Il ruolo dell'AIFA

Entela Xoxi

26 giugno 2013

Agenzia Italiana del Farmaco
AIFA

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	Precedenti 2 anni	Da oltre 2 a 5 anni precedenti	Oltre 5 anni precedenti (facoltativo)
Interessi diretti:					
Impiego in una società	x				
Consulenza per una società	x				
Consulente strategico per una società	x				
Interessi finanziari	x				
Titolarità di un brevetto	x				
Interessi indiretti:					
Sperimentatore principale	x				
Sperimentatore	x				
Sovvenzioni o altri fondi finanziari	x				

* Entela Xoxi, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 26.01.2012 e pubblicato sulla Gazzetta Ufficiale del 20.03.2012 in accordo con la policy 0044 EMA/513078/2010 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. Per questo intervento non ricevo alcun compenso

Outlines of this talk

① Appropriateness;

② Registries *et al.*,

③ Managed Entry Agreements;

④ Rheumatology area;

⑤ New web platform;

⑥ Conclusions

J Med Biogr. 2012 May;20(2):91-2. doi: 10.1258/jmb.2011.011028.

Pierre-Auguste Renoir (1841-1919) and rheumatoid arthritis.

da Mota LM, Neubarth F, Diniz LR, de Carvalho JF, dos Santos Neto LL.

Universidade de Brasília School of Medicine, Centro Médico de Brasília, Asa Sul, Brasília/DF, Brazil. licia@unb.br

Abstract

Pierre-Auguste Renoir (1841-1919), one of the world's most celebrated impressionist painters, suffered from rheumatoid arthritis for most of his life. His symptoms developed when he was in his 50s and they became aggressive at about the age of 60 years that led to almost complete disability when he was 70 years old. Although the deformities he suffered because of the rheumatoid arthritis were disabling, Renoir never stopped painting nor decreased the quality of his work. The transition between styles adopted by the painter (Impressionist, Dry and Pearly periods) bear no relationship to the stages of flare-ups or the establishment of joint deformities due to rheumatoid arthritis. His work shows aspects of the body's ability to overcome pain and physical limitation.

PMID: 22791879 [PubMed - indexed for MEDLINE]

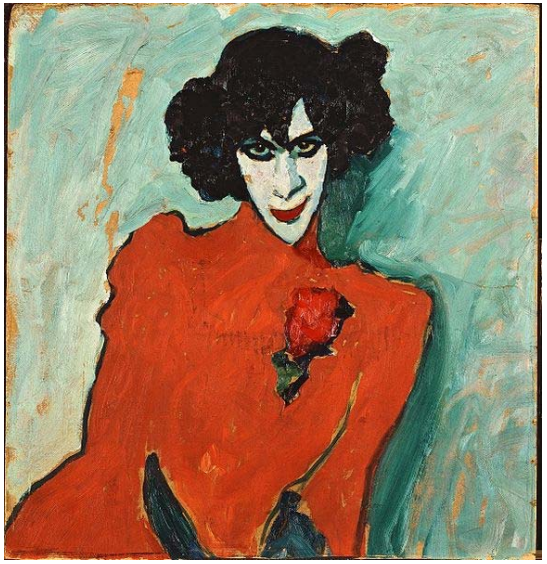
Z Rheumatol. 2011 Jun;70(4):336-57. doi: 10.1007/s00393-010-0658-5.

["Memories of my sick hands": life and medical history of the painter Alexej von Jawlensky].

[Article in German]

Zeidler H.

Emeritus, Medizinische Hochschule Hannover, Wolfsburger Damm 26c, 30625, Hannover, Deutschland. henningzeidler@aol.com



Abstract

Alexej von Jawlensky (1864-1941), one of the most important expressionist painters and a member the artist group "The Blue Four", suffered from severe rheumatoid arthritis. He was the first painter in the twentieth century to create extensive series of paintings especially of human faces. The medical history of Jawlensky as documented in his letters, is a harrowing document of a great artist who suffered from rheumatoid arthritis at a time when medical treatment was limited to physical therapy, pain medication and other relatively ineffective modalities, including the unnecessary extraction of teeth. Jawlensky's disease was characterized by a rapidly progressive course with severe pain, rapid onset of disability and ending up with complete immobilization and paralysis for several years until his death.The artistic processing and sublimation of his illness and suffering resulting in a series of over 1,000 small format meditations are the impressive and touching example of creative coping with rheumatoid arthritis. The meditations are unique in the history of art and often compared with icons. However, knowing the medical condition of Jawlensky these paintings can also be seen as metaphors of suffering and in each image the great physical and mental effort is reflected in the artistic details. Therefore, his art agent Galka E. Scheyer formulated in a letter to him: "You are the painter of the human soul. I know of no other modern painter of the human soul."

