Rispetta le Regole, Proteggi la Scienza –
Norme Regolatorie e Buone Pratiche nella Ricerca Scientifica: l'Esempio delle Neoplasie del Polmone

Il paradigma regolatorio tra evidenze condizionate, real-world data e responsabilità etica

Dott.ssa Cristina Migali
Dirigente medico - Ufficio Procedure Centralizzate - AIFA
Membro SAWP - EMA

25/09/2025

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo AIFA o EMA

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

* Cristina Migali, 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.

Responsabilità etica…

MANDATO ISTITUZIONALE:
Promozione e tutela della salute pubblica attraverso i farmaci

MISSION 1:
Garantire l'unitarietà delle attività in materia di farmaceutica

MISSION 2:
Monitorare il consumo e la spesa farmaceutica

MISSION 3:
Favorire in Italia l'informazione indipendente e gli investimenti in ricerca e sviluppo

COSTITUZIONE della Repubblica Italiana

Articolo 32:

La Repubblica tutela la salute come fondamentale diritto dell'individuo e interesse della collettività…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

What we do
Protect human and animal health

- Facilitate development and access to medicines
- Evaluate applications for marketing authorisation
- Monitor the safety of medicines across their life cycle
- Provide reliable information on human and veterinary medicines in lay language

CODICE DI DEONTOLOGIA MEDICA

…giuro:

-di mettere le mie conoscenze a disposizione del progresso della medicina, fondato sul rigore etico e scientifico della ricerca, i cui fini sono la tutela della salute e della vita

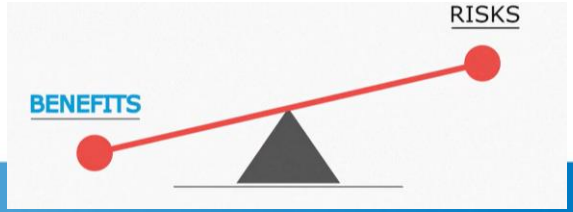
Guiding principle of medicine's assessment

- All new active substances for **cancer** are assessed through the **Centralised Procedure** (mandatory scope)
  (Directive 2001/83/EC - Regulation (EC) No 726/2004)

- The **quality**, **safety** and **efficacy** of the medicinal product should be demonstrated.

- The **balance between the benefits and risks** of a medicinal product is the key principle guiding the assessment.

- A medicinal product can only be authorised if its benefits outweigh the risks, i.e. if the **benefit/risk balance** is considered **favourable**



Benefit/Risk balance

BENEFIT **RISK**

FAVOURABLE EFFECTS

Positive effect on clinical outcomes

UNFAVOURABLE EFFECTS

Mainly related to safety profile

UNCERTAINTIES AND LIMITATIONS about favourable effects

e.g. variation, important sources of bias, methodological flaws or deficiencies (including GCP, compliance, etc.), effects in subgroups etc.

UNCERTAINTIES AND LIMITATIONS about unfavourable effects

Limitations of safety data-base (e.g. sample size, duration of follow-up) and implications in predicting the safety profile of the product

BALANCE OF BENEFITS AND RISKS

Trade-off based on values judgment

+ management of uncertainties

Support for early access

- Efforts to enable **early patient's access** to new medicines, particularly those that target an **unmet medical need** or are of **major public health interest**

- Regulatory tools:
  - **Conditional Marketing Authorization (CMA)**
  - **Accelerated Assessment (AA)**

- Support scheme for medicine development:
  - **PRIME - priority medicines**

Conditional Marketing Authorization

Regulation (EC) No 726/2004 - Regulation (EC) No 507/2006

- Applicable to medicines intended for treating, preventing or diagnosing **seriously debilitating or life-threatening diseases**, or **orphan** medicines, or medicines for **public health emergencies**
- **All criteria** should be met:
  - the benefit-risk balance of the medicine is positive
  - it is likely that the applicant will be able to provide comprehensive data post-authorization
  - the medicine fulfils an unmet medical need (no satisfactory methods exist or major therapeutic advantage over existing optons)
  - the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required
- The MAH must fulfil **specific obligations** within **defined timelines**, that could include completing ongoing or new studies or collecting additional data to **confirm** that the **benefit-risk** balance remains **positive**.

