EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance to R&D programmes: Scientific Advice and the PRIME network

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Stiina Aarum on 8 March 2018
Product Development Scientific Support Department

This session:

Scientific advice and protocol assistance – Scope, value and current developments

- Parallel EMA/HTA scientific consultation
- Qualification of novel methodologies and biomarkers
- Modelling and simulation
- PRIME-Legal basis, value and experience so far

The typical long road of bringing medicines to patients

Regulatory provisions targeting the risk of development failure and the time to access:

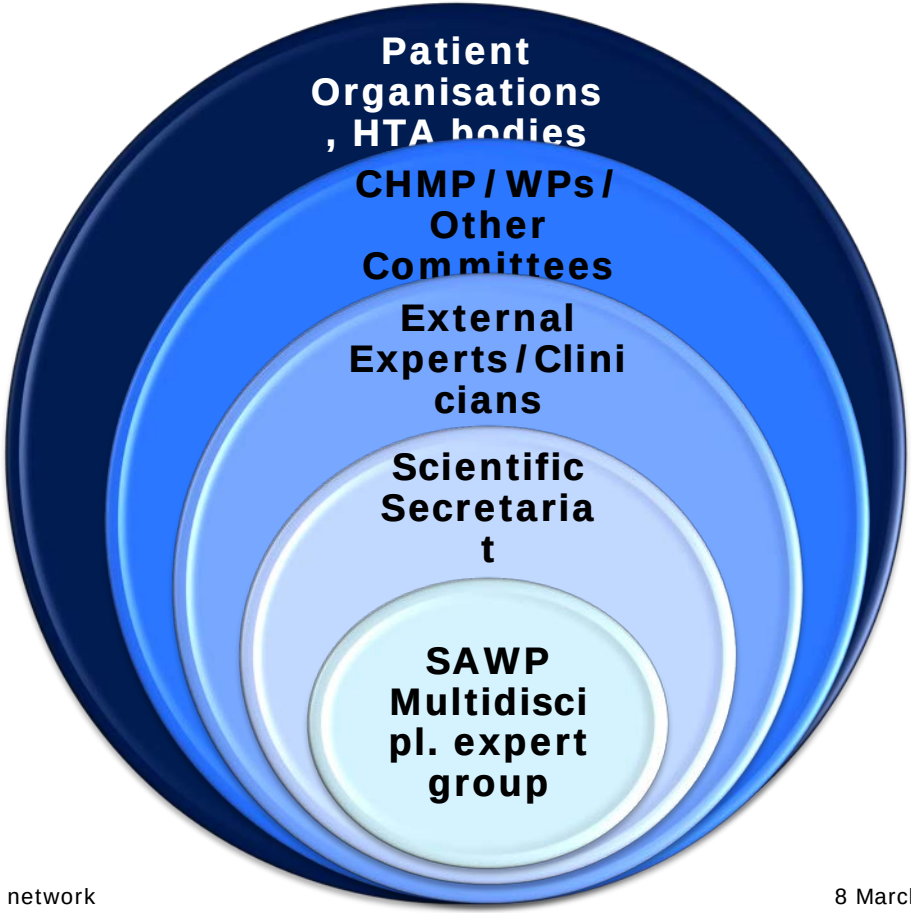
- **Scientific advice**
- Support to small/medium-sized enterprises
- **PRIority MEdicines scheme (PRIME)**
- Conditional marketing authorisation
- Accelerated Assessment
- Compassionate Use

Scientific Advice

- Legal basis: According to Article 57-1 (n) of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004
- One of the tasks of the Agency is "advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products".
- Prospective in nature- focusing on development strategies rather than pre-evaluation of data to support a MAA.
- Advising Applicants on the scientific requirements for marketing authorisation (MA):
  - Before the first MA: companies ask questions on manufacturing, non-clinical and clinical trials, risk-management plans, ways to develop generics, hybrids and biosimilars; significant benefit for orphan medicines; development in children etc.
  - Post-MA: extension of indication to different age groups and stages of the disease; different conditions; & safety aspects.

Scientific Advice Network

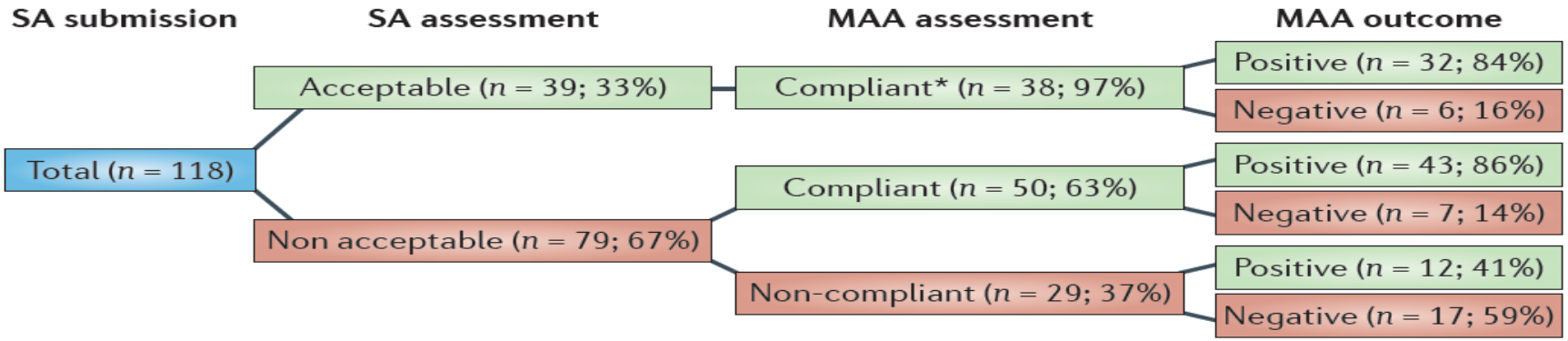
For human medicines, SA/PA is given by the Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP).



