

Regulatory Opportunities and Challenges in Europe: *From Registries to PRIME and Return*

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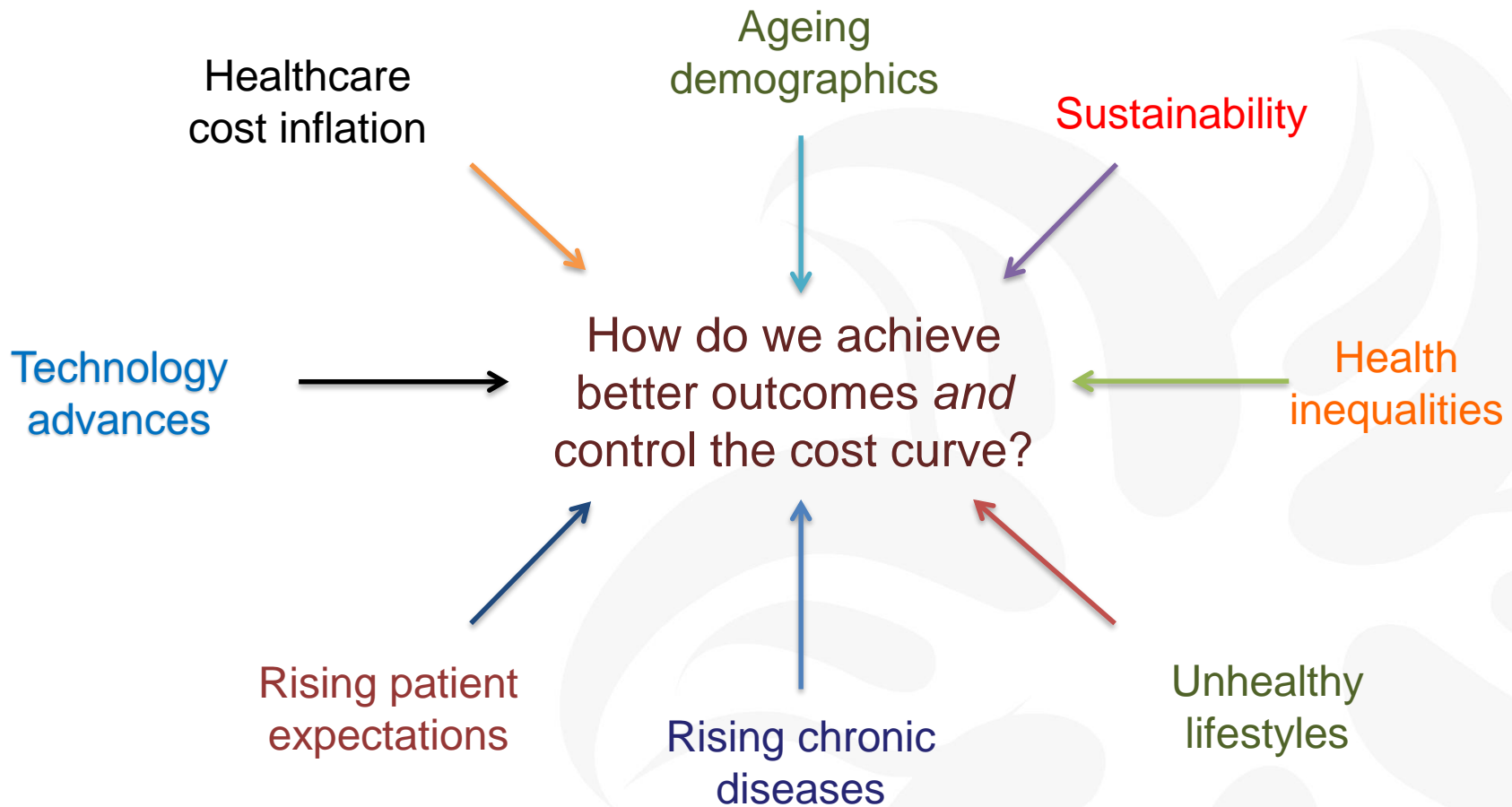