Conditional marketing authorisation

Report on ten years of experience at the European Medicines Agency

2006-2016

- Most of CMA were in **oncology** (21 out of 36)
- In oncology, 17 out of 21 applications were based on single arm study
- Overall, ~70% of SOB were completed with specific timeline, and 36% were converted to full MA. Median time from granting CMA to conversion to standard MA 4.2 years
- One third (7 out of 21) of the oncology CMA were were converted. One CMA was later withdrawn (Lartruvo)

CMA: examples from lung cancer

Drug	BM	line	Date opinion	MA	CHMP vote	ORR	DOR	Studies
Crizotinib	ALK	2L	07.2012	CMA	Consensus	60.3% (51, 69.1) 48% (44, 51)	48.1 (35.7, 64.1) 47.3 (36, 54)	A8081001 A8081005
Ceritinib	ALK	2L	02.2015	CMA	Consensus	46% (38.2, 54) 35.7% (27.8, 44.2)	8.8 (6.0, 13.1) 12.9 (9.3, 18.4)	X2101 A2201
Alectinib	ALK	2L	12.2016	CMA	Consensus	50.8% (41.6, 60) 52.2% (39.7, 64.6)	15.2 (11.2, 24.9) 14.9 (6.9, NE)	NP28673 NP28761
Brigatinib	ALK	2L	09.2018	Full	Consensus	56.4% (45.2, 67)	13.8 (10.2, 19.3)	AP26113-13-201
Lorlatinib	ALK	2L	02.2019	CMA	Majority (-5)	42.4% (32.5, 52.8) 39.6% (30.5, 49.4)	NE (7.8, NE) 9.9 (5.7, 24.4)	B7461001
Crizotinib	ROS1	any	07.2016	EoI (no PAES)	Consensus	72% (58, 83)	24.7 (15.2, 45.3)	1001
Entrectinib	ROS1	any	05.2020	CMA	Majority (-2)	67.1% (59.25, 74.2)	16.5 (14.6, 28.6)	Pooled

CMA: examples from lung cancer

Drug	BM	line	Date opinion	MA	CHMP vote	ORR	DOR	Studies
Selpercatinib	RET	2L	12.2020	CMA	Consensus	63.8% (53.9, 73)	17.51 (12.1, NE)	LIBRETTO-001
Pralsetinib	RET	any	09.2021	CMA	Consensus	64.4% (57.9, 70.5)	19.1 (14.5, 27.3)	ARROW
Sotorasib	KRAS G12C	2L	11.2021	CMA	Majority (-1)	37.1% (28.6, 46.2)	11.1 (6.9, 15)	CodeBreaK 100
Adagrasib	KRAS G12C	2L	11.2023	CMA	Majority (-4) *Re-examination*	41.4% (32.3, 50.9)	8.5 (6.2, 13.8)	KRYSTAL-1
Tepotinib	METex14	2L	12.2021	CMA	Majority (-12)	51.4% (45.8, 57.1)	18 (12.4, 46.4)	VISION
Capmatinib	METex14	2L	04.2022	Full	Majority (-11)	44% (34.1, 54.3)	9.72 (5.6, 13)	GEOMETRY mono-1
Amivantamab	EGFR ex20ins	2L	10.2021	CMA	Consensus	37% (28, 46)	12.5 (6.5, 16.1)	CHRYSALIS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application

Considerations on evidence from single-arm trials

- **RCTs** are the **standard** for providing **confirmatory evidence** on the efficacy of investigational treatment
- If the pivotal clinical data in a MAA intended to be supported by **SAT**, it is the **responsibility of the applicant** to **justify** the **reasons** for deviating from the standard, and the **appropriateness** of SAT as alternative
- Reflection paper discusses **key issues** and **requirements** for SATs submitted as pivotal evidence
- **Acceptability of SAT for regulatory decision-making** strongly **depend** on the **full clinical context** and **attributes** of the investigational treatment. Scientific advice is recommended.