Scientific Advice Working Party (SAWP)

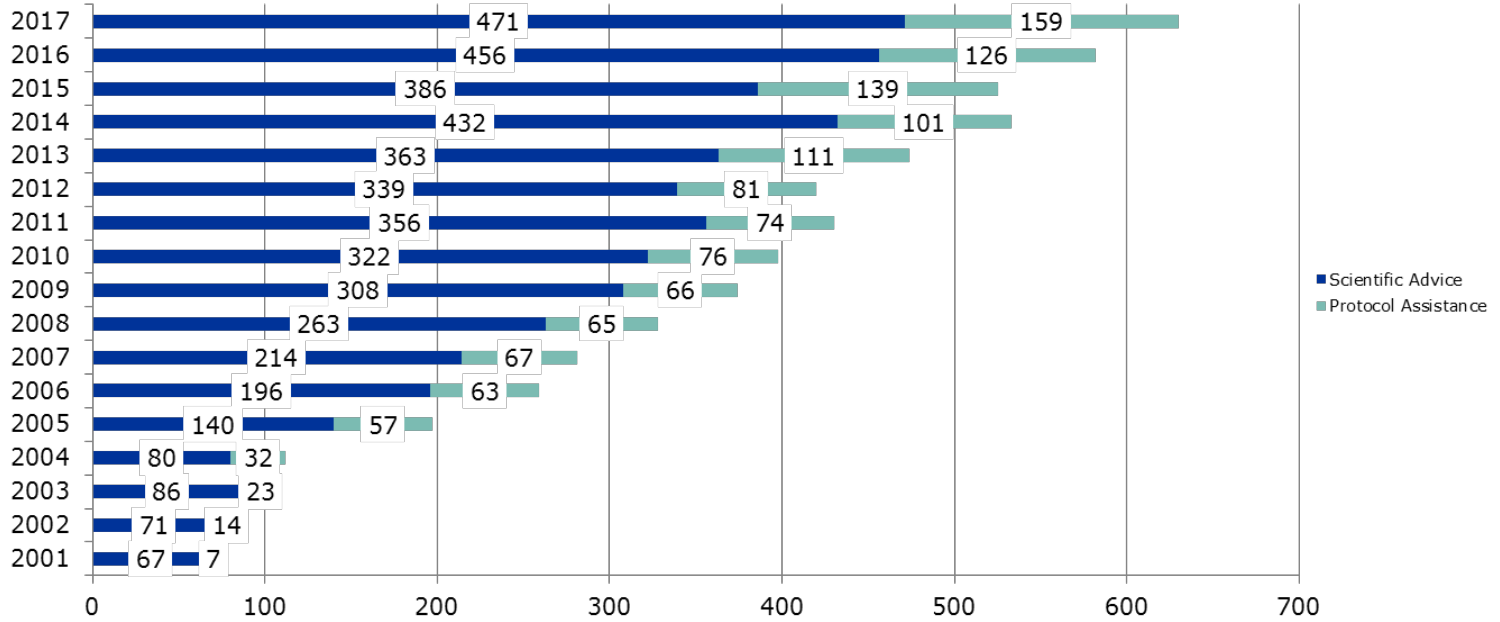
- Experts from national authorities, universities and hospitals selected for expertise: e.g. oncology, cardiology, psychiatry, neurology, immunotherapy, gene and cell therapy, advanced therapies, pediatrics, geriatrics; quality, non—clinical and statistical methodologies.
- Joint members across Committees not only CHMP, but also Paediatrics, Orphan, Advanced Medicinal Products, PRAC
- Scientific and logistic support from EMA secretariat: medical doctors /pharmacists and assistants

SA can help to guide changes in the pivotal clinical development towards improved regulatory acceptability



- Obtaining and complying SA is strongly associated with a positive outcome of a MAA: almost 90% of those who obtain and follow SA receive a positive opinion compared to 40% for those who do not follow SA; *Hofer et al. 2015*

Scientific Advice main activity so far: scientific advice and protocol assistance



Parallel EMA/HTA scientific consultation

Starting point: Newly licensed medicines do not reach all patients in need

Regulators and HTAs

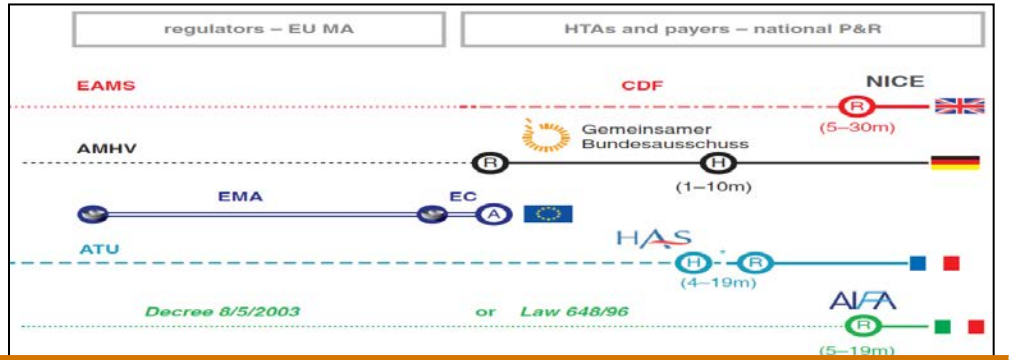
- answer different questions
- have different requirements in terms of evidence

Aim: decision makers come together early to discuss

- the planned development including populations / comparators / design of trial /endpoints
- the requirements for post-licensing evidence generation

Expectation: Optimised development plan ➔ Improve access for patients

Reality check: from EU regulatory approval to national HTA/P&R decisions for oncology products



Drug	Indication	EU MA Approval	Time for HTA/P&R after MA (month)			
bosutinib (Bosulif)	chronic myeloid leukaemia	03/2013	7	7	11	18
vismodegib (Erivedge)*	basal cell carcinoma	07/2013	n/a	7	5	20
cabozantinib (Cometriq)*	medullary thyroid cancer	03/2014	n/a	10	8	n/a

Martinalbo et al., Early access to cancer drugs in the EU. *Ann Oncol* 27: 96–105, 2016

Align regulatory and HTA thinking; what constitutes success?

Tripartite understanding of roles, remits and standards

Common language

Common understanding of methodology

Common understanding of science and methodology; different application?