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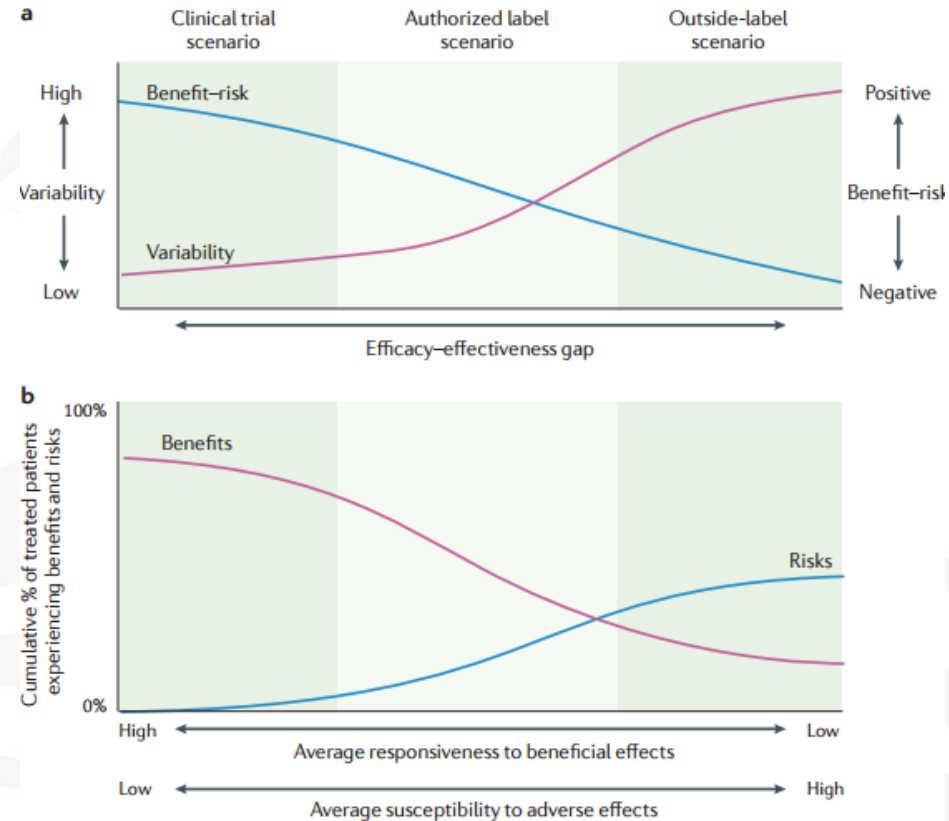
* See also the Revised Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.





Patients are not equally responsive to beneficial effects, and not equally susceptible to AEs.

Regulatory decisions are based on population-level information, with an understanding that the B-R will not necessarily be positive for all treated patients.





Clinical
development

Market
entry

Real world
effectiveness
and safety

Further
regulatory/
policy
actions

Early
dialogue/scientific
advice

Conditional
Reimbursement
(MEAs)

Monitoring
Registries

Re-assessment





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MONITORING REGISTRIES AT ITALIAN MEDICINES AGENCY: FOSTERING ACCESS, GUARANTEEING SUSTAINABILITY

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Objectives: The AIFA (*Agenzia Italiana del Farmaco*—Italian Medicines Agency) Monitoring Registries track the eligibility of patients and the complete flow of treatments, guaranteeing appropriateness in use of pharmaceutical products, according to approved indications.

Methods: This study describes the Italian pharmaceutical context and the aims and functioning of AIFA Monitoring Registries, focusing on the applications to the Managed Entry Agreements (MEAs) and HTA approaches.

Results: The AIFA Monitoring Registries System has been operational in Italy since 2005. In 2012, the system became part of the NHS Information Technology system, aiming at enhancing appropriate use of pharmaceuticals and efficiency of the administrative activity. Currently, seventy-six medicines are monitored through the system, corresponding to fifty-eight therapeutic indications; individual treatments recorded are more than 515,000, for a population of approximately 505,000 patients. For each monitored product, patients eligible for treatment are registered in the specific therapeutic indication dynamic monitoring database to collect epidemiologic and clinical data, including data on the safety profile, and ex-post information missing at first evaluation stage.

Conclusions: AIFA Monitoring Registries allow the evaluation of the pharmaceuticals' performance in clinical practice and may promote innovation and quicker access to medicines at affordable prices, for the benefit of patients.

Keywords: Drug monitoring, Registries, Real clinical practice data collection, Managed entry agreements



RWD is an umbrella term including effects of health interventions that are not collected in the context of conventional RCTs.

Registries are one of the main sources of RWD.

