Procedure di Scientific Advice europeo (SAWP) e nazionale

TECHNOLOGY TRANSFER SCHOOL
Ministero della Salute, Network PerfeTTO, APRE

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	☒	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	☒	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	☒	☐	☐	☐ facoltativo
2. Consulenza per una società	☒	☐	☐	☐ facoltativo
3. Consulente strategico per una società	☒	☐	☐	☐ facoltativo
4. Interessi finanziari	☒	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	☒	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	☒	☐	☐	☐ facoltativo
7. Sperimentatore	☒	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	☒	☐	☐	☐ facoltativo
9. Interessi Familiari	☒	☐	☐	☐ facoltativo
10. Gravi ragioni di convenienza	☒	☐	☐	☐ facoltativo

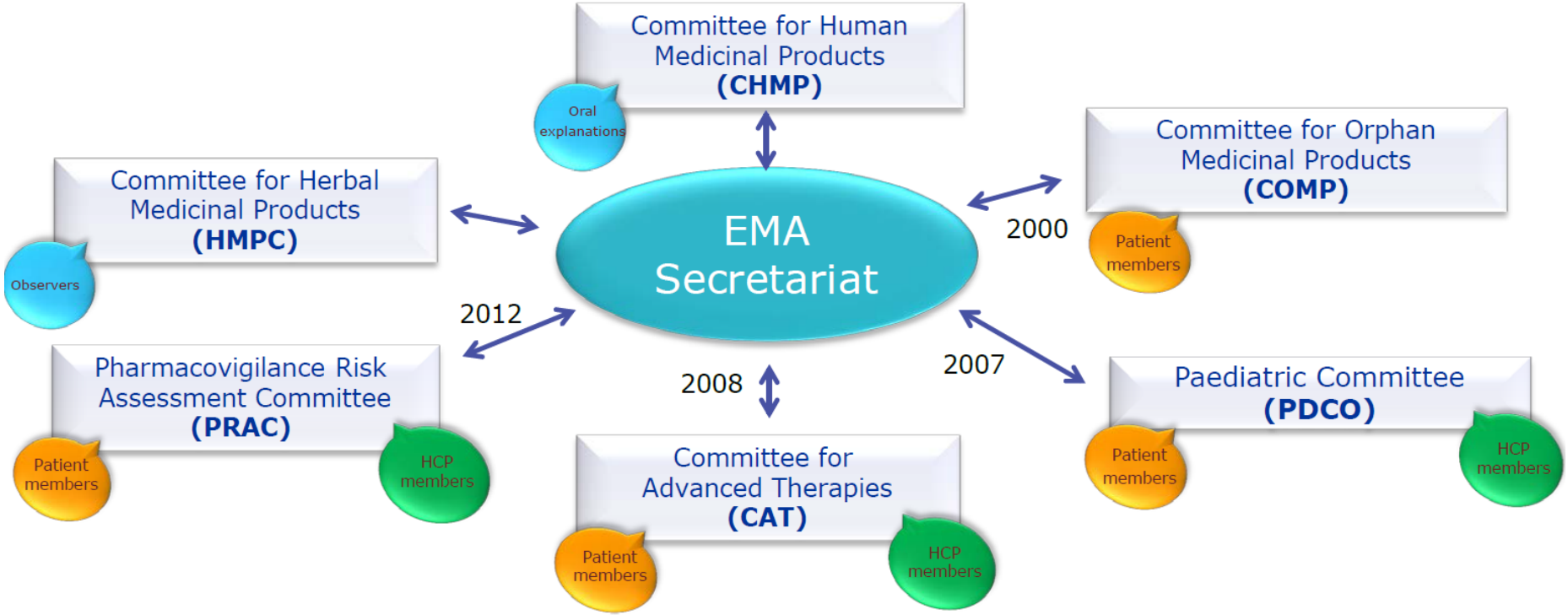
* Maria Di Marzo, secondo il Regolamento per la prevenzione e gestione dei conflitti di interessi all'interno dell'Agenzia Italiana del Farmaco approvato con Delibera CdA n.9 del 12 febbraio 2025.

N.B. Per questo intervento non ricevo alcun compenso

Agenda

- Scientific advice (SA): different types of procedures (EU, National)
- EU Scientific advice: SAWP and CHMP
- What is meant for…
- Scientific Advice – aim & issues covered
- Novel methodologies
- PRIME scheme
- Take home message

EMA scientific committees



AIFA participation – EMA Committees & Working Parties

PDCO (Paediatric)

CHMP

PRAC (Pharmacovigilance)

CAT (Advanced Therapies)

COMP

SAWP (scientific advice)
Italian Chair

CNSWP (neurology)

NCWP (non clinical)

CVSWP (cardiovascular)

MWP (methodology)

RIWP (rheumatology immunology)

IDWP (Infectious Diseases)

HAEMWP (haematology)

VWP (vaccines)

ONCWP (oncology)