Evidence generation without undue delay: avoid sequential thinking

Alignment of the perspectives of EU regulators and HTA bodies published: Tafuri et al, Br J Clin Pharmacol (2016):

Studied population, comparator, endpoints, overall package for E and S, other study design characteristics

Qualification of novel methodologies and biomarkers

Vision: Speed up/optimise drug development and utilisation, improve public health

Procedure to guide the development of new more efficient ways to develop drugs, e.g. development of new endpoints for clinical trials

Examples:

- Methods to predict toxicity; IC to enrich a patient population for a clinical trial: Volume of certain brain structures and level of certain biochemicals in the cerebrospinal fluid for trials in Alzheimer's disease
- Surrogate clinical endpoints: new sensitive scales to measure efficacy of a new drug instead of hard clinical endpoints
- Patient and caregiver reported outcomes

Qualification of Novel Methodologies for drug development

CHMP Qualification Advice on future protocols and methods for further method development towards qualification.

CHMP Qualification Opinion on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.

Who can apply? Consortia, Networks, Public / Private partnerships, Learned societies, Pharmaceutical industry.

122 procedures since start in 2008

Modelling and simulation- regulatory value

Early: Enable early informed discussion with sponsors regarding study designs, endpoints, dose regimens, paediatric questions, data needed to support benefit risk decisions

At MAA: Support benefit risk decisions by investigating uncertainties & untested scenarios, and their clinical consequences

Translate benefit risk from the population to individual

Inform SmPC especially for special populations

Support Subgroup analysis

Post Marketing: Inform the contents of the RMP

Lifecycle management of products

Eligibility to PRIority Medicines (PRIME) scheme

Legal base-accelerated assessment

(Recital 33 and Article 14(9) of Regulation (EC) No 726/2004)

Medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation.

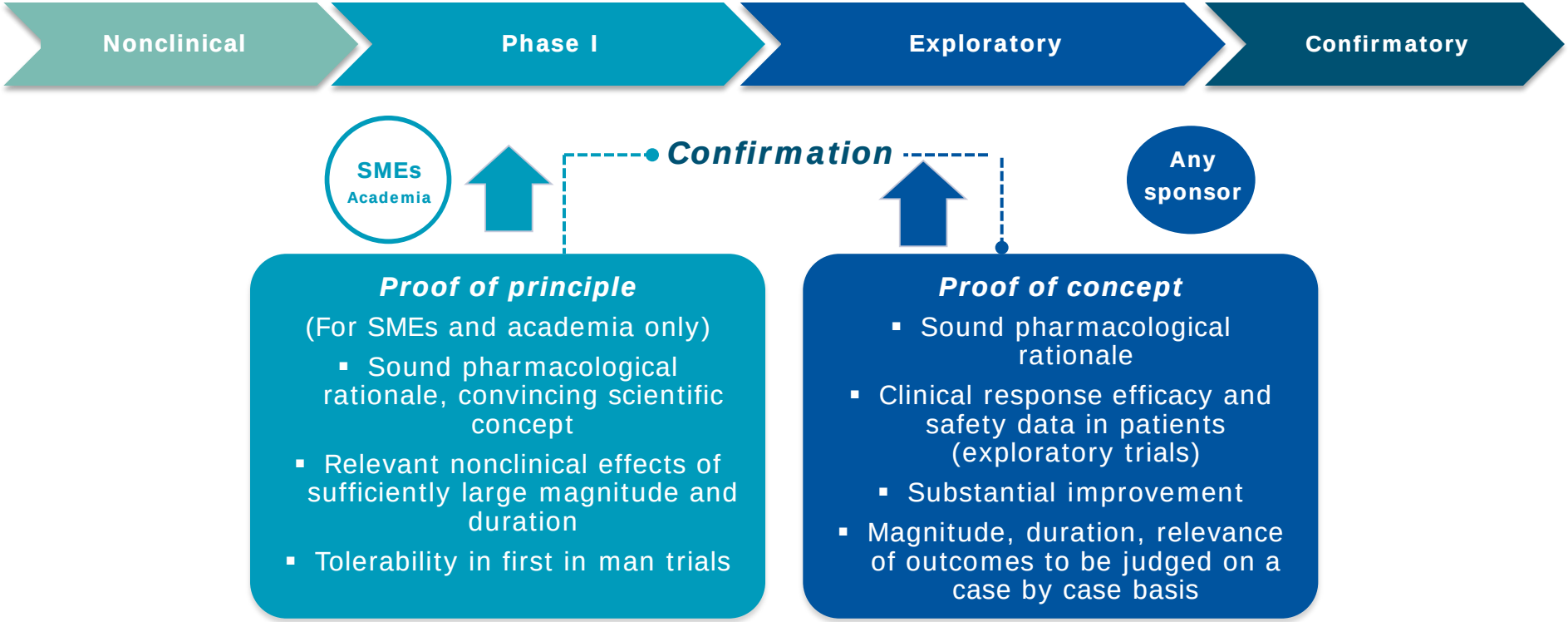
- Potential to address to a significant extent **an unmet medical need**
- Scientific justification, based on **data and evidence** available from nonclinical and clinical development, to address the UMN.

No satisfactory method or if method exists, bring a major therapeutic advantage

Introducing new methods or improving existing ones

Meaningful improvement of efficacy (impact on onset, duration, improving morbidity, mortality)

Entry points PRIME eligibility and required evidence



Features of the PRIME scheme

Early access tool, supporting patient access to innovative medicines.

- **Written confirmation of PRIME eligibility** and **potential for accelerated assessment**;
- **Early CHMP Rapporteur appointment** during development;
- **Kick off meeting** with multidisciplinary expertise from EU network;
- **Enhanced scientific advice** at key development milestones/decision points;
- **EMA dedicated contact point**;
- **Fee incentives** for SMEs and academics on Scientific Advice requests.