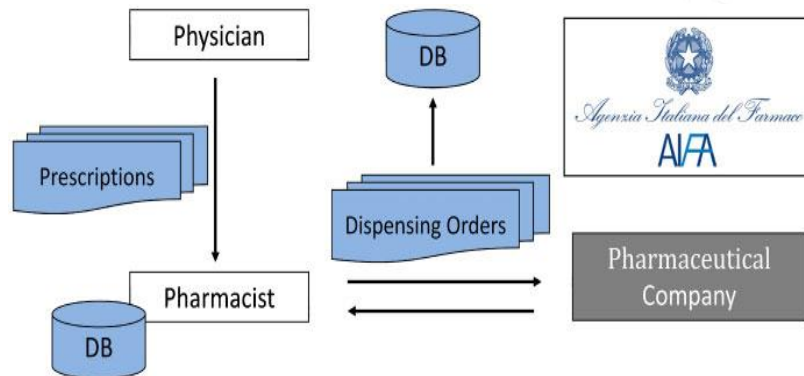
Alternative / Additional tools are:

- Electronic medical records
- Observational studies
- Administrative data
- Claims databases
- Health surveys & patient reported outcomes (PROs).

AIFA drug-product Registries are web tools placed in the early phases after MA and also for some “authorized” *off label* use.

Pharmaceutical Programming 2012 VOL. 5 NO. 1&2

Xoxi et al. The Italian post-marketing registries



Measure RW effectiveness
and
Apply MEAs procedures.

Figure 1 Patients' case report forms must be filled in, in a specific web-based monitoring register (RFM). The register tracks the eligibility of the registered patients and the complete flow of the treatments

In 2012 AIFA Registries officially became part of the NHS Information Technology (IT) Law n. 135/2012.

Y 2006
Version 1.0

Y 2013
Version 2.0



AIFA
Agenzia Italiana del Farmaco

Farmaci sottoposti a monitoraggio

Programmi generali:

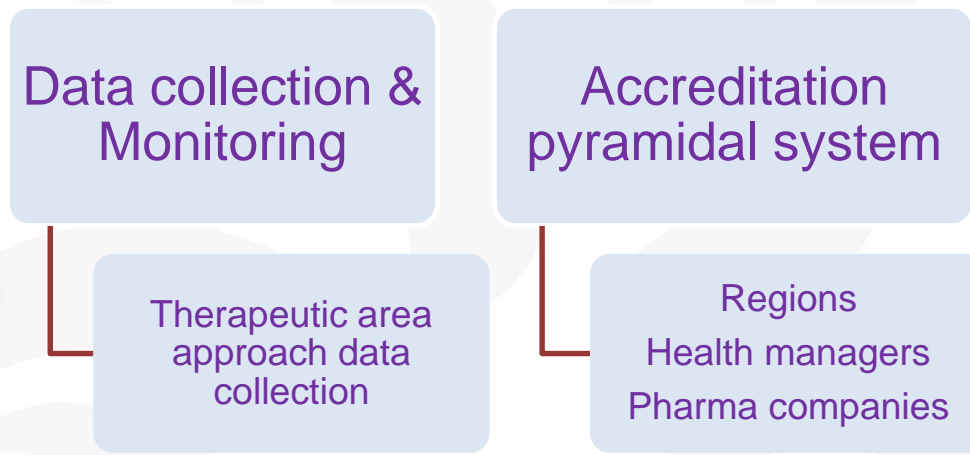
- Farmaci antineoplastici
- Farmaci orfani
- Farmaci per la psoriasi
- Farmaci anti HIV
- Farmaci antipsicotici
- Farmaci antidiabetici
- Farmaci cardiovascolari

Progetti specifici:

- Tysabri
- ADHD
- Xolair
- Xagrid
- Xigris

Con il Registro dei farmaci a monitoraggio l'agenzia Italiana del Farmaco AIFA, intende mettere a disposizione degli operatori sanitari un punto di accesso unificato ai progetti di monitoraggio che sono richiesti, laddove necessario, a complemento delle determinazioni di immissione in commercio delle singole specialità medicinali (in luogo delle precedenti schede di rilevazione dati cartacee).

Il Registro unificato intende porsi come strumento innovativo di comunicazione con l'Autorità regolatoria, per una efficace semplificazione degli iter burocratici richiesti dalle procedure e per l'avvio di un processo virtuoso in grado di supportare una sempre migliore pratica clinica a tutela del paziente.



What's next?

