Agenda item 4 - Real world evidence data collection

Italian Experience on Registries

Entela Xoxi

Commission expert group on "Safe and Timely Access to Medicines for Patients"
(STAMP) Brussels, 10 March 2016

Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	x	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	x	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	x	☐	☐	☐ optional
2. Consultancy for a company	x	☐	☐	☐ optional
3. Strategic advisory role for a company	x	☐	☐	☐ optional
4. Financial interests	x	☐	☐	☐ optional
5. Ownership of a patent	x	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	x	☐	☐	☐ optional
7. Investigator	x	☐	☐	☐ optional
8. Grant or other funding	x	☐	☐	☐ optional
9. Family members interests	x	☐	☐	☐ optional

*Entela Xoxi, in accordance with the 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.

N.B. < I am not receiving any compensation>

Italian Health Care System

The National Healthcare System SSN (Servizio Sanitario Nazionale) provides healthcare coverage to the Italian population. Although it is under the responsibility of the Ministry of Health, the system is decentralized resulting in three levels:

National level: The Ministry of Health formulates every three years a healthcare plan PSN (Piano Sanitario Nazionale) that determines healthcare policies.
Regional level: Twenty regions implement the PSN with their own resources and can adjust to region-specific needs. As a consequence, geographic disparity in terms of healthcare access or the level of co-payments exists.
Local level: Local health units ASL (Azienda Sanitaria Locale) provide the health care services – e.g. primary medical services, coordination of all non-emergency admissions to public hospitals.

Since January 1st, 2004, prices of all medicines reimbursed by the NHS are set through negotiation procedure between AIFA and pharmaceutical companies, following methods and criteria previously adopted for medicines approved under European procedures only.
During negotiations, the parameters taken into account are those defined by the CIPE Resolution n. 3 of 2001 (*CIPE- Comitato Interministeriale per la Programmazione*, Interministerial Committee for Economic Planning):

- economic impact on the NHS;
- prices in other EU countries;
- cost of treatment per day compared to the cost of medicines with similar effectiveness;
- benefit/risk ratio compared to medicines with the same therapeutic indication;
- cost/effectiveness ratio when other treatment options are available;
- level of innovation.

According to the new AIFA Regulation of October 2009, the pricing and reimbursement process occurs in four stages, which can be summarized as follows:

1. pharmaceutical company applies for the pricing and reimbursement procedure by submitting the dossier to AIFA;
2. CTS provides its judgment concerning the reimbursement condition according to clinical-therapeutic evaluations;
3. CPR evaluates the dossier and then meets the pharmaceutical company for the negotiation procedure;
4. result of the negotiation are submitted to the Board of Directors for a final evaluation.

Strategy based on simple principles

How to achieve better outcomes and control the cost curves? What is the cut-off to be considered between therapeutic utility of a new medicine and its costs?

Reimbursement is the only field for actions: it is here that national regulatory agencies may intervene

An innovative drug should be reimbursed only if effective

The welfare systems cannot take anymore responsibility for the failures in front of such high costs

Identification of responders patients in order to ensure an effective therapy against the poor prediction of clinical response at the time of recruitment

AIFA Registries

Pharmaceutical Programming 2012 VOL. 5 NO. 1&2
Xoxi et al. The Italian post-marketing registries

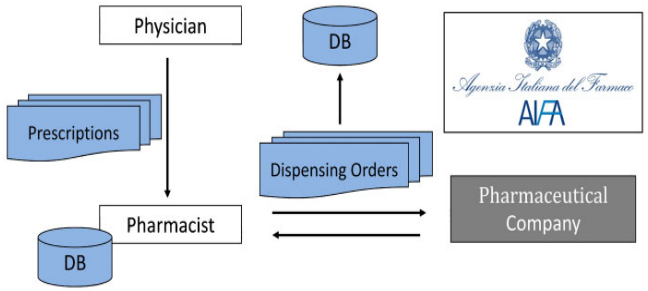


Figure 1 Patients' case report forms must be filled in, in a specific web-based monitoring register (RFM). The register tracks the eligibility of the registered patients and the complete flow of the treatments