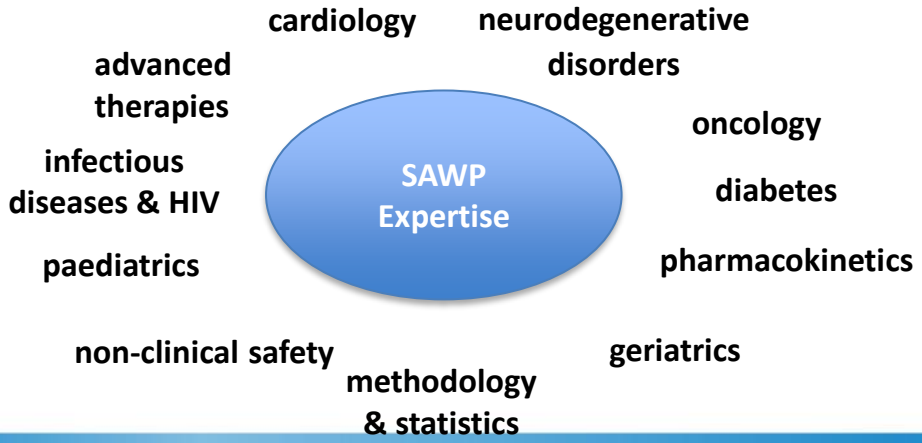
BWP (biologics)

QWP (quality)

QIG (Quality Innovation Group)

SAWP - COMPOSITION

- **Multidisciplinary Expert Group**: Chairperson and 36 members with alternates. Membership is based on complimentary scientific expertise, not on nationality.
- Some SAWP members are also delegated members from the COMP, PDCO, CAT, PRAC.
- Access to a **network of European experts** (confidentiality agreements). Interactions with the FDA, WHO and patient organisations.
- The SAWP is supported by the EMA **SAWP Secretariat**.



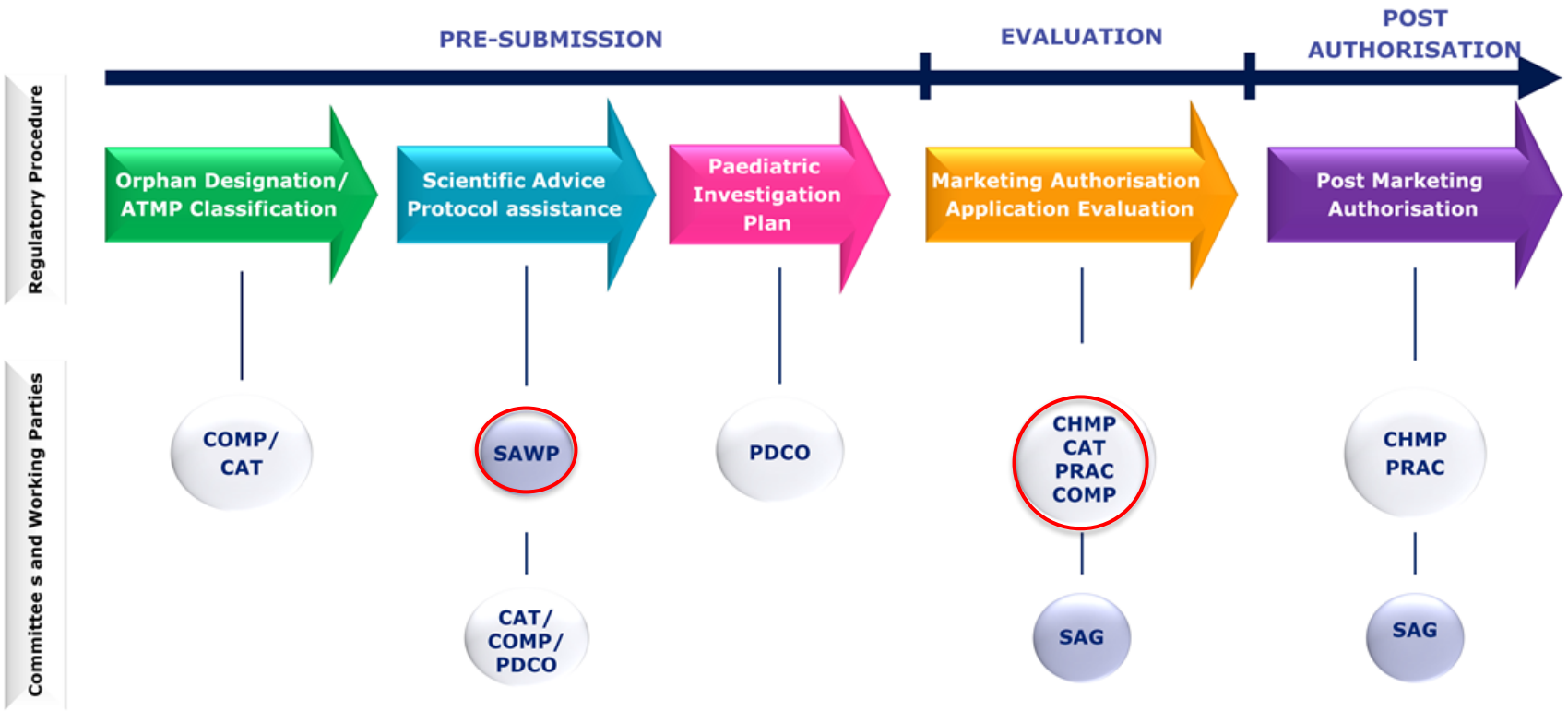
Types of advice procedures

Advice: support to developers on product/technology/methodology specific questions during development *to meet regulatory and scientific requirements.*