The Benefit/Risk Assessment – reality check

Single Arm Trials in Marketing Authorisation

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Single-arm trials supporting the approval of anticancer medicinal products in the European Union: contextualization of trial results and observed clinical benefit

J. Mulder[1*], S. Teerenstra[1,2], P. B. van Hennik[1], A. M. G. Pasmooij[1], V. Stoyanova-Beninska[1], E. E. Voest[3,4] & A. de Boer[1,5]

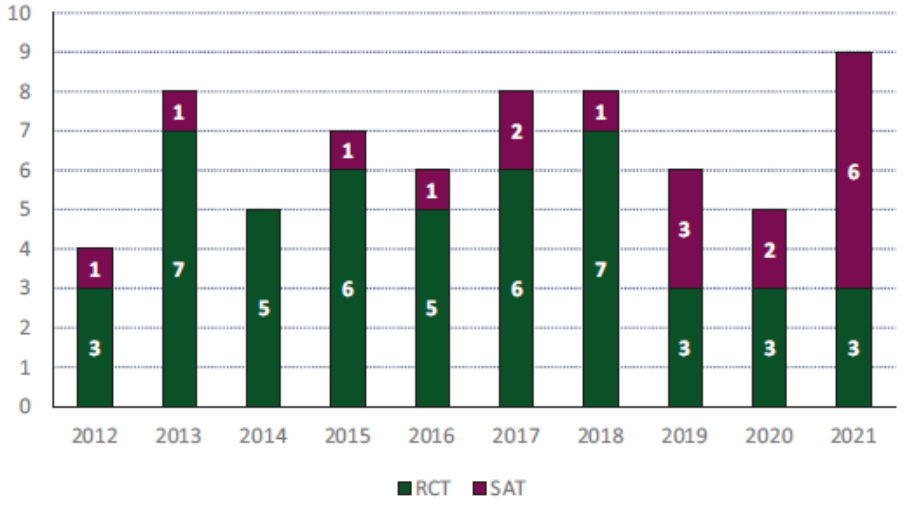
[1]Dutch Medicines Evaluation Board, Utrecht; [2]Department for Health Evidence, Biostatistics Section, Radboud University Medical Center, Nijmegen; [3]The Netherlands Cancer Institute, Amsterdam; [4]Oncode Institute, Amsterdam; [5]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Available online 11 April 2023

- 18/66 anticancer products were approved based on SATs
- 21 therapeutic indications

Observation period: 2012-2021

- Total MA granted in EU: 731
- Anticancer products: 66



Accelerated Assessment

Regulation (EC) No 726/2004 Article 14(9)

- Applications may be eligible for accelerated assessment if the Committee for Medicinal Products for Human Use (CHMP) decides the product is of **major public health interest**, particularly from the point of view of **therapeutic innovation.**
- The claim of **major public health interest** to be justified by the Applicant based on:
  - Existence of unmet medical need(s)
  - How the product could address the unmet medical need(s)
  - Strength of evidence expected at time of MAA
- Accelerated assessment can reduce the timeframe for the CHMP review **from up to 210 days to 150 days** (excluding clock-stop required by the applicants to provide additional information)
- AA can be reverted to standard time, main reason Major Objections not resolvable under AA

PRIority MEdicines (PRIME)

- **PRIME** is a scheme run by EMA to **enhance support** and **early dialogue** for the development of medicines that target an **unmet medical need**, e.g. through iterative scientific advice and timely appointment of Rapporteur
- A medicine must demonstrate the **potential** to **address an unmet medical need to a significant extent,** i.e. a meaningful improvement of clinical outcomes
- **SMEs** and applicants from the **academic sector** may be granted **Early Entry PRIME** status if they demonstrate proof of principle
- Use of the existing regulatory framework such as **scientific advice** and **accelerated assessment**