PMID: 21614629 [PubMed - indexed for MEDLINE]

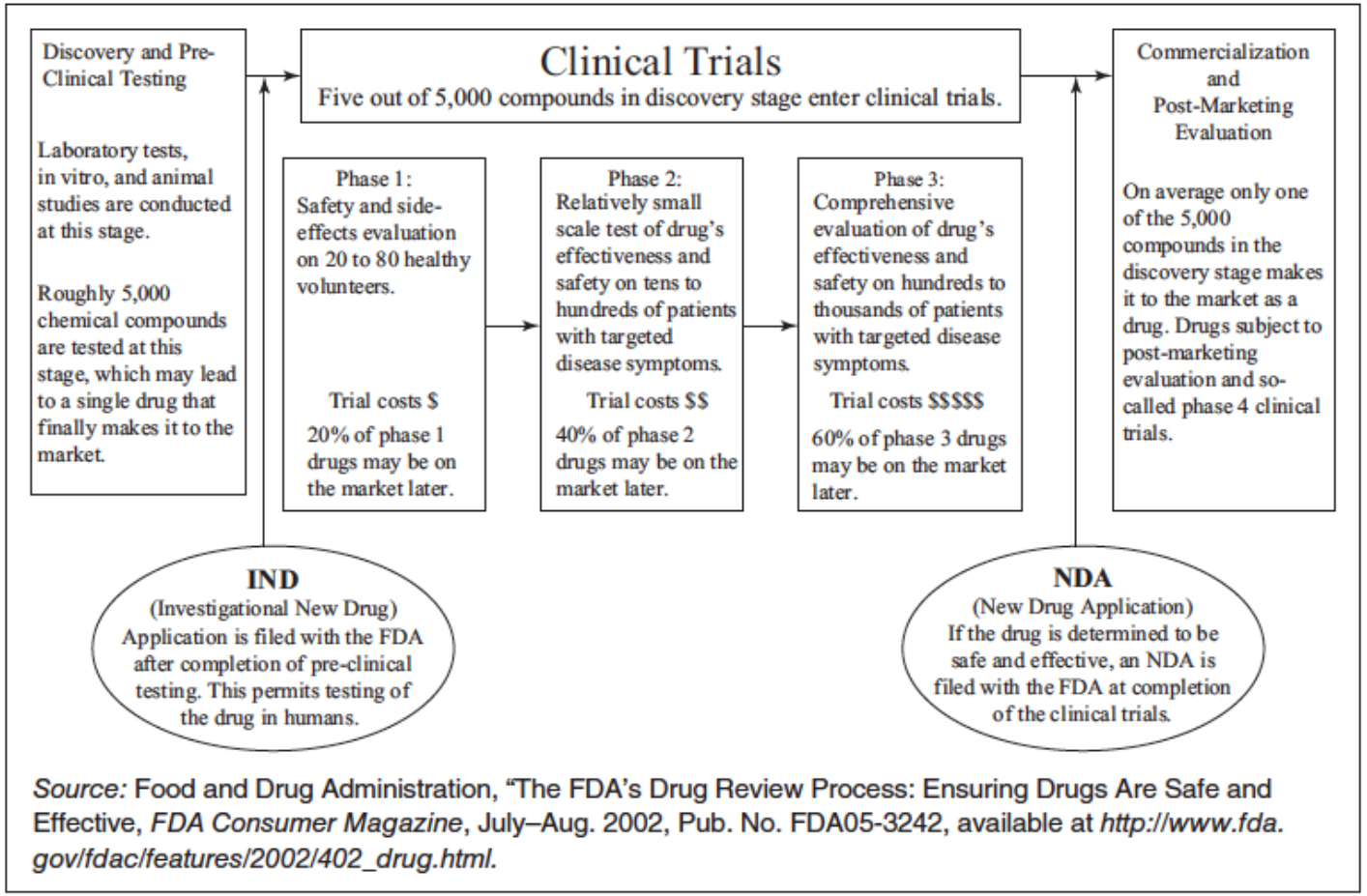
① Appropriateness

What is a clinical trial?

A prospective study of the effect of a drug in humans conducted under conditions pre-specified;

A controlled trial is a prospective study that compares the effect of a drug compared to a control treatment (including no treatment).

The drug discovery & FDA approval process



Source: Food and Drug Administration, "The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, *FDA Consumer Magazine*, July–Aug. 2002, Pub. No. FDA05-3242, available at *http://www.fda.gov/fdac/features/2002/402_drug.html.*

Translational Approach

- Discovery (PoT);
- Pre-clinical (PoP);
- Clinical (PoC, PoA);
- Marketing (post marketing surveillance).