Type of advice	Granting authority
EU Scientific advice on specific products OR on broad issues	EMA CHMP upon SAWP recommendation
EU Protocol assistance for orphan medicinal products	(for products targeting a (potential) public health emergency: CHMP upon ETF recommendation)
EU Qualification advice / opinion on new methods/technology	
EU PRIME Scheme Eligibility (PRIority Medicines)	
EU Parallel SA with FDA	
EU Parallel SA with HTA bodies	
EU Consolidated advice on CTs pilots (e.g. SAWP-CTCG, pre-CTA, etc) → ACT-EU (Accelerating Clinical Trials in EU*)	CHMP / CTCG
EU QIG 1-to-1 Meetings with developers on innovative manufacturing issues	QIG (Quality Innovation Group) - EMA
National Scientific Advice	single National Competent Authorities (NCAs)

*ACT-EU: https://accelerating-clinical-trials.europa.eu/index_en --> consolidated advice on CTs

EMA Committees/Working Parties & Regulatory Procedures

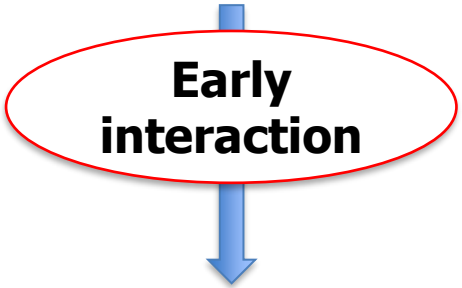


SA and PA are **given by** the **CHMP on the recommendation of** the **SAWP**

Scientific Advice – what is meant for

- At **any stage** of a medicine's development
- **Guidance and direction** on **methods and study** designs to generate **robust information**
- Avoid **patients** taking part in studies that will not produce useful evidence

Regulators/Developers



development and availability
of high-quality effective and safe medicines

When scientific advice is most useful

- **Innovative medicines**: no or insufficient relevant detail in EU guidelines or guidance documents, or in Pharmacopoeia monographs, including draft documents or monographs released for consultation;
- **New or repurposed medicines** (targeting (re)emerging pathogens): unmet medical need but insufficient or no guidance is available;
- Deviation from **scientific guidelines**;
- **Limited knowledge** about medicine regulation.

Scientific advice features

- **Voluntary** procedure
- **Not legally binding**
- **Alongside** product life cycle
- Focused on **specific questions** from the applicant (Q; NC; C; Regulatory)
- **Prospective** (on development strategy), not a pre-assessment of data and of B/R
- All advice given is extensively **peer reviewed** and approved by the CHMP. The SA given **reflects evidentiary standards** that the CHMP will apply by the time of MAA to establish whether there is a positive B/R or not.
- Fees apply*, reductions or exemption for some products (orphans, paediatric, ATMP..)/type of Applicant (SMEs, no-profit, ..)

*EMA Fees: https://www.ema.europa.eu/en/fees-payable-european-medicines-agency-fees-charges-remuneration-assessment-procedures-services-relating-medicinal-products-human-use#1-scientific-advice-75022