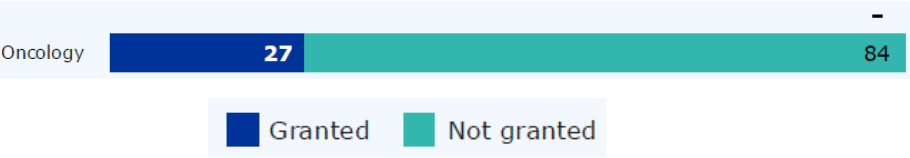
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PRIME:
Analysis of the first 5 years' experience

Findings, learnings and recommendations

March 2016 –

Figure 3. Outcome of PRIME eligibility requests per therapeutic area



- Oncology products constituted the vast majority of PRIME applications (29%)
- Successful PRIME applications were between 21-30% each year
- 56% of PRIME products were orphan
- Majority of PRIME eligibility requests were from SMEs (54%), although success rate applications is lower for SMEs than non-SMEs (19% vs 33%)
- Of a total of **95 PRIME products**, **24 were submitted** for marketing authorization and **21 concluded the MAA** procedure (**18 positive opinions, 1 negative opinion and 2 withdrawn**). Of those, 17 started under AA.

Scientific Advice and Protocol Assistance

- Main form of **regulatory support from the EU regulatory system to medicines developers** towards optimization of **scientific evidence generation** to **support approval** of new medicines, new uses of existing medicines and/or other major post-authorization changes
- SA and PA are **given by the CHMP** on the **recommendation of the SAWP** (Scientific Advice Working Party)
- Medicine developers can request scientific advice either during the **initial development** or during the **post-authorisation phase**, on **any aspects** of the medicine development and any part of the dossier (e.g. quality, non-clinical, clinical, , methodology, regulatory)
- **Fee reductions/waivers** for orphan drugs, drugs for public health emergencies, SMEs
- Scientific advice is **prospective** in nature, it is **not a pre-assessment** of data and it is **not legally binding** for any future MAA

Scientific Advice and Protocol Assistance

- **Qualification of novel methodologies**: **regulatory acceptability** of novel methodologies for use in medicines development within a specific context
- **Novel methodologies** include e.g. novel biomarkers for patients' selection, novel patient reported outcomes (PROs), novel clinical endpoints in confirmatory clinical trials
- Once the CHMP/SAWP concluded that the proposed method can be qualified for a well-defined context of use, a qualification opinion is **published** and subjected to public consultation before being finalized

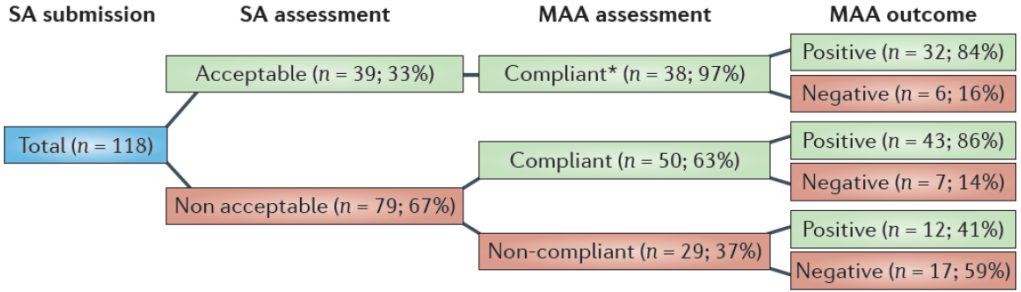
Scientific Advice and Protocol Assistance

- Scientific advice can be made **in cooperation** with other decision-making bodies:
  - Consolidated scientific advice on clinical trials SAWP-CTCG (Clinical Trials Coordination Group)
  - Joint Scientific Consultation (JSC) with health technology assessment (HTA) bodies (Reg EU 2021/228)
  - Parallel scientific advice with FDA
- Scientific advice for **special product types**, e.g.
  - medicine repurposing
  - biosimilar medicines