%

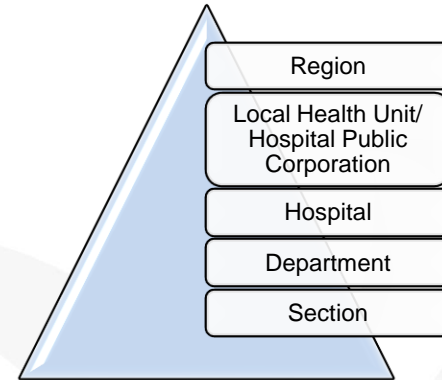
128 registries: *drug-based*

31 registries: *disease-approach based*

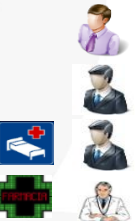
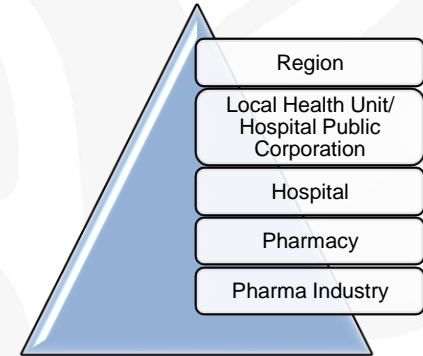
Data Vital Statistics

- ≈ 48 MAH
- > 1,000,000 patients uniquely ID
- ≈ 29,000 physicians
- ≈ 2,000 pharmacists
- ≈ 1,700 Health managers
- 49 Regional referral managers

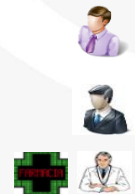
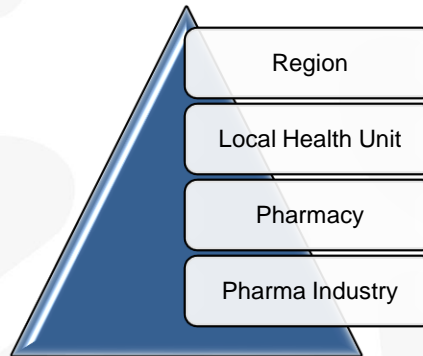
Hospital - Physician