Scientific Advice – what is NOT meant for

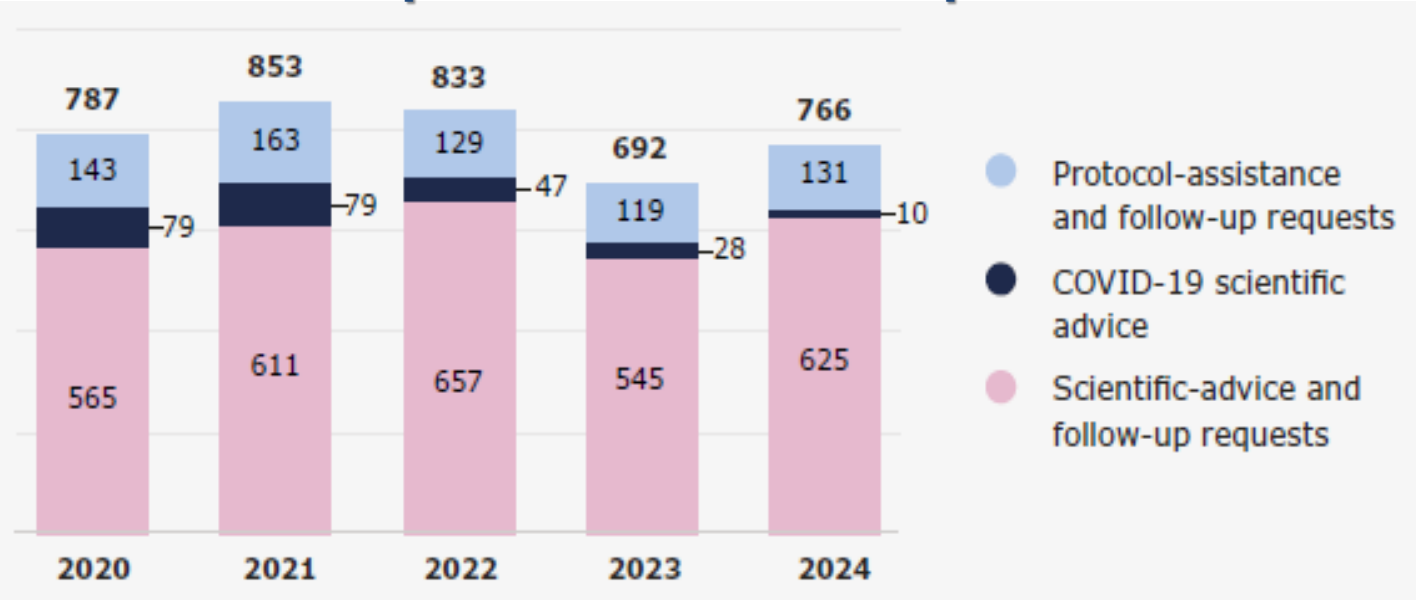
- Compassionate use, ATMP classification, PRIME eligibility, accelerated assessment
- Changes to the key elements of Paediatric Investigation Plan (PIP) measures and paediatric waivers or deferrals → PDCO
- Matters of a purely regulatory nature
- Adequacy of existing data for pre-assessment of a regulatory application (e.g. a clinical trial application or a Marketing authorization application)

Types of questions addressed

- **Quality** (e.g. manufacturing, chemical, pharmaceutical and biological testing of the medicine);
- **Non-clinical** (e.g. toxicological and pharmacological tests designed to show the activity of the medicine in the laboratory);
- **Clinical** (e.g. appropriateness of studies in patients or healthy volunteers, selection of endpoints, i.e. how best to measure effects in a study, post-authorisation activities including risk management plans);
- **Methodological** issues (e.g. statistical tests to use, data analysis, modelling and simulation);
- Overall **development/filing strategy** (e.g., conditional marketing authorisation, bridging strategy for generics, safety database), significant benefit for maintaining orphan designation, and paediatric developments.