Are telematic tools

@National level

placed in the early phases after MA

in some cases for the 'authorized' off-label* use

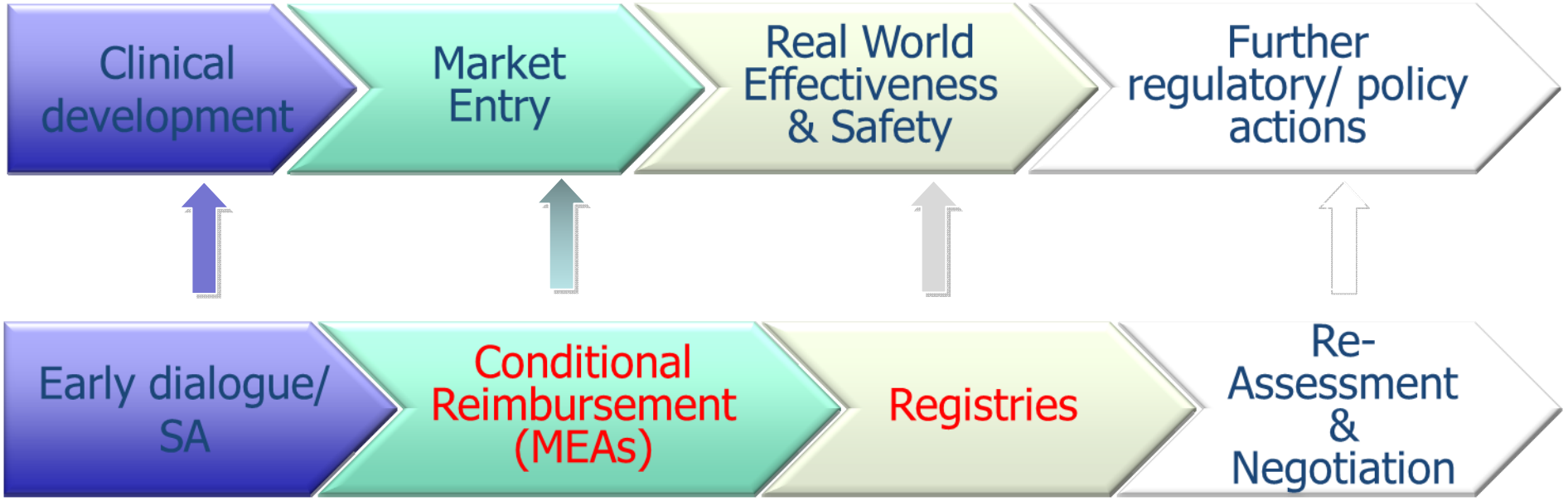
designed to collect RWD

safety, effectiveness & to apply the MEAs

(*) 648/96 Law: that enables the NSH deliver temporarily when there's no valid therapeutic option

The Italian model:

Data collection & Conditional reimbursement



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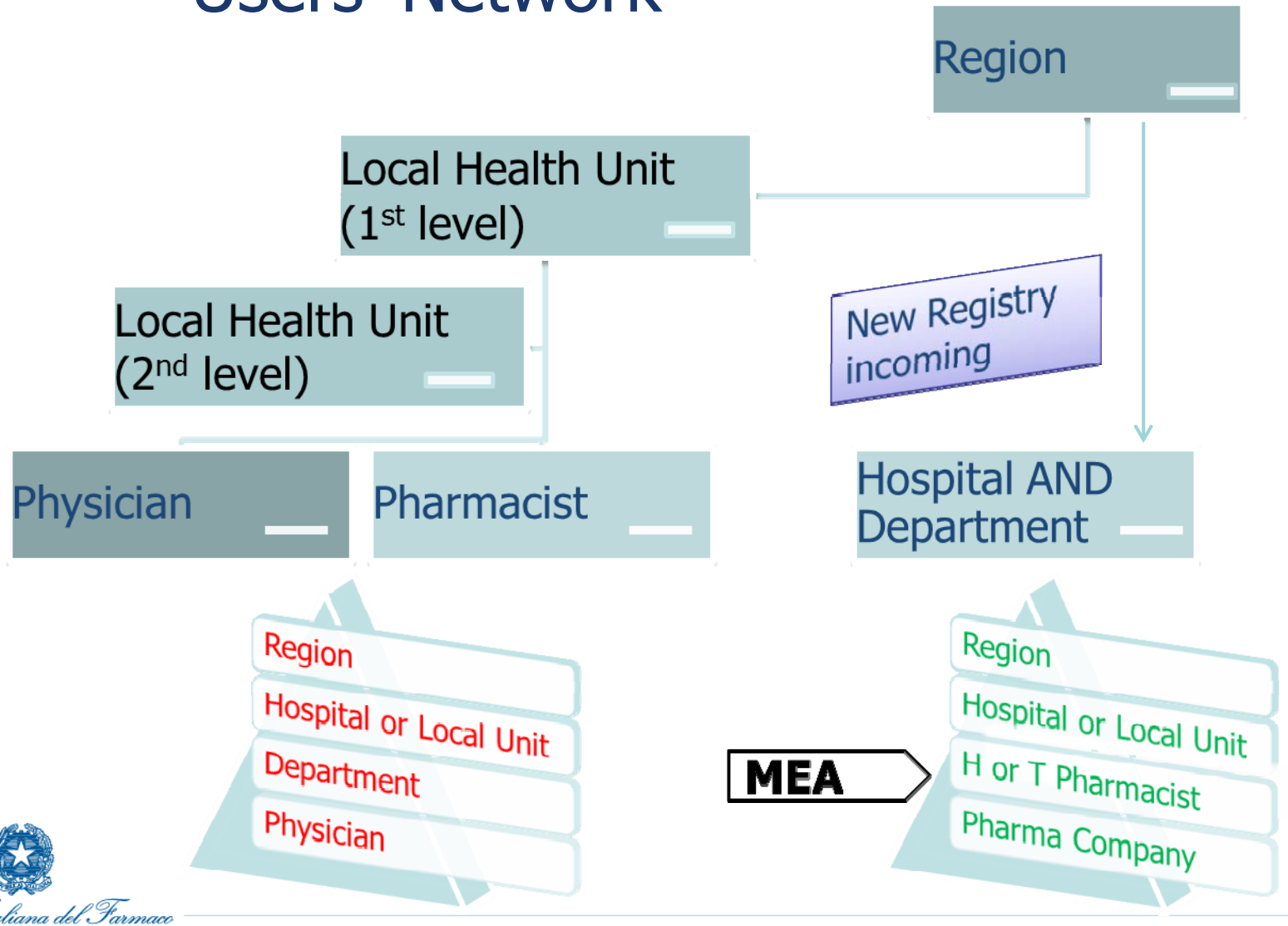
(R)Evolution