What is meant by “Required under Accelerated Approval”

On December 11, 1992, FDA published the final rule to accelerate the approval of new drugs for serious and life-threatening diseases when the drug provides meaningful therapeutic benefit over existing products.

Under 21 CFR 314.510 and 21 CFR 601.41, FDA may approve drugs based on surrogate endpoints that reasonably predict that a drug provides clinical benefit. This clinical benefit is then confirmed through additional human studies or clinical trials that will be completed after marketing approval.

FDA Takes Slow Road Toward Withdrawal of Drug Approved With Fast-Track Process

JAMA, March 9, 2011 – Vol. 305, N. 10

The accelerated approval process for prescription drugs remains a problem for the US FDA. For such approval, the FDA expects the drug maker to conduct post-market studies to evaluate the drug's clinical benefits and adverse events, but companies often do not do such studies in a timely manner.

European Medicines Agency
Press office

London, 27 April 2007
Doc. Ref. EMEA/184876/2007

PRESS RELEASE

EMEA concludes first accelerated assessment for a medicine for human use

The European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending the granting of a marketing authorisation for the first medicinal product for human use that was evaluated by accelerated assessment.

A frequent scene

"Indulgence"of EMA and FDA

Registration
Wider than the trial
(eg. associated drugs or patient characteristics)

1 drug –1 trial
Large
To detect small HR
"Selected" population
Positive result

"Tummyache" of peripheral agencies

Practice
Legitimate marketing
Use extension
Off-label...

Profit-non profit "cooperation"

Further studies +/- that drug
eg. pure confirmatory, special populations...
... are discouraged
... soon become "subtractive"
... therefore "not attractive"

Appropriate Prescribing of Medications: An Eight-Step Approach

MADELYN POLLOCK, M.D., *University of Kansas Medical Center, Kansas City, Kansas*
ORALIA V. BAZALDUA, PHARM.D., *University of Texas Health Science Center at San Antonio, San Antonio, Texas*
ALISON E. DOBBIE, M.D., *University of Texas Southwestern Medical School at Dallas, Dallas, Texas*

A systematic approach advocated by the World Health Organization can help minimize poor-quality and erroneous prescribing. This six-step approach to prescribing suggests that the physician should (1) evaluate and clearly define the patient's problem; (2) specify the therapeutic objective; (3) select the appropriate drug therapy; (4) initiate therapy with appropriate details and consider nonpharmacologic therapies; (5) give information, instructions, and warnings; and (6) evaluate therapy regularly (e.g., monitor treatment results, consider discontinuation of the drug). The authors add two additional steps: (7) consider drug cost when prescribing; and (8) use computers and other tools to reduce prescribing errors. These eight steps, along with ongoing self-directed learning, compose a systematic approach to prescribing that is efficient and practical for the family physician. Using prescribing software and having access to electronic drug references on a desktop or handheld computer can also improve the legibility and accuracy of prescriptions and help physicians avoid errors. (Am Fam Physician 2007;75:231-6, 239-40.

“Appropriateness: the next frontier”

a. Da che cosa si richieda ai clinici;
b. Da dove essi vivono e lavorano;
c. Dal peso che essi danno ai diversi tipi di evidenza e agli obiettivi finali;
d. Dal fatto che essi considerino le esigenze del paziente;
e. Dai livelli delle risorse presenti in un dato SSN;
f. Dai valori che prevalgono sia in quel SS che nella società dove i clinici prestano la loro opera.

British Medical Journal 1994; 308: 218-19

② Registries

Which therapeutic areas are involved

- ✓Highly Innovative;
- ✓Biological/ Biotechnological;
- ✓High priced.

Why are they considered positive at regulatory level

- ✓ Placed in the early phases after MA;
- ✓ Partiality of information related to efficacy, safety and place in therapy coming from CT;
- ✓ Drugs and treatments are highly innovative but high priced.

The role of Registry

- ✓ To increase the patient's protection by promoting drugs' appropriate use;
- ✓ To verify effectiveness & tolerability;
- ✓ To apply the Managed Entry Agreements procedure by the Italian regulatory position.

The Italian post-marketing registries

Entela Xoxi, Carlo Tomino, Luca de Nigro, Luca Pani

Italian Medicines Agency, Roma, Italy

The post-marketing registries, established by the Italian Medicines Agency in 2005, represent the example of a national application of an automated workflow handling the personalized drug distribution in hospital pharmacies and local public pharmaceutical services, with the intent of both improving the efficacy/efficiency of analysis and regulatory activities themselves, as well as closely monitoring the clinical activity. In fact, within the correct clinical practice the prescriber shall take into account the parameters, such as therapeutic drug indication, actual benefit the patient should gain in comparison to the trials, potential and actual risk of adverse reactions, drugs interactions, and cost of the therapy. On the track of the cancer registry's experience, the Italian Medicines Agency has extended the scope to the following areas: ophthalmology, rheumatology, dermatology, orphan drugs, cardiology, diabetology, respiratory, and neurological diseases. It involves more than 60 drugs (most of them with risk sharing schemes on a population of over 400 000 patients) and is available from http://monitoraggio-farmaci.agenziafarmaco.it.