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

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**: 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*

PERSPECTIVE

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 117 NUMBER 4 | April 2025

Clinical Evidence 2030

Peter Arlett[1], Denise Umuhire[1,*], Patrice Verpillat[1], Paolo Foggi[2], Ulla Wändel Liminga[3], Bruno Sepodes[4], Marianne Lunzer[5], Brian Aylward[6], Spiros Vamvakas[1], Kit Roes[7], Frank Pétavy[1], Steffen Thirstrup[1], Maria Lamas[8], Emer Cooke[1] and Karl Broich[9]

Building on existing practices, our vision is that by 2030, clinical evidence generation will be further guided by the patient voice and informed by existing data and knowledge; study design will be driven by research questions to be addressed; clinical trials will be more efficient and impactful; real-world evidence (RWE) will be enabled and its value fully established; and trust will be built through transparency (Figure 1).

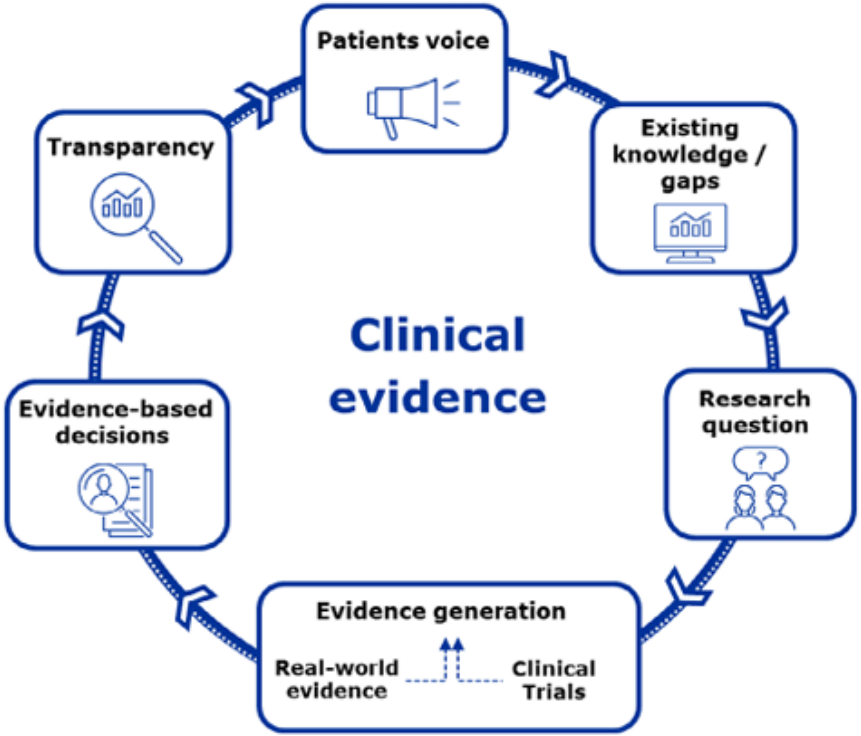


Figure 1 Representation of the vision for clinical evidence 2030.

Some reflections…

- Il principio del beneficio/rischio guida la decisione sull'autorizzazione all'immissione in commercio
- Decisione regolatoria come trade-off tra accesso precoce e robustezza delle evidenze
- Disponibilità di meccanismi regolatori per accelerare lo sviluppo e l'autorizzazione in caso di unmet medical need
- Scientific Advice EMA come supporto regolatorio per generare le migliori evidenze
- Promuovere interazione precoce tra sviluppatori e regolatorio, in collaborazione con altri stakeholders, per favorire l'arrivo di farmaci realmente efficaci ai pazienti
- Obiettivo finale: salvaguardia della salute pubblica

Dott.ssa Cristina Migali
c.migali@aifa.gov.it