PRIME eligibility recommendations adopted by 25 January 2018

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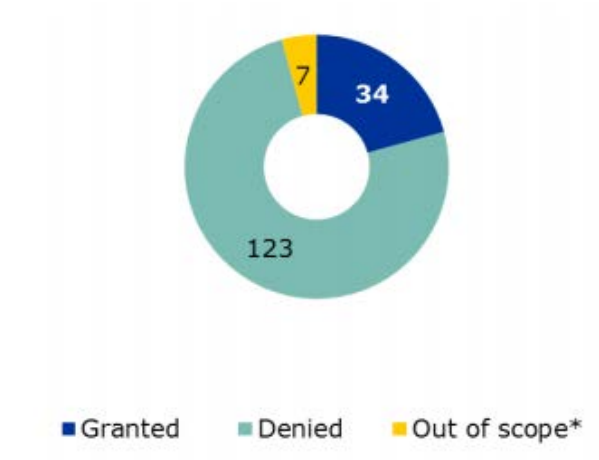
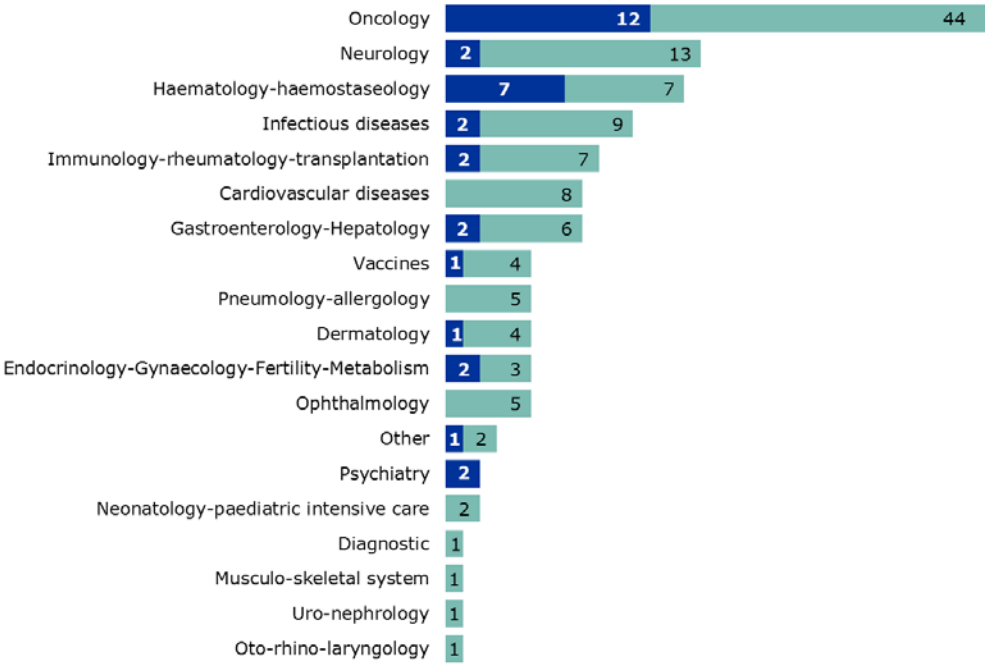
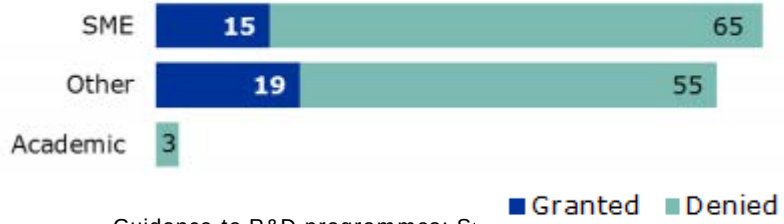


22% success rate

>160 eligibility requests

34 granted*





Take home message- Scientific Advice and PRIME

- **Key tool to promote the collection of robust data on the benefits and risks of medicines**
- **Benefits patients as it promotes the generation of robust data and protects them from participating in badly designed or irrelevant clinical trials**
- **Key platform for our collaboration with health technology assessment (HTA) bodies** which aims to facilitate patients' access to new medicines
- **Central activity to stimulate innovation**
- **Regulatory incentive via PRIME is possible for medicinal products of major public health interest** and in particular from the viewpoint of **therapeutic innovation**

Thank you for your attention

Further information

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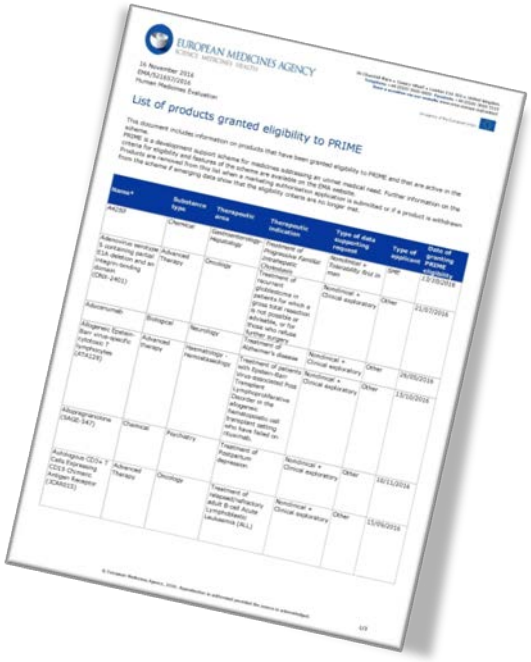
Backup/extra slides