Y 2006
Version 1.0

Y 2013
Version 2.0

Law n. 135/2012
Law Decree 19/06/2015

Users' Network



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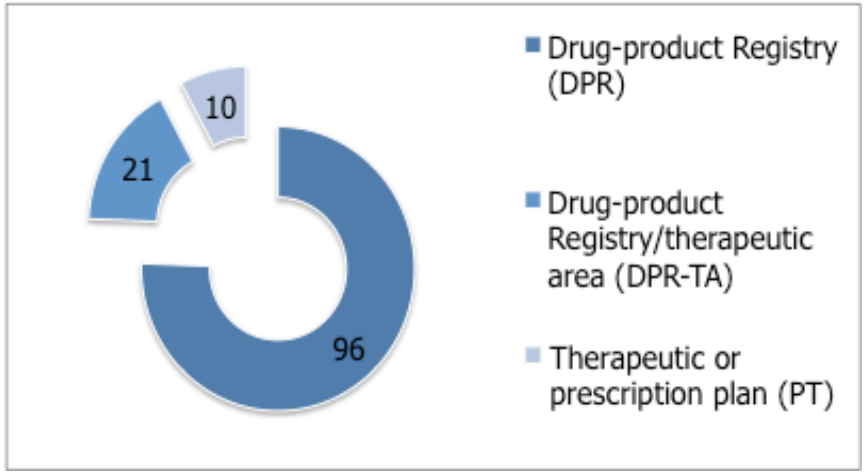
Figures



127 Registries - 32 MAH

All drug product-based

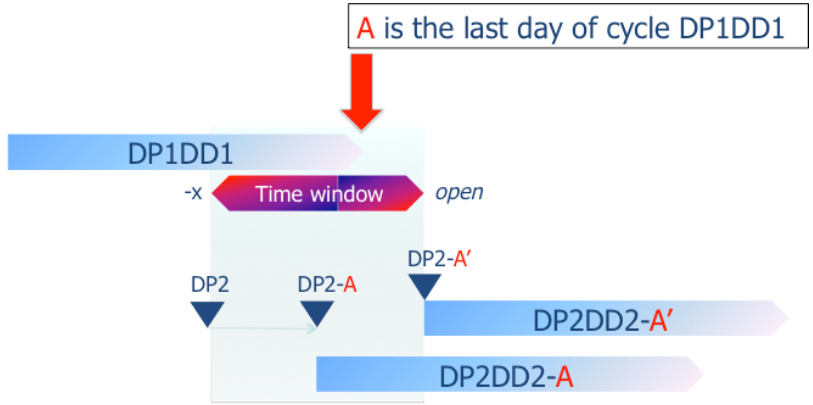
21 registries with standardized DC (therapeutic area)