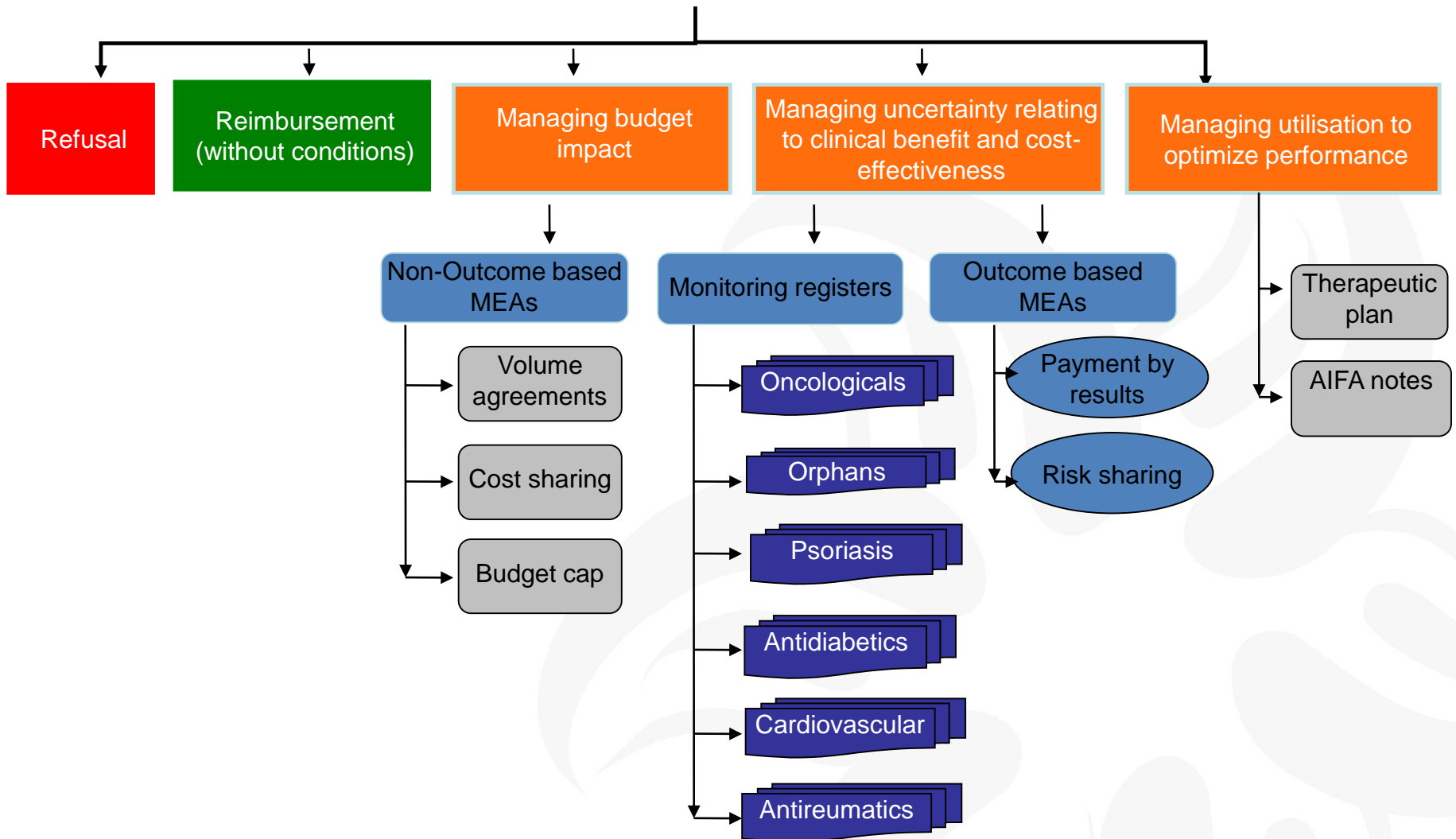
Hospital Pharmacy



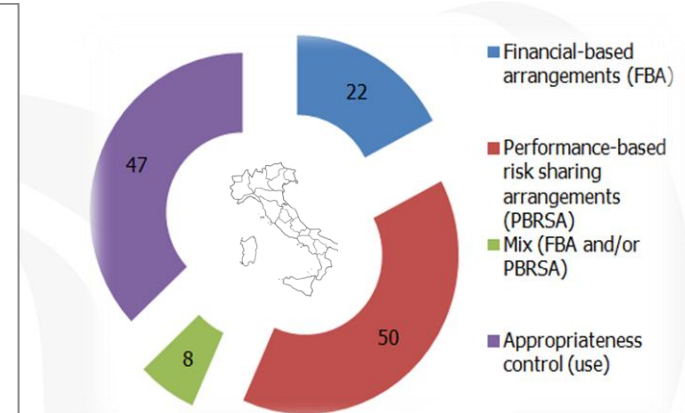
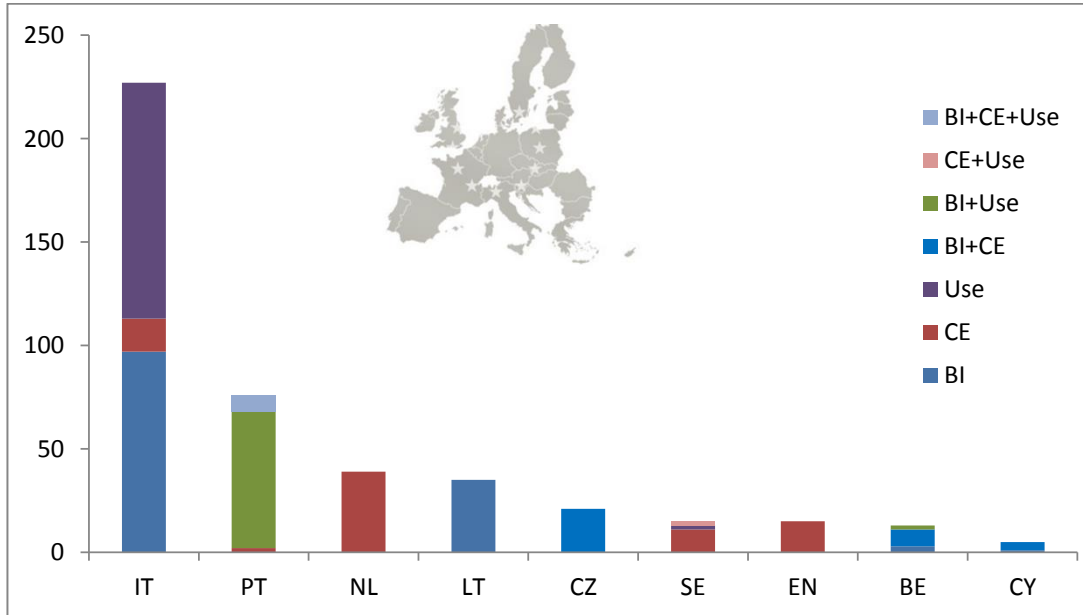
Territory Pharmacy



The Italian Medicines Agency Strategy: A range of Managed Entry Agreements (MEAs)



MEAs in EU vs. MEAs in Italy



85% of all Italian Registries are associated with a MEA; PbRs are the most frequently used schemes.