Transparency

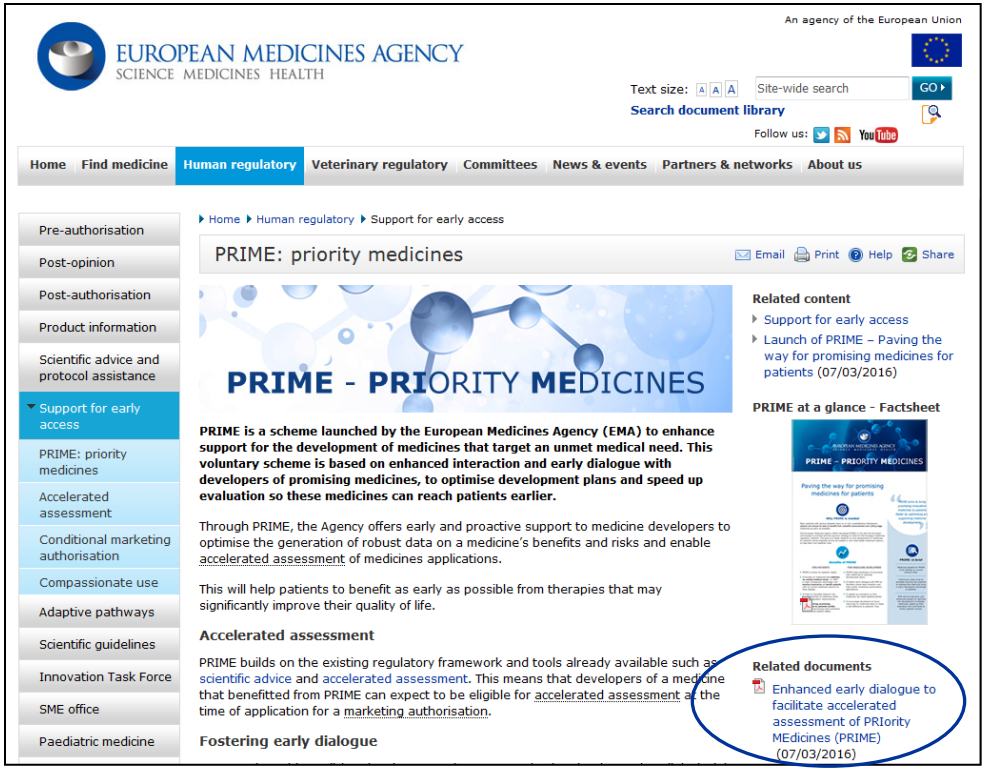
Publication of monthly reports

- Broad characteristics
- Active substance (for eligible products only)
- High-level statistics

List of products granted eligibility to PRIME



PRIME webpage and supporting documents



Factsheet in lay language

Q&A, templates, application form for applicants

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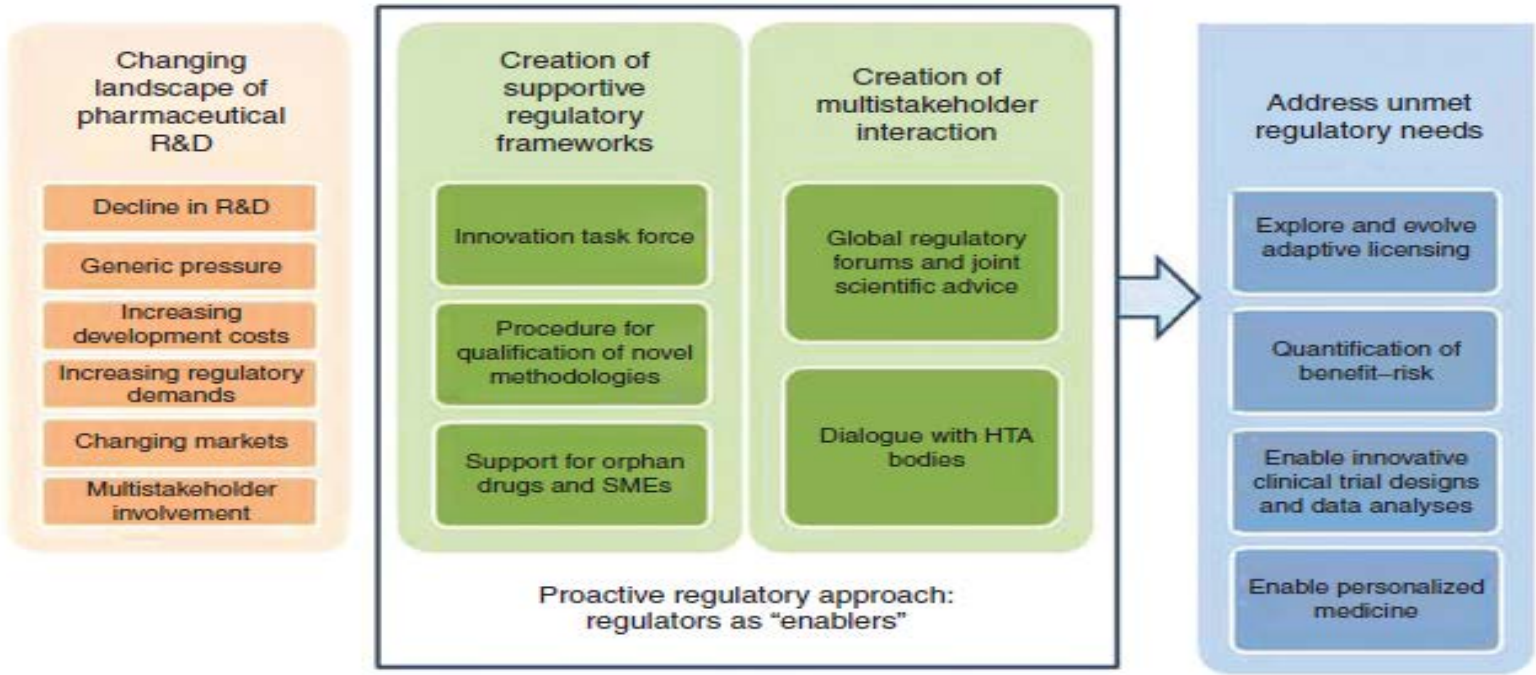
Early engagement in medicine development: The Innovation Task Force (ITF)

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by: Falk Ehmann on 8 March 2018
Science and Innovation Office; Human Medicines Research and Development Support Division; 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**

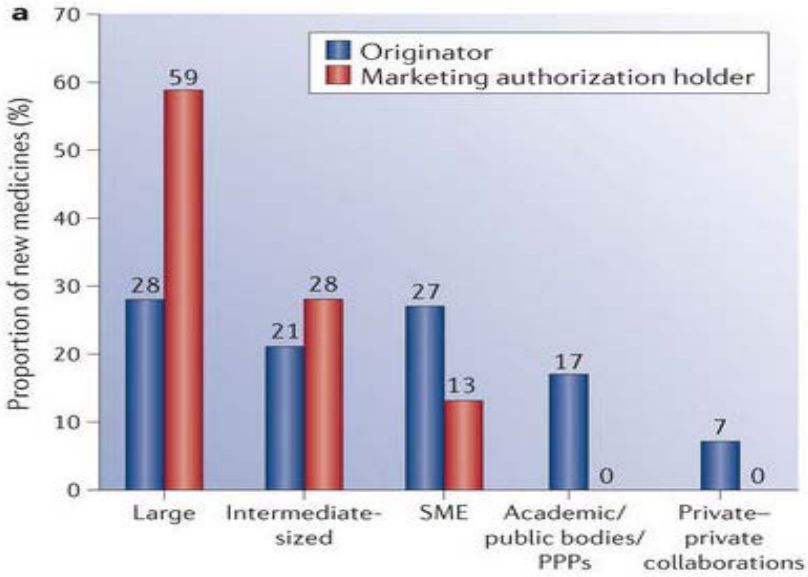
innovative methods, technologies and medicines

