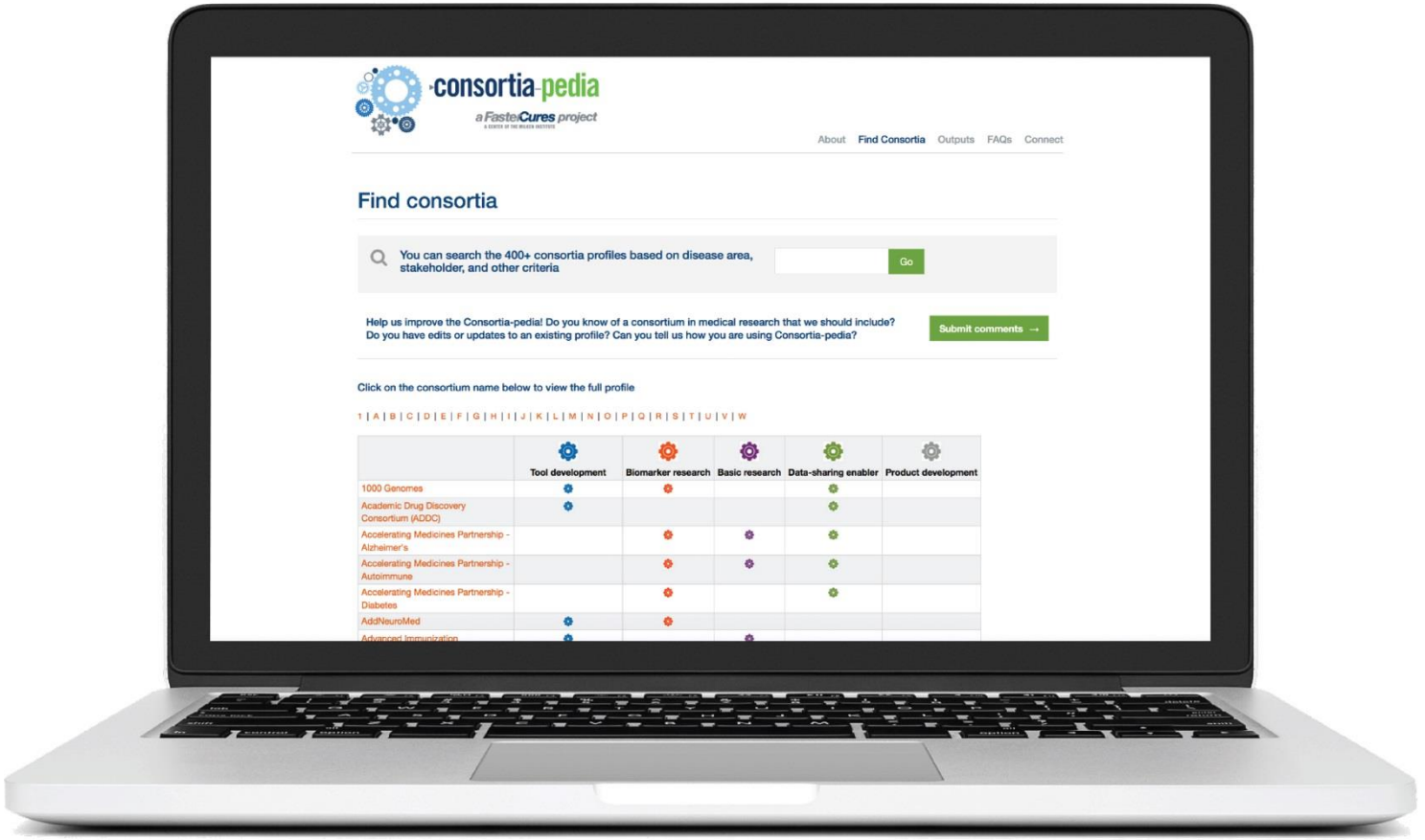
- Plan the interaction in your workplan

- Remember start early!

innovative medicines initiative

FDA back-up slides

FIND CONSORTIA



http://consortiapedia.fastercures.org/

Predictive Safety Testing Consortium (PSTC)

CDER Biomarker Qualification Program

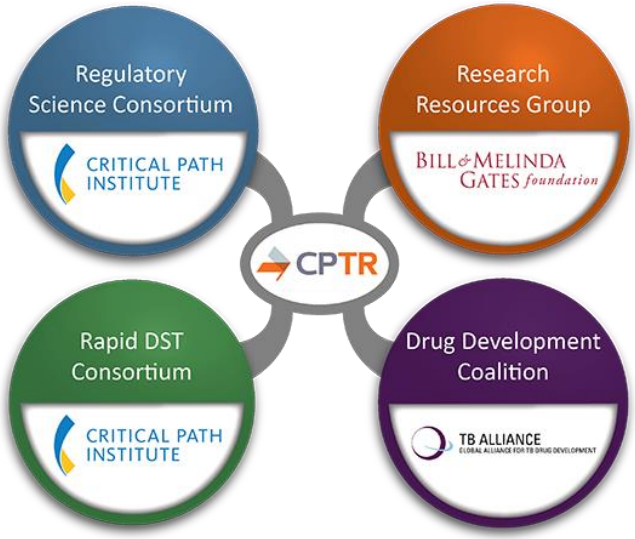
Validation of a biomarker for a specific context of use