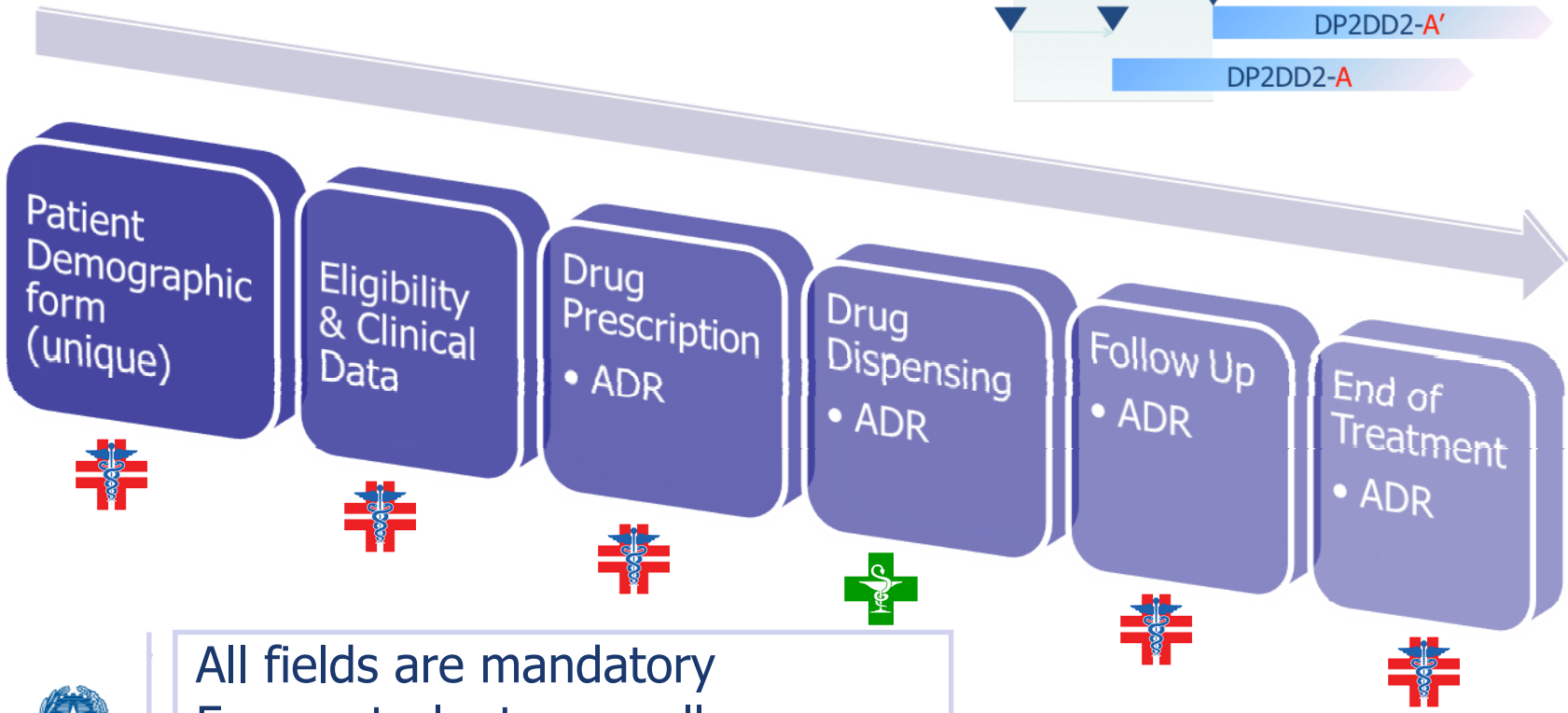
>880,000 Patients

~ 24,000 physicians/ ~ 1,325 pharmacist

~ 900 Health managers/ 48 Regional responsibles

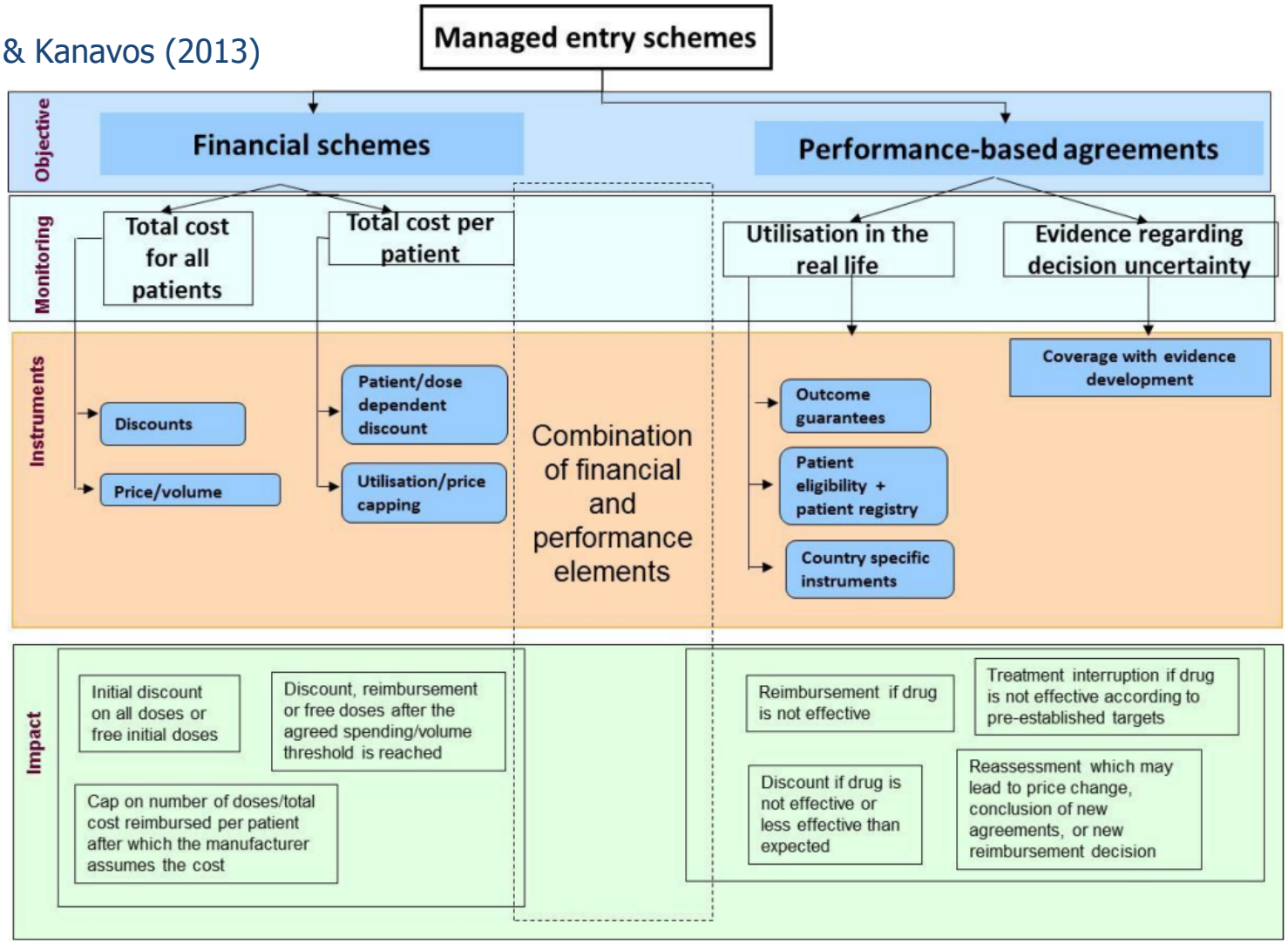
Treatment record



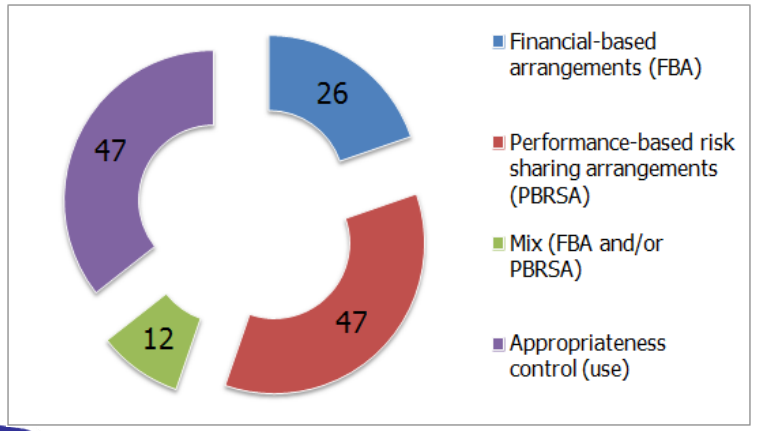


All fields are mandatory
Fup controls: temporally range

Ferrario & Kanavos (2013)