ITF objectives (ASAP):

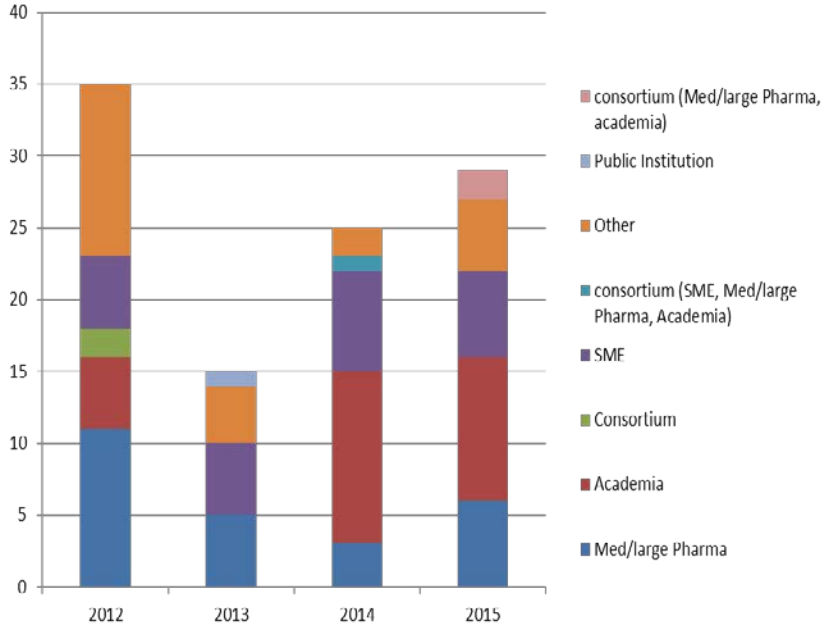
- **Assist Knowledge exchange** on innovative strategies involving **regulatory network**
- **Support drug development** via early dialogue on
  - **Scientific, legal and regulatory** issues
  - Products, **methodologies and technologies**
- **Address the impact of emerging therapies and technologies** on current regulatory system
- **Preparing for formal procedures**

Users of the Innovation Task Force

Originator and the marketing authorization holder for 94 approved products evaluated, divided according to organization type



Regulatory watch: Where do new medicines originate from in the EU? Nature Reviews Drug Discovery Volume: 13, Pages: 92–93; Published online 31 January 2014



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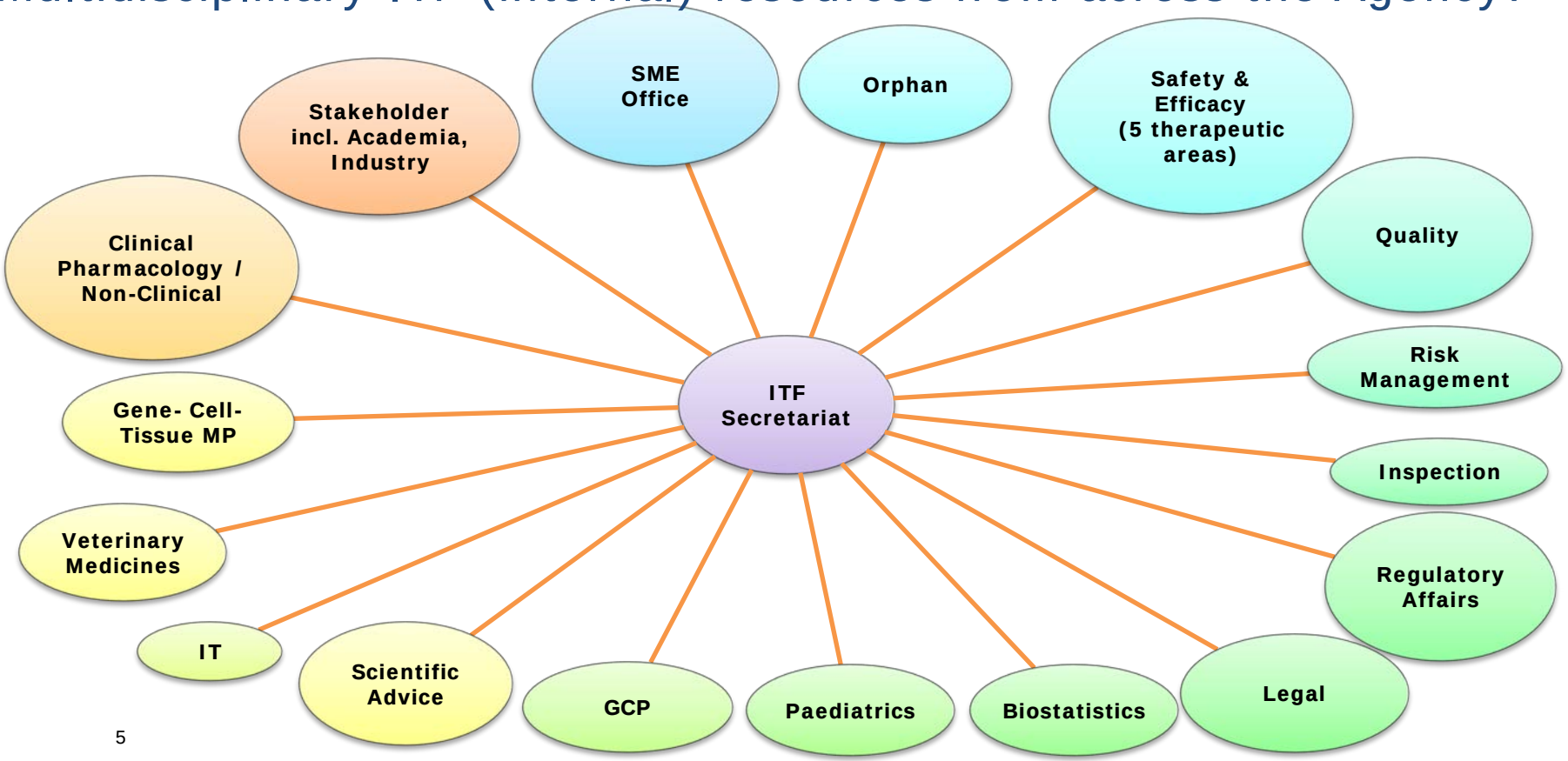
ITF users 2012-2015