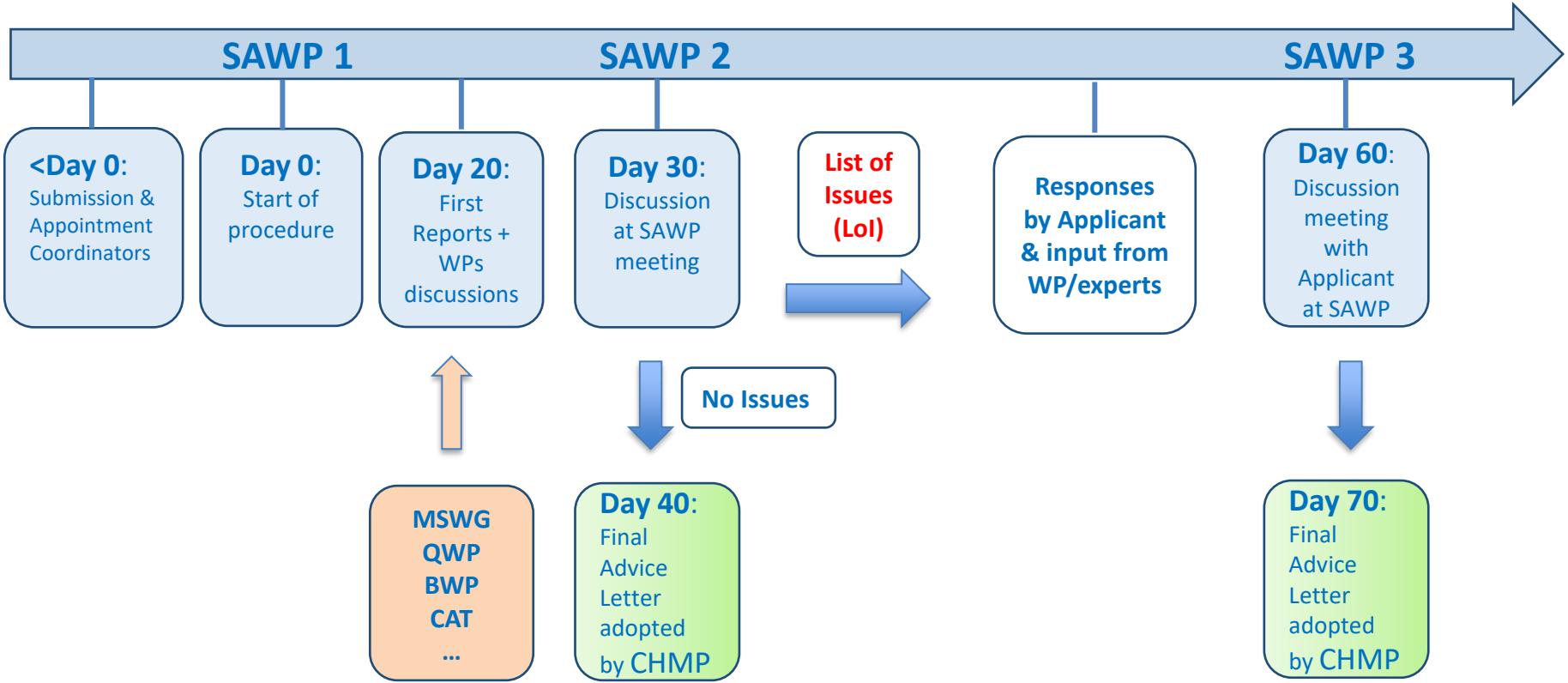
SAWP figures

EMA Annual Report 2024: SA & PA requests received - Total



EMA receives monthly requests based on planned timeslots

Scientific Advice Procedure (40 or 70 Days)



SA: clinical questions

- Proposal for **waiving certain studies**
- **Deviations** or interpretation of CHMP **guidelines**
- **Clinical Pharmacology**

  - Pharmacokinetics
    - specific designs issue
    - impact of PK parameters
    - population PK
    - use of modelling and simulation
    - population issues, Intra- and inter-individual variability
    - interactions
    - genetic polymorphism issues

  - Pharmacodynamics
    - Mechanism of action
    - Primary pharmacology
    - Secondary pharmacology
    - PK/PD modeling
    - PD interactions

SA: clinical questions

- **Clinical efficacy**
  - Dose-finding strategy
  - Choice of dose
  - Primary/Secondary endpoints – Magnitude of benefit and clinical relevance
  - Trial duration
  - Choice of control, background/rescue medication
  - Methodology (population for analysis: ITT vs PP, statistical analyses, sample size, adaptive design, multiplicity issues, pooling/meta-analysis)
  - Target population (inclusion/exclusion criteria, special populations)
  - Comparability
- **Clinical safety** (exposure, database, specific safety issues, QT effect assessment, RMP, immunogenicity)
- **Pediatric development**
- **Strategy** (interim analyses, number of studies, conditional or exceptional circumstances MA)

PA (orphan products): clinical questions

- Demonstration of **SIGNIFICANT BENEFIT** (Reg. 847/2000 art 3.2: a clinically relevant advantage or a major contribution to patient care.)*
- **Development** of medicinal products for rare conditions (small population)
- Study design to demonstrate **clinical superiority** over similar orphan products authorised for the same indication
  - **Greater efficacy**: direct comparative studies generally needed, but surrogate endpoints, adequately justified, might be acceptable
  - **Greater safety**: in a significant proportion of target population: direct comparative clinical trials might be necessary
  - **Exceptional cases**: neither greater efficacy and safety has been shown but a demonstration that the medicinal product otherwise makes a **major contribution** to diagnosis or patient care

(*) The SAWP will not provide pre-evaluation of data with which the sponsor aim to demonstrate significant benefit

Qualification of novel methodologies

Procedure to guide the development of novel, more efficient ways to develop medicines (development of new endpoints for clinical trials, new imaging method, new biomarker…)

Vision

- Speed up/optimise drug development and utilisation
- Improve public health

Who can apply?

- Consortia / networks
- Public / Private partnerships
- Academic developers
- SMEs
- Pharmaceutical industry

Output

- Qualification advice (optional "letter of support")
- Qualification opinion (published with public consultation)

Source: EMA (European Medicines Agency)

Qualification Advice & Opinion - Novel methodologies

Voluntary, scientific pathway for innovative methods or drug development tools not yet integrated in the drug development and clinical management paradigm

Qualification advice

- On future protocols and methods for further development towards qualification
- Evaluation of scientific rationale and preliminary data
- Confidential

100 days

Qualification opinion

- On the acceptability of a specific use of the proposed method in an R&D context
- Assessment of submitted data
- Publicly available

130 days + 60 days public consultation

E.g. methods to predict toxicity, strategies to enrich a patient population for a clinical trial, surrogate clinical endpoints, patient/caregiver reported outcomes, patient registries…

Source: EMA (European Medicines Agency)

Qualification Advice & Opinion - Novel methodologies

Preclinical development

- pharmacological screening
- mechanism of action
- predict activity/safety
- toxicogenomics