Italian management in red Ξ #Registries



Combination

Managing uncertainty relating to clinical benefit & cost effectiveness

Outcome based
- Payment by result
- Risk sharing
- Success fee

Managing budget impact

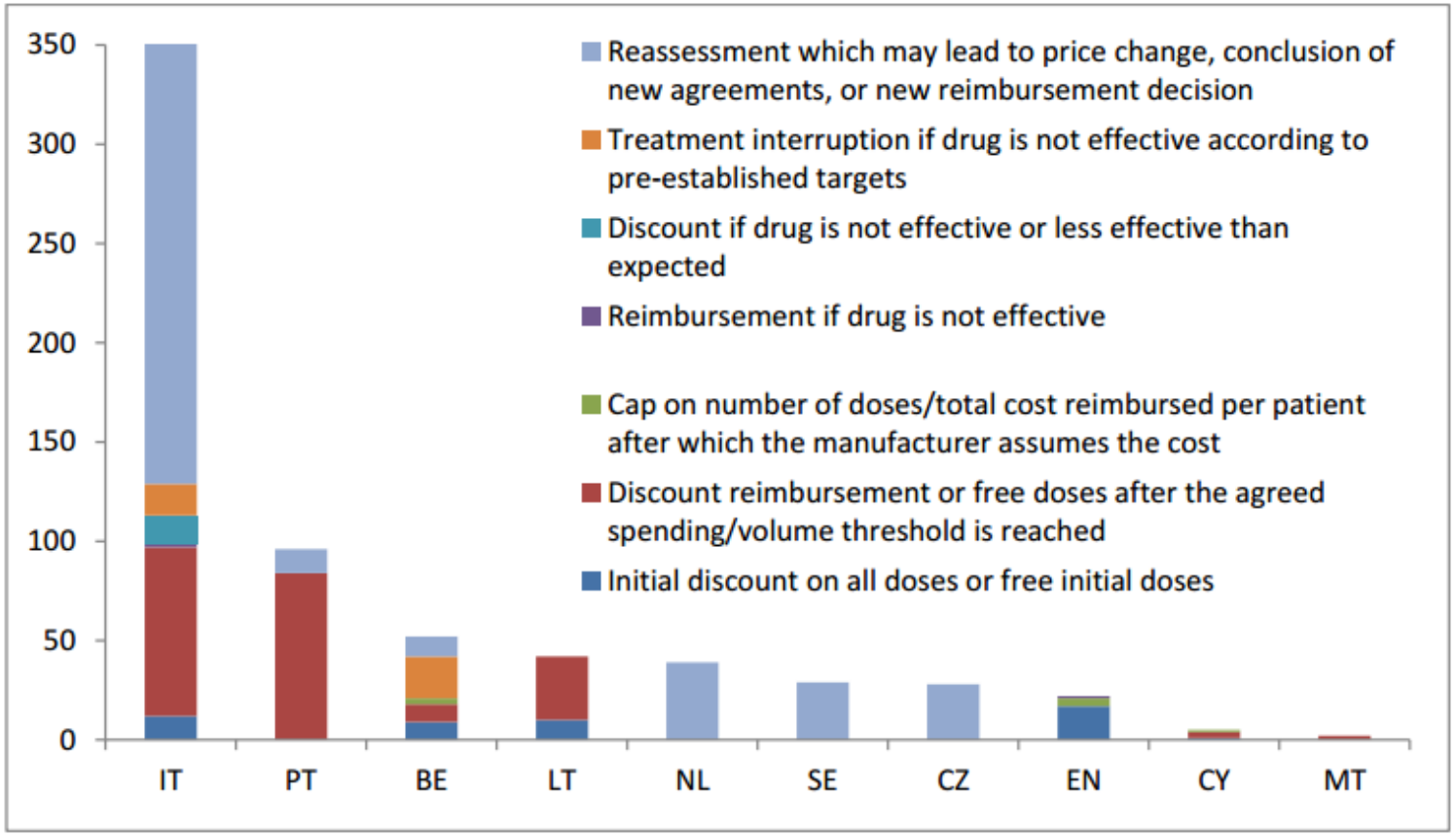
Non Outcome based
- Cost sharing
- Capping
- Price volume

Managing utilization to optimize

Appropriateness
- Safety monitoring
- Prescription plans
- AIFA Notes

AIFA Registries & value based price

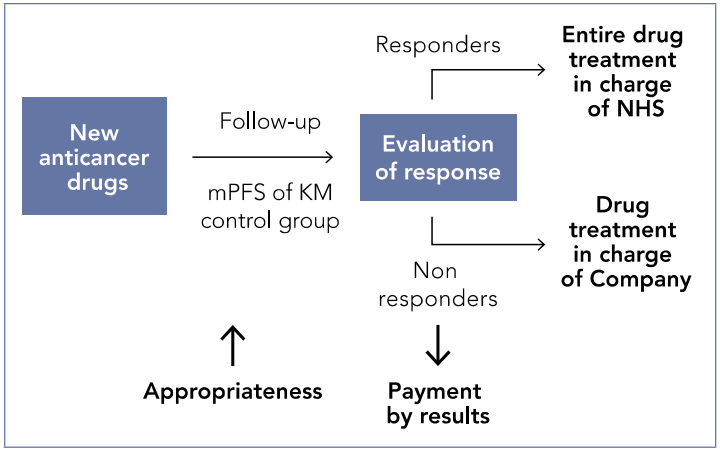
1. Even if cost-effectiveness analysis did provide a reliable way forward, there is still a budgetary problem to be considered (Bach, *N Engl J Med* 2015).
2. Specific MEA for each therapeutic indication (Bach, *Jama* 2014) 'when costs are essentially the same but benefit differs widely, value is not the same' → crude metric of value: cost per Y of life gained
3. The economic effect will reflect the actual effectiveness and the costs will be lower in indications with a high number of non-responders