Legend: BI: Limit budget impact, CE: Address uncertainties regarding the cost-effectiveness, Use: Monitor use in clinical practice, Access+CE: Improve patient access and cost-effectiveness. BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden

MEAs allow value-based pricing negotiations under Uncertainty

Clinical

- Long-term and comparative effectiveness
- Place in therapy
- Long-term safety profile

Economic

- Future costs
- Cost-effectiveness
- Measures of QoL

Utilisation

- Number of eligible patients
- Market share
- Treatment duration

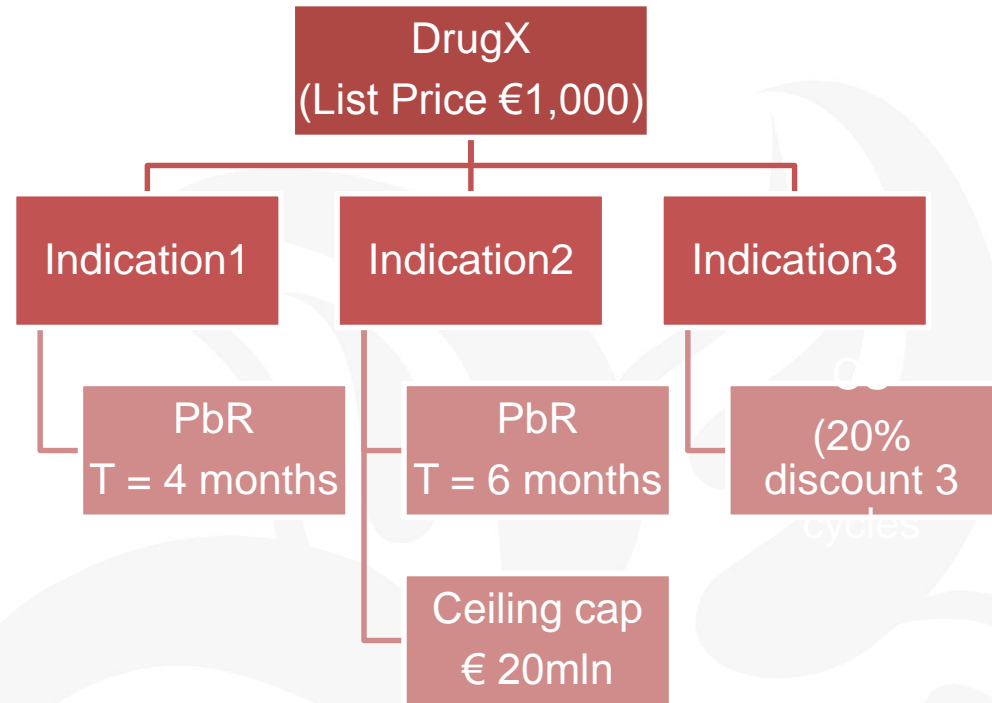
Financial

- Overall impact on healthcare budget

Even if cost effectiveness analysis did provide a reliable way forward, **there is still a budgetary problem to be considered.**

(Bach, *N Engl J Med* 2015).

Same list price,
value-based cost



Specific MEA for each therapeutic indication (Bach, Jama 2014)
“when costs are essentially the same but benefit differs widely, value is not the same” → crude metric value cost / Years of life gained

When New Cancer Treatments Fail, Italy Wants Its Money Back

The Italian Medicines Agency has devised deals with pharma companies that set payment based on how well a patient responds to treatment, and in some cases where the medication fails to help, the drugmaker gives a full refund. Italy is signing more such contracts as growing numbers of medications receive regulatory approval after mid-stage trials of fewer than 100 patients rather than awaiting final-stage assessments involving thousands.