Clinical development

- verify mechanism
- dose-response
- proof of concept
- design optimisation
- **surrogate endpoint**

Drug utilisation

- optimise target population
- guide treatment regimen

Source: EMA (European Medicines Agency)

EMA QA/QO on Novel Methodologies: examples

- **AI-based measurement** of non-alcoholic steatohepatitis histology in liver biopsies to determine disease activity in NASH/MASH clinical trials (2025)
- **Centiloid measure of Amyloid PET** to quantify brain amyloid deposition (2024)
- **GFR slope as a Validated Surrogate Endpoint** for RCT in CKD (2023)
- **iBox Scoring System:** secondary efficacy endpoint in CTs investigating novel immunosuppressive medicines in kidney transplant patients (2022)
- **IMI PREFER framework** to provide suggestions on how patients' perspectives could be measured through patient preference studies and then incorporated into regulatory decision processes (2022)
- **Islet Autoantibodies (AAs)** as Enrichment Biomarkers for Type 1 Diabetes (T1D) Prevention Clinical Trials (2022)
- **Multiple sclerosis clinical outcome assessment (MSCOA):** tool comprised of a battery of 4 performance outcome measures assessing important dimensions of multiple sclerosis (MS) - walking (T25FW); hand dexterity (9HPT); vision (LCLA), and mental processing speed (SDMT)) to assess treatment benefit in CTs of therapies for MS (2020)
- **Stride velocity 95th centile:** secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device (2019)
- **Cellular therapy module** of the European Society for Blood & Marrow Transplantation (EBMT) Registry (2019)
- **Molecular neuroimaging of the dopamine transporter:** biomarker to identify patients with early manifest Parkinsonism in Parkinson's disease (2018)

https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance/opinions-letters-support-qualification-novel-methodologies-medicine-development

EMA Letters of Support on Novel Methodologies: examples

EMA may propose a **letter of support** when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data, to encourage data-sharing and to facilitate studies aimed at eventual qualification

- Model-based **Clinical Trial Simulation Platform** (CTSP) for Duchenne Muscular Dystrophy (2022)
- Model-based **Clinical Trial Simulation Platform** to Optimize Design of Efficacy Evaluation Studies in Parkinson's Disease (2022)
- **Global Platform Study** of Novel Medicines in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (Glo-BNHL platform) (2022)
- **Registry-based post authorisation safety studies** (PASS) in Multiple Sclerosis (MS) using data of the Big MS Data Network (BMSD) (2022)
- **Mobilise-D digital mobility outcomes** as monitoring biomarkers (BM) derived from mobile wearable devices and associated algorithms, as BM for clinical benefit (i.e., as surrogate, primary or key secondary endpoints) in pivotal CTs for treatment of conditions that impact upon mobility. (2020 & Follow-up in 2021)
- Development of **Patient-Reported Outcomes tools** for use as an endpoint in Inflammatory Bowel Disease (IBD) CTs (2019)

EMA PRIority MEdicines scheme (PRIME)

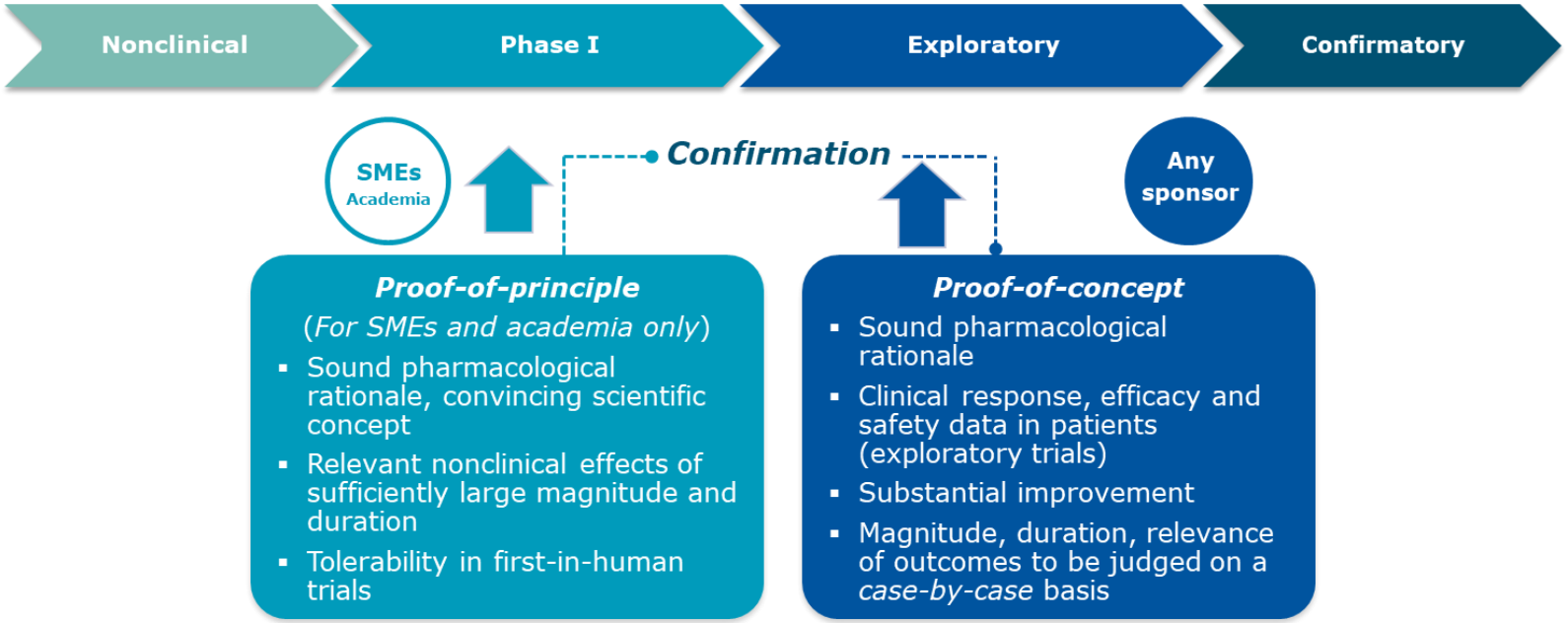
PRIME: set up in 2016 to provide **early and enhanced scientific and regulatory support** to medicines that have the potential to significantly address patients' **unmet medical needs** (UMN), i.e. major therapeutic advantage over existing treatments, or for patients with no current treatment options.