Notes: BE: Belgium, CY: Cyprus, CZ: Czech Republic, EN: England, IT: Italy, LT: Lithuania, MT: Malta, NL: Netherlands, PT: Portugal, SE: Sweden

Ferrario & Kanavos (2013)

Methodology in cancer area

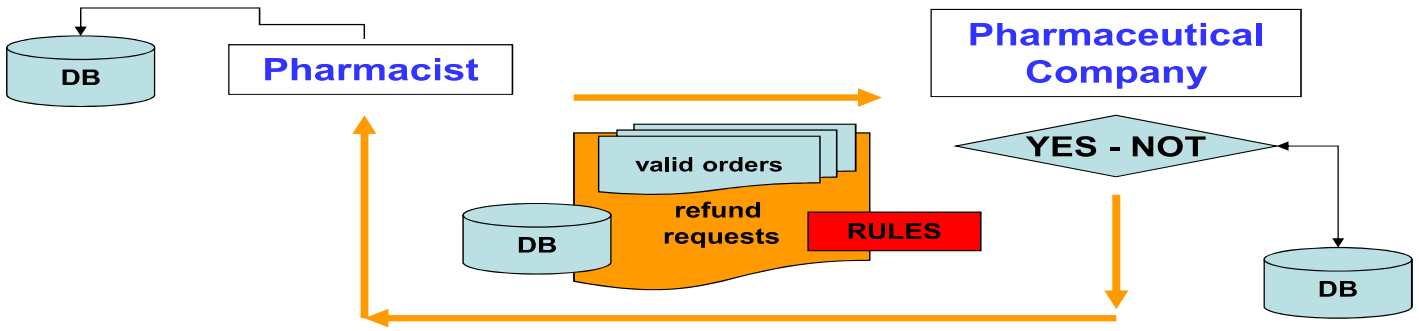


mPFS of KM: tempo di follow-up calcolato sulla mediana della PFS della curva di Kaplan-Meier nel gruppo di controllo

1. Tumor progression
2. Dropouts due to side effects (discontinuation of treatment)
3. Patient death

Kaplan-Meier curves

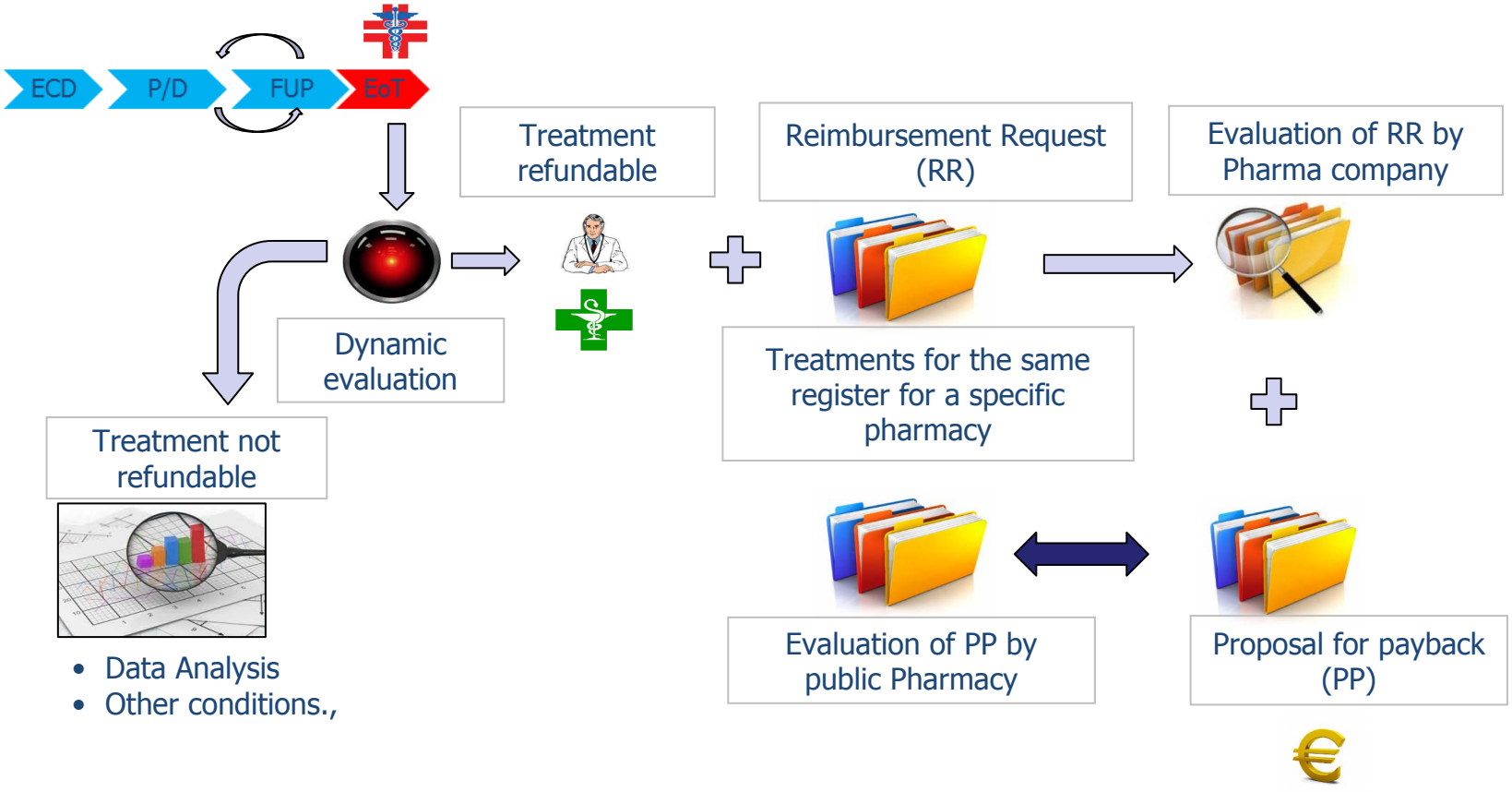
Time of mPFS in the control group, which expresses the incremental effect of PFS of the new drug compared to control. This value is weighted for the duration of the treatment, on the basis of TToT curve of KM curves.