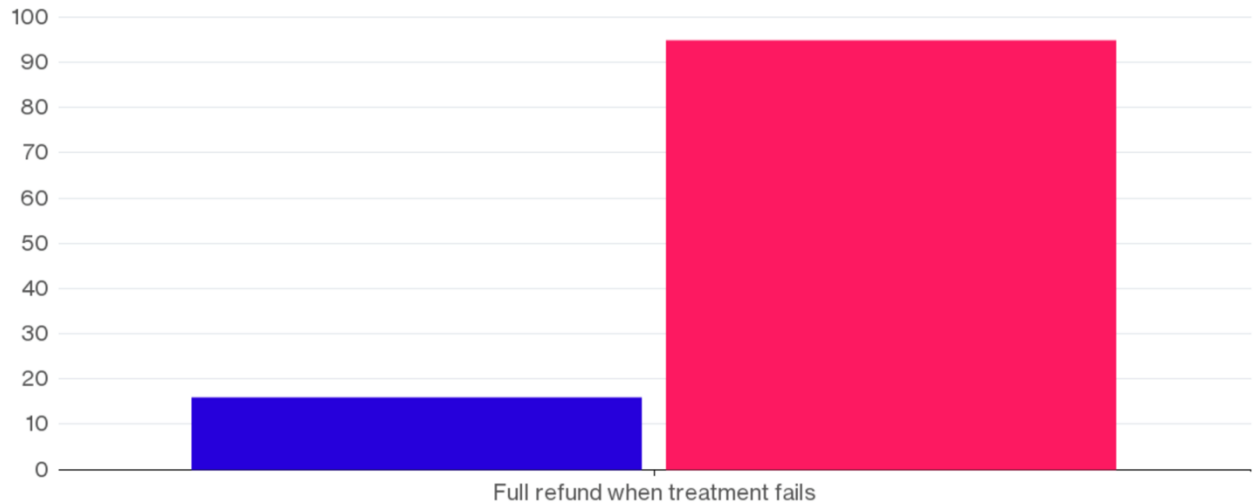
Drug contracts with money-back guarantees

Italy is signing more contracts stipulating refunds when treatments fail, allowing it to take a chance on medicines getting approved with smaller trials

by Makiko Kitamura Johannes Koch
[@maki_kitamura](#)

January 15, 2016 – 6:00 AM CET

■ 2012 ■ 2014



Proven track of records on:

1. Accelerated access to drugs for sub-clusters of patients;
2. Prevent exclusion of drugs with potential efficacy;
3. Early exclusion of drugs with safety issues;
4. Real world data generation;
5. Containing NHS expenditure optimizing allocation of resources and supporting economical sustainability;

Could this be a powerful IT platform to be used in adaptive clinical trials designs such as PRIME?

PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier.



Eligibility is based on **prioritization evaluation** and optimization of the system resources for products:

- Unmet medical need
- Supporting evidence
- **At the earlier stage** of proof of principle (prior to phase II/exploratory clinical studies) focusing on SMEs.
- **At proof of concept** (prior to phase III/confirmatory clinical studies).
- With major public health interests

Prime products must be game changer!

1. The scheme focuses on medicines that may offer a **major therapeutic advantage** over existing treatments, or benefit patients without treatment options.
2. To be accepted for PRIME, a medicine has to show its potential to benefit patients with **unmet medical needs** based on **early clinical data**.
3. Must have an **iterative** development plan (start in a well-defined subpopulation and **expand**, or have a Conditional Marketing Authorization, maybe surrogate endpoints to **confirm**);
4. **Real World Data** (safety and efficacy) can be acquired and used to supplement the Clinical Trials;

Once a candidate medicine has been selected for PRIME, the Agency will:

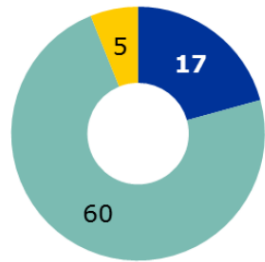
- Appoint a rapporteur from the Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT) in the case of an advanced therapy to provide continuous support and help to build knowledge ahead of a marketing-authorisation application;
- Organise a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts, so that they provide guidance on the overall development plan and regulatory strategy;
- Assign a dedicated contact point;
- Provide scientific advice at key development milestones, involving additional stakeholders such as health-technology-assessment bodies, to facilitate quicker access for patients to the new medicine;
- Confirm potential for accelerated assessment at the time of an application for marketing authorisation.

- PRIME builds on the existing regulatory framework and tools already available such as scientific advice and accelerated assessment. This means that developers of a medicine that benefitted from PRIME can expect to be eligible for accelerated assessment at the time of application for a marketing authorisation.
- Early dialogue and scientific advice also ensure that patients only participate in trials designed to provide the data necessary for an application, making the best use of limited resources.
- Incorporation in Scientific Advice provides optimization of resource use and facilitates high quality input.