Aim: generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications, and **speed up patients access**.

The scheme builds on the **existing regulatory tools**, i.e., **Scientific advice (SA)/Protocol Assistance** (PA) & Marketing Authorization Application (MAA) under **accelerated timetable** (potential).

PRIME medicines include the first CAR T-cell therapies to be authorised, one-time potentially curative gene therapies, rare cancer treatments and a vaccine for the Ebola virus.

PRIME – eligibility criteria and pathway



Benefits

- **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

Source: adapted by EMA (European Medicines Agency)

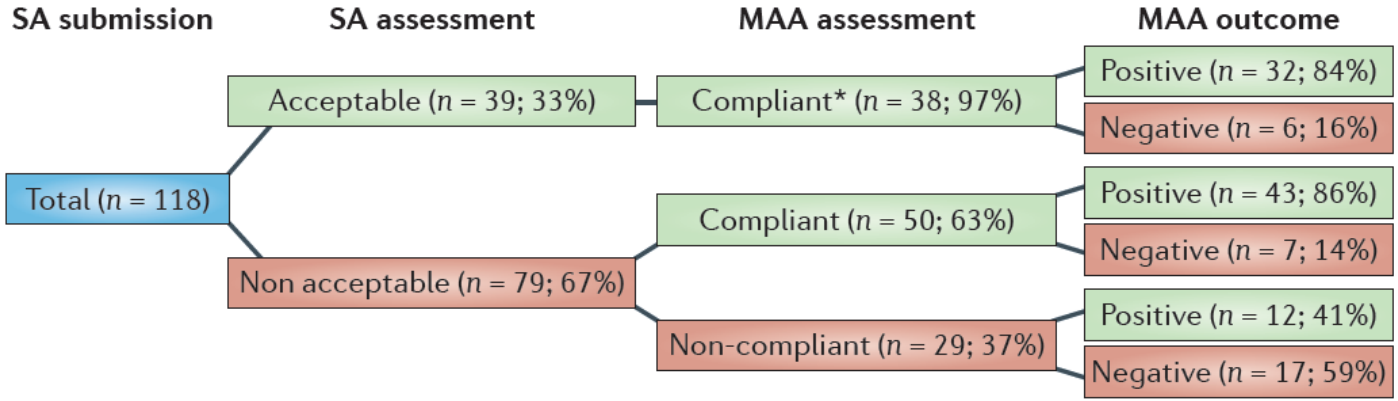
Scientific Advice – impact

- The overall attrition rate for developing a drug is currently calculated to be 10,000:1.
- The average cost of bringing a drug to the market is approaching 1 billion dollars.
- Increased regulatory requirements/scrutiny

Support developers/sponsors in finding optimal drug development strategies resulting in safe and efficacious medicines for the market

Scientific Advice – impact

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**: ~85% 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*

Take-home message

Receiving a SA/PA (and being compliant!) increases the chance of a successful development and the availability of high-quality effective and safe medicines for the benefit of patients

Developers should be encouraged to seek for SA/Follow-up SA

- Early in development and at major transition points (critical steps)
- When not complying with previous SA or changing the plan
- When there are no GLs or "state-of-the-art" or when deviating from them
- When there are uncertainties or critical findings
- SMEs and Orphans
- Advanced therapies
- Establish a relationship with regulators