- Cost Sharing, special discount applied to the initial cycles of therapy for all eligible patients
- Risk Sharing, special discount applied to the initial cycles for non-responder patients after re-evaluation
- Payment by Results, total refund applied to the initial cycles for non-responder patients after re-evaluation

① Inclusion criteria - appropriateness: for all registries!
② Continuation treatment: generally for all registries
③ Definition of non responders: only for outcome-based
④ Follow up timing: generally for all registries
⑤ Reimbursement rate: is specific for each registries with MEA

Payback flow



The value cashed in 2015 is about €353.9mln

MEAs in reimbursement and Innovation

TESTO COORDINATO DEL DECRETO-LEGGE 19 giugno 2015, n. 78

Testo del decreto-legge 19 giugno 2015, n. 78 (in Supplemento ordinario n. 32/L alla Gazzetta Ufficiale - serie generale - n. 140 del 19 giugno 2015), coordinato con la legge di conversione 6 agosto 2015 , n. 125 (in questo stesso Supplemento ordinario alla pag. 1), recante: «Disposizioni urgenti in materia di enti territoriali. Disposizioni per garantire la continuita' dei dispositivi di sicurezza e di controllo del territorio. Razionalizzazione delle spese del Servizio sanitario nazionale nonche' norme in materia di rifiuti e di emissioni industriali. ». (15A06371)

(GU n.188 del 14-8-2015 - Suppl. Ordinario n. 49)

Vigente al: 14-8-2015

11. All'articolo 48 del decreto-legge 30 settembre 2003, n. 269, convertito, con modificazioni, dalla legge 24 novembre 2003, n. 326, e successive modificazioni, dopo il comma 33 sono inseriti i seguenti:

33-ter. Al fine di ridurre il prezzo di rimborso da parte del Servizio sanitario nazionale dei medicinali soggetti a rimborsabilita' condizionata nell'ambito dei registri di monitoraggio presso l'Agenzia, i cui benefici rilevati, decorsi due anni dal rilascio dell'autorizzazione all'immissione in commercio, siano risultati inferiori rispetto a quelli individuati nell'ambito dell'accordo negoziale, l'Agenzia medesima avvia una nuova procedura di contrattazione con il titolare dell'autorizzazione in commercio ai sensi del comma 33.».

National Market Authorisation

Web monitoring by registry (timing)

If MEA: analysis of data collection & MEAs after 2 Ys

If the benefits obtained are lower than those expected, AIFA must initiate a process of re-negotiation with MAH: in order to reduce NHS costs

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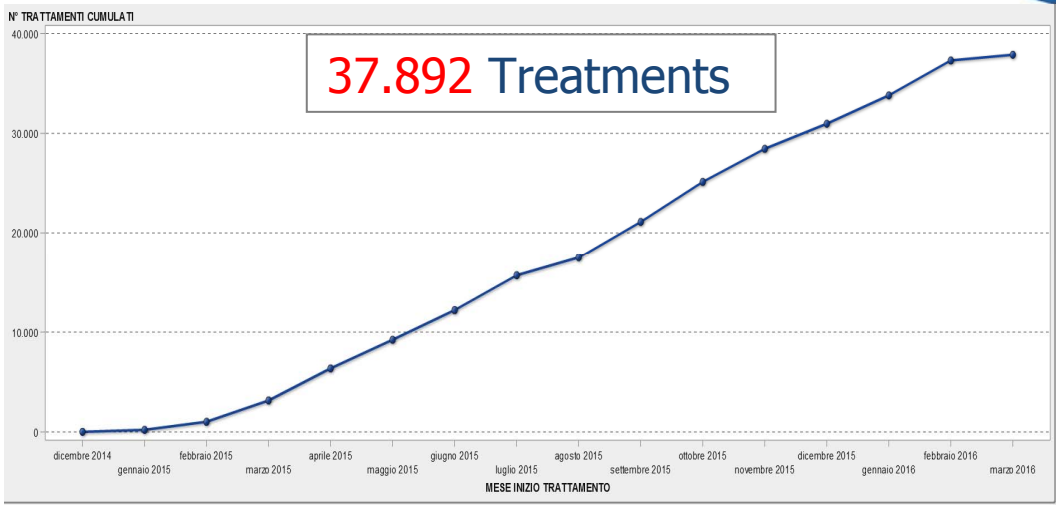
Y 2015: Hepatitis C Financial-based MEA