* Dedicated e-mail: prime@ema.europa.eu

- By engaging with medicine developers early on, PRIME is aimed at improving clinical trial designs so that the data generated is suitable for evaluating a marketing-authorisation application.
- “Real World Data” for regulatory use (including IMI initiatives and Registries)
- PhV including PASS and PAES
- Interactions with EUnetHTA – including structure of EPARs, use of Effects Tables etc
- Joint advice with national HTA/payer bodies
- Increased focus on post approval development

- PRIME is not always applicable and may not be applied to all drugs in the same manner. Under an PRIME scenario what is needed is:
 - Acknowledgment of acceptable levels of uncertainty;
 - Improved public communication and perception of safety and efficacy;
 - Greater adherence to use in treatment-eligible populations;
 - Increased need for prescription controls and support;
 - Surveillance and evidence generation.
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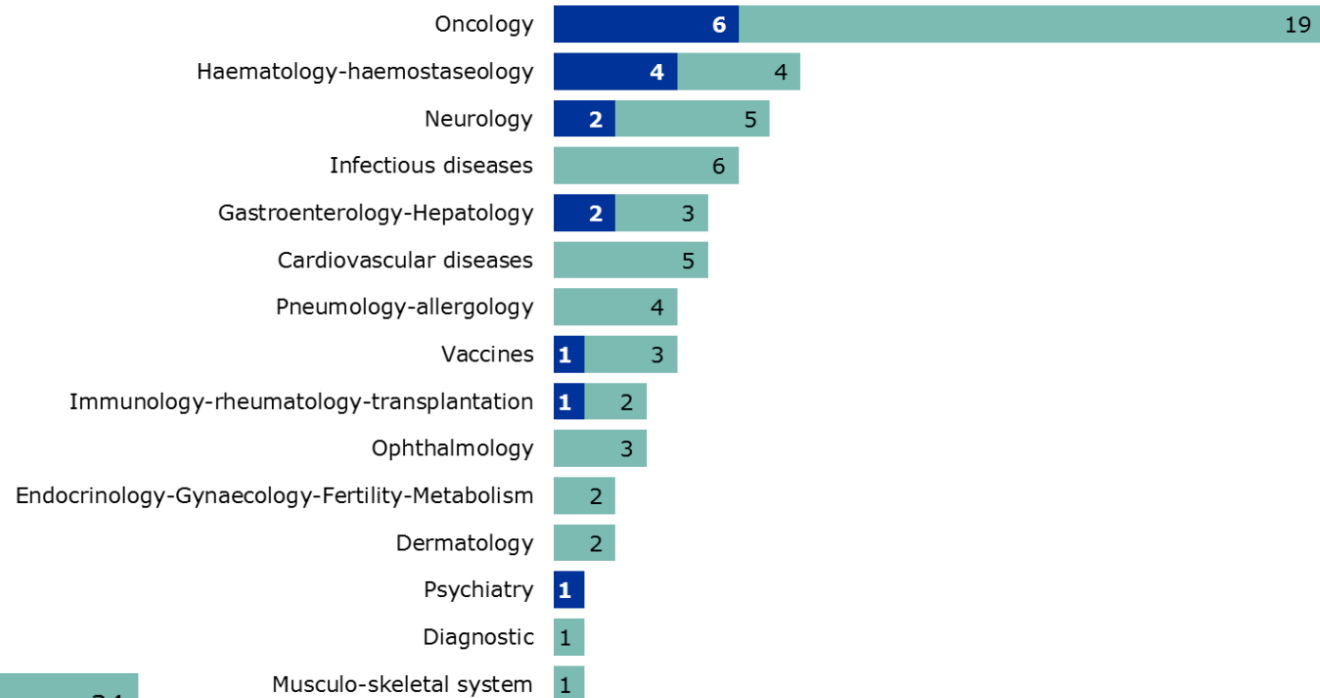


■ Granted ■ Denied ■ Out of scope*

By type of applicant



By therapeutic area



■ Granted ■ Denied

- Are adaptive approaches and RWD Registries feasible for all drugs or only a particular subset of them?
 - Are decision-makers prepared or willing to rely more on observational (big)data for evidence collection?
 - Is it possible to shift current roles, obligations and responsibilities of patients, public, clinicians, regulators, payers and industry in regards to drug registration and diffusion?
 - Are we able to revisit and change the current overlapping legal and ethical responsibilities of industry, regulators, those conducting clinical research, and those providing care?
 - How the costs of these adaptive approaches should be met?
-