Multidisciplinary ITF (internal) resources from across the Agency:



ITF (external) ITF resources from EU and beyond:

- EU **regulatory network i**ncluding **Committees, WPs and experts**
- **Research and other EU Public Institutions** (Karolinska, Italian Nano Centre, Max-Planck, Frauenhofer)
- **EU Institutions** e.g. Joint Research Centre, EFSA, ECHA, EDQM, DG Research, -Sante, -Growth
- Expertise from International Regulators, e.g. FDA, PMDA/MHLW, HC, Swissmedic, TGA
- International Institutions (US-Nano Characterisation Laboratory, Mayo Clinic)
- Other bodies within the EU (ECDC, Medical device authorities)

Main tasks of the Innovation Task Force (ITF)

- Coordination of ITF briefing meetings
- ATMP classification review
- Art. 57 Scientific Opinion

→ With focus on:

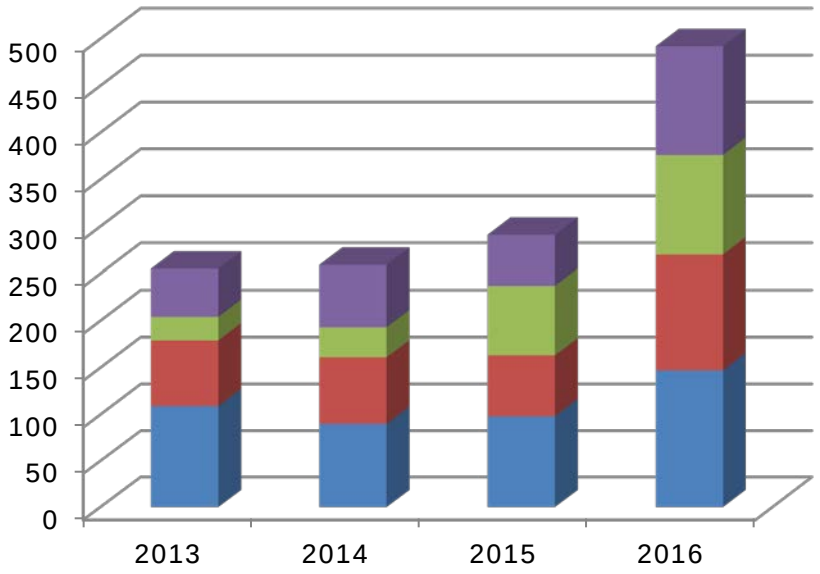
Emerging therapies and technologies

e.g. Nanomedicines, Synthetic Biology, Epigenetics, Biomaterial, Health technologies (e- and m-health)

Borderline and combination products

e.g. devices, cosmetics, food

Involvement in ITF Briefing Meetings (internal and external):



Year of meetings	2013	2014	2015	2016
Number of meetings	23	27	33	41
ITF attendees	51	66	54	116
EMA attendees (non ITF)	25	32	74	106
WP experts from EU Regulatory Network	70	71	65	123
Industry attendees	109	90	98	147
Total	255	259	291	492

Impact of Innovation Task Force on other EMA procedures:

92 ITF Briefing meetings organised between 2014 – 2016, of which **80%** were submitted by **academia, SMEs and consortia** (ITF support focus)

- 15% are Advanced Therapies (Gene, Cell, Tissue engineered products)
- 14% consider seeking EU Orphan Drug designation (rare diseases)
- 20% consider interaction with the EMA Paediatric Committee (PDCO)
- 30% of applicants consider applying a formal scientific advice request
- 11% consider Qualification of methodology (e.g. Biomarker qualification)
- 10% consider Marketing Authorisation Application within foreseeable future

ITF Outcomes: Intel gathering and dissemination

ITF Briefing meetings and minutes ATMP classifications Art. 57 opinions

- ITF-BM **Tracking database** as constant tracking and intel gathering tool
- Annual **intelligence gathering including stakeholder consultation**

- Monthly briefing and **feed-back** provided **to CHMP** and **other Committees**
- **Trainings organised (internal and external)**
- **Awareness sessions broadcasted** via EU-NTC
- Recommendations for the organisation of **workshops, expert meetings**
- Recommendations for **Drafting guidance**
- **Input in Horizon Scanning and EU Innovation Network**

Take home messages

- Regulators became gatekeepers and enablers
- The EMA is open to discuss scientific, regulatory and technical aspects of innovative developments
- The ITF is the Regulator's tool for informal early engagement and feed-back