Early interaction offers the opportunity to impact on future clinical developments

National Scientific advice

- **National formal entry point**
- Targeting **any Applicant**
- Cover **regulatory, technical and scientific concerns** on the different phases of the development of new and existing human medicinal products at any time before or after the authorisation
- Guidance and direction on the best methods and study designs **to generate robust data**
- **Not legally binding** on either NCA/EMA/Applicant
- **Not** constitute **a pre-assessment** of the data provided
- Fees applied (exemption reductions available depending on Applicant or product type)

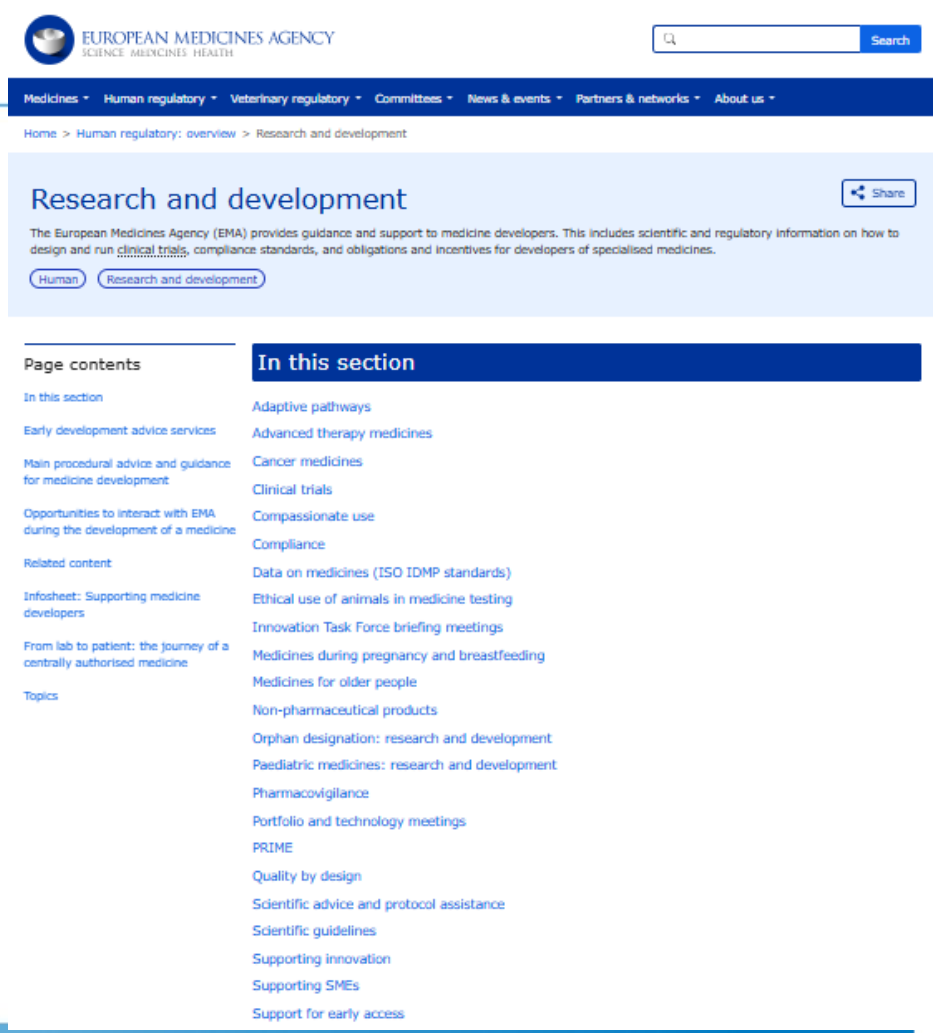
AIFA is working to resume the national SA procedures according to the new Organizational Regulation

EMA Research & Development

EMA R&D Webpage:
https://www.ema.europa.eu/en/human-regulatory-overview/research-development#early-development-advice-services-38734

EMA EVENTS webpage: https://www.ema.europa.eu/en/events/upcoming-events

EM-HMA PILOT EDUCATIONAL PROGRAMME ONCOLOGY:
https://www.youtube.com/playlist?list=PL7K5dNgKnawbqMVuBm4yapsI_YilKvv2E



Interactions across the medicine life cycle

Dedicated entry point for small, medium-sized enterprises (SMEs) **SME office**

Innovation Task Force (ITF)

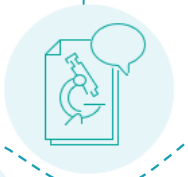
Dedicated **academia entry point**

Orphan Drug Designation

Qualification of novel methodologies

PRIority MEdicines (**PRIME** designation)

Scientific Advice (SA) / **Protocol Assistance** (PA)



ATMP classification & certification

EU Health Technology Assessment (HTA)

Paediatric Investigation Plan (PIP)

Submission of **Marketing Authorization Application**

Post-authorization activities

Source: EMA

THANK YOU

Any questions?

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