1st regulatory biomarker qualification:

7 biomarkers for preclinical prediction of drug-induced kidney injury

www.fda.gov https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm

Critical Path to Tuberculosis Drug Regimens (CPTR)

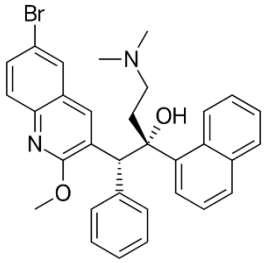


Critical Path to Tuberculosis Drug Regimens (CPTR)

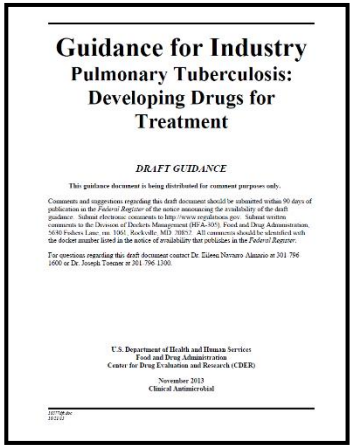
Liquid Culture Model

Accurate testing sputum in resource-poor areas

2012 FDA Approval of Bedaquiline



Incorporated into draft FDA guidance



Guidance for Industry
Pulmonary Tuberculosis: Developing Drugs for Treatment

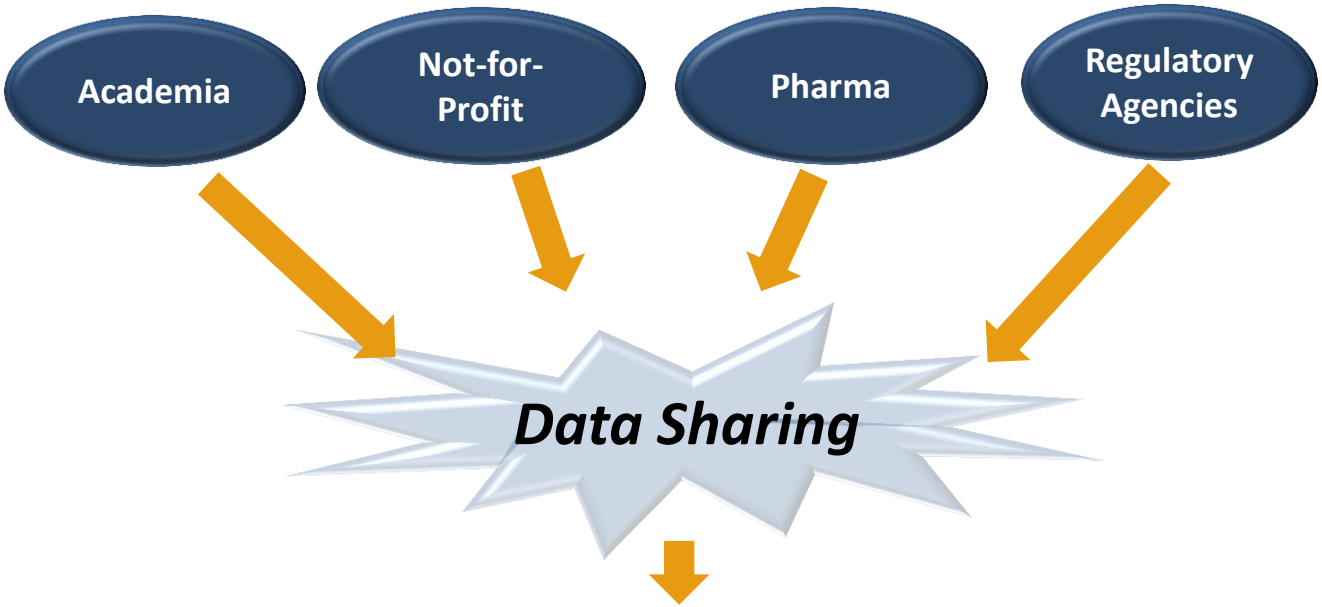
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2013
Clinical Antimicrobial

Coalition Against Major Diseases (CAMD)



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

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm

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

2006 2010 2011 2014 2017

…. 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.

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.

https://blogs.fda.gov/fdavoice/index.php/tag/in-silico-tools/

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