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

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PHARMACEUTICAL SCIENCES

LABORATORY OF PHARMACEUTICAL BIOTECHNOLOGY

The role of the academic experts in Scientific Advice

Prof.Dr.Apr. Dieter Deforce

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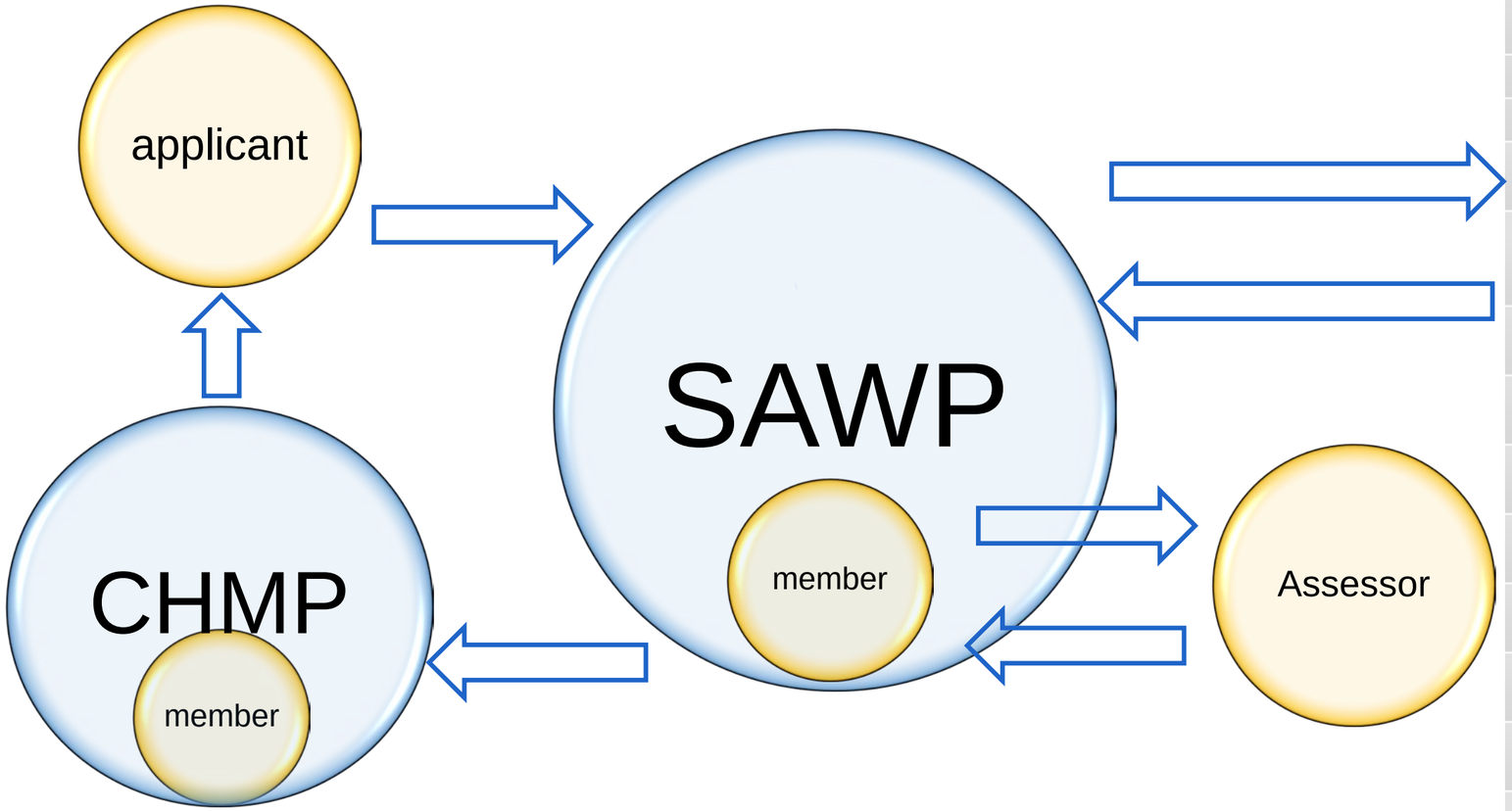
ROLE OF ACADEMIC EXPERTS



- Working parties and other groups
  - CHMP
    - Biologics Working Party
    - Patients' and Consumers' Working Party
    - Healthcare Professionals' Working Party
    - Quality Working Party
    - Safety Working Party
    - Scientific Advice Working Party
    - Biosimilar Medicinal Products Working Party
    - Biostatistics Working Party
    - Blood Products Working Party
    - Cardiovascular Working Party
    - Central Nervous System Working Party
    - Excipients Drafting Group
    - Gastroenterology Drafting Group
    - Infectious Diseases Working Party
    - Inter-Committee Scientific Advisory Group on Oncology
    - (Invented) Name Review Group
    - Oncology Working Party
    - Pharmacogenomics Working Party
    - Pharmacokinetics Working Party
    - Radio-pharmaceuticals Drafting Group
    - Respiratory Drafting Group
    - Rheumatology / Immunology Working Party
    - Vaccines Working Party
    - Scientific Advisory Group on Cardiovascular Issues
    - Scientific Advisory Group on Anti-infectives
    - Scientific Advisory Group on Diabetes / Endocrinology
    - Scientific Advisory Group on HIV/Viral Diseases
    - Scientific Advisory Group on Neurology
    - Scientific Advisory Group on Psychiatry
    - Scientific Advisory Group on Vaccines
    - Working Group on Quality Review of Documents
    - Expert Group on 3Rs
    - Active Substance Master File Working Group
    - Geriatric Expert Group
    - SmPC Advisory Group
    - Modelling and Simulation Working Group

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ROLE OF (ACADEMIC) EXPERTS

- **As member of the SAWP**
- **As assessor**
  - **Conflict of Interest**
- **As member of CHMP**
- **As member of Working parties and other groups**

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MEMBERS

- **Academic Experts and Non-Academic Experts and in-between**
- **Experts in different fields:**
  - **Quality: biologics and non-biologics**
  - **Non-clinical**
  - **Clinical**
  - **Statistics**

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ASSESSORS

- **Internal experts:**
  - **Staff National Agencies**
  - **Some also clinical appointments**
  - **Some also academic appointments**
- **External experts:**
  - **Academic appointments**
  - **Clinical appointments**

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THE MAKING OF A SCIENTIFIC ADVICE

- **Two member coordinators appointed per advice**
- **Coordinators involve (several) internal/external experts**
  - **Provide responses to questions**
- **Coordinators draft each a first report**
- **Discussion at SAWP**
  - **Two outcomes:**
    - **Joint Report OR Discussion Meeting**

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THE MAKING OF A SCIENTIFIC ADVICE (CONT)

- **Discussion meeting:**
  - **Involve additional SAWP members**
  - **Involvement of assessors and additional (external/academic) experts**
  - **Patient Representatives**

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THE MAKING OF A SCIENTIFIC ADVICE (CONT)

- **Joint Report:**
  - **Involve other Working parties and groups**
  - **Consensus between coordinators/SAWP group/assessors**
  - **Peer Review**
  - **Discussion at CHMP**
  - **Final advice letter**

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EXTERNAL EXPERTS: WIN-WIN

- **SAWP:**
- **Clinical practice**
- **Recent scientific developments**

- **External/academic:**
- **Latest developments industry/trials**
- **Regulatory framework**

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Ask Scientific Advice!

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