1. AIFA established the National HCV Technical Board
2. Stimulate the activation of the compassionate use (D.M. 08/05/2003) to try to manage in a timely manner the definition of price and reimbursement
3. Made available an Algorithm to support the prescription
4. Developed with priority the Registries of these therapies
5. Support to the Ministry of Health in the development of standards that would guarantee the financing of new innovative medicines & in the technical definition of the decree provided for in the 2015 Stability Law

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DAAs Treatments/ Criterion & Regional mosaic

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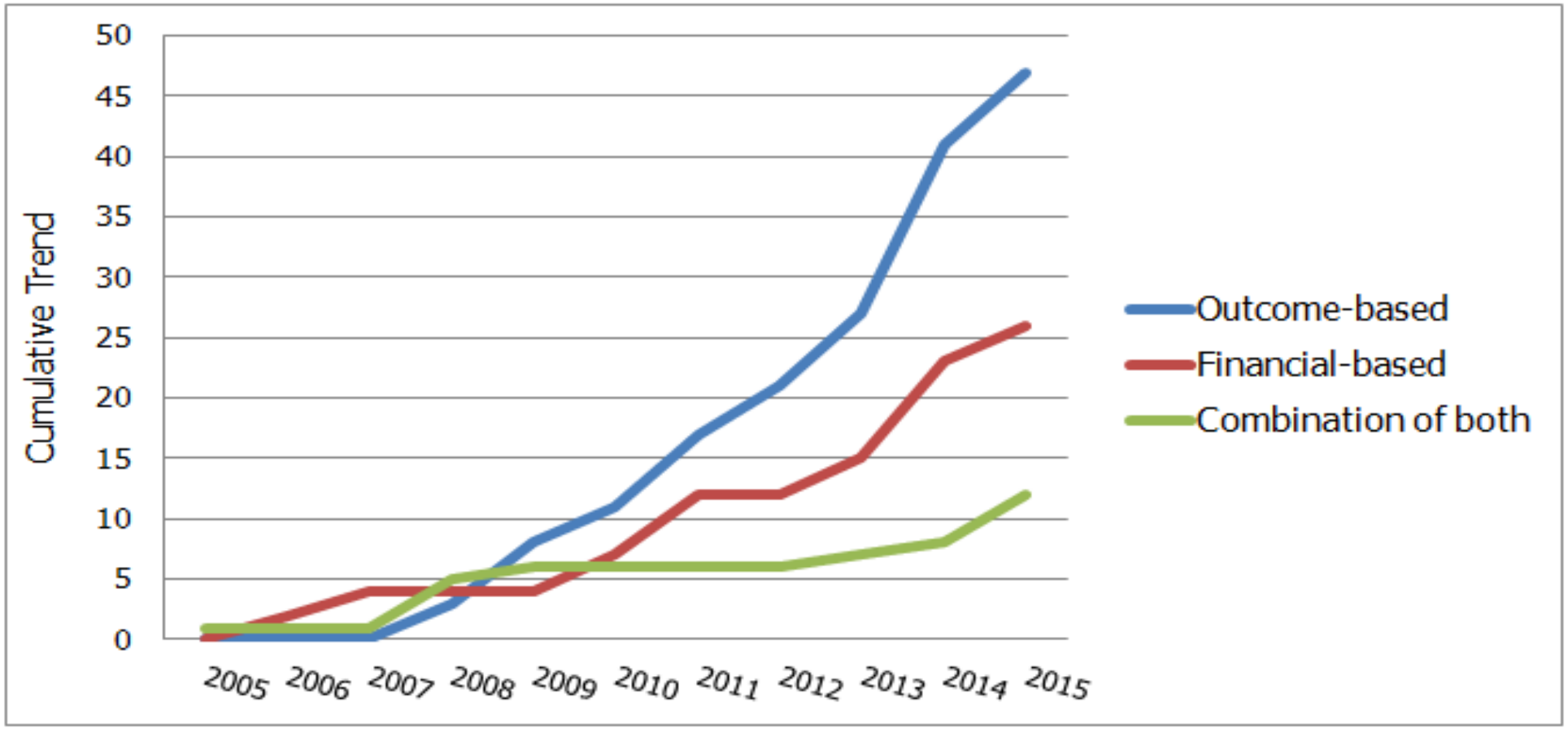
From HER2+ to DAAs to PDL1 to ..



A strengthened scientific dialogue
Drug evaluation becomes a continuum

- Academia & Industry
- Regulators & Payers & HTA bodies
- RCTs: B/R
- RWD: P&R AND MEAs
- DBs AND Interoperability
- **Patients**

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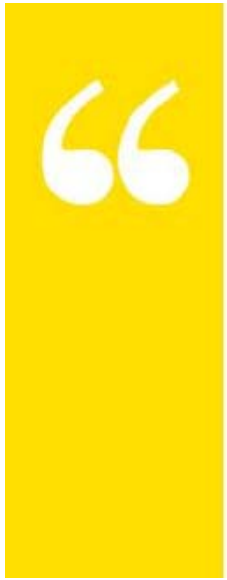
Conclusions

① MEAs' mechanisms are intended to share costs & responsibility with all the stakeholders.

② As main result of this approach to appropriateness in prescribing, it turns easy to use new drugs with a better level of confidence, to obtain early drug activity indicators and to better manage the expenditure controls.

③ Creating synergies with existing initiatives as the EU initiatives on Registries and the EMA's proposal of introducing a system of Progressive Patient schemes & post-marketing studies (PAES, PASS)



Reality is what we take to be true. What we take to be true is what we believe. . . What we believe determines what we take to be true.

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