Published by Maney
DOI 10.1179/1757092112Z.0000000009

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Why the Italian Registers exist?

a) To support the regulatory, administrative and clinical activities of the National Health Service;

b) To improve the public health governance, the analysis of real clinical practice after the conclusion of the clinical trials and the marketing authorization processes, the effective governance of public costs.

Collecting data: more info from the real world --> Comparative Effectiveness Research (CER)

A necessity for:

- ✓ Academy;
- ✓ Regulatory;
- ✓ Pharma industry.

Required for:

- ✓Health economic data;
- ✓Experiences data;
- ✓Patient-reported outcomes;
- ✓Reimbursement data;
- ✓Safety surveillance data.

HOW WE WORK

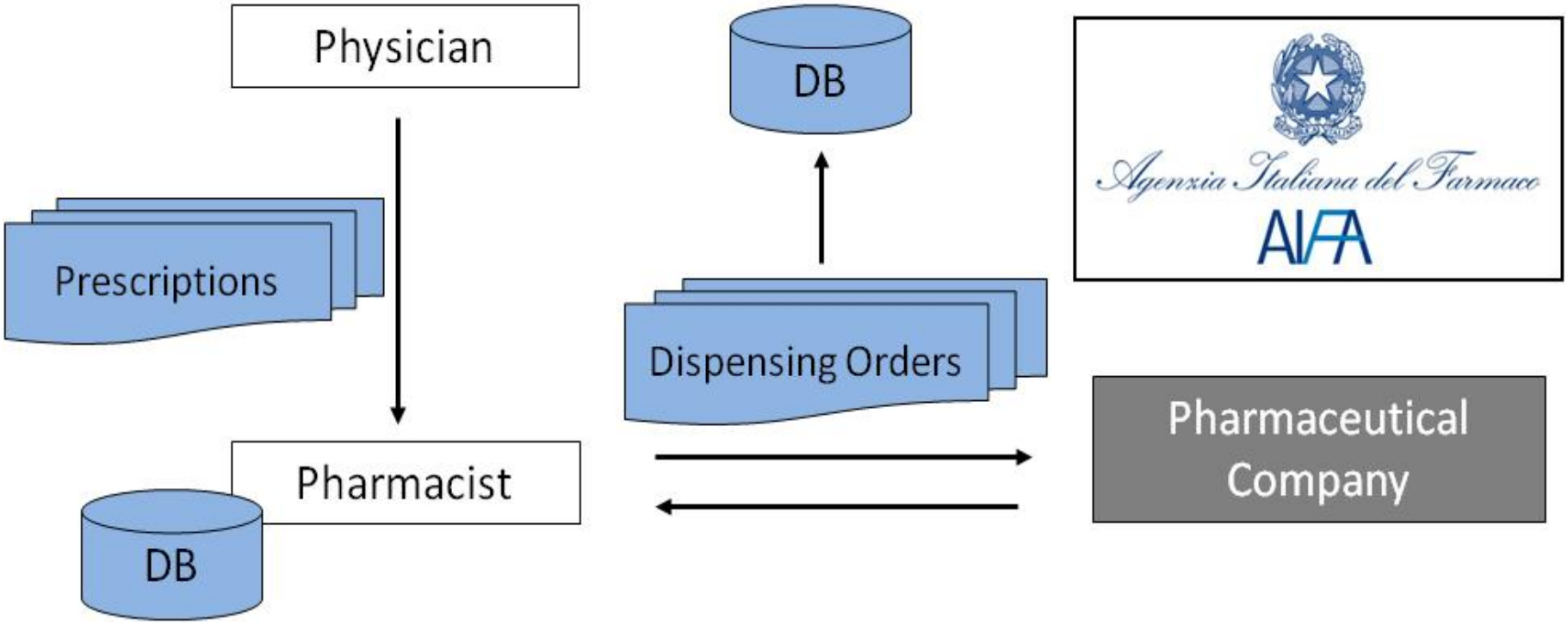
- ✓ Drug & Pathology analysis;
- ✓ National context;
- ✓ Appropriateness & Managed Entry Agreements.

How Registry works:

Patients' Case Report Forms must be filled in, in a specific *web based* platform.

The Registry tracks the eligibility of the registered patients and the complete flow of the treatments.

Data entry


Physician
DB
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Prescriptions
Dispensing Orders
Pharmaceutical Company
Pharmacist
DB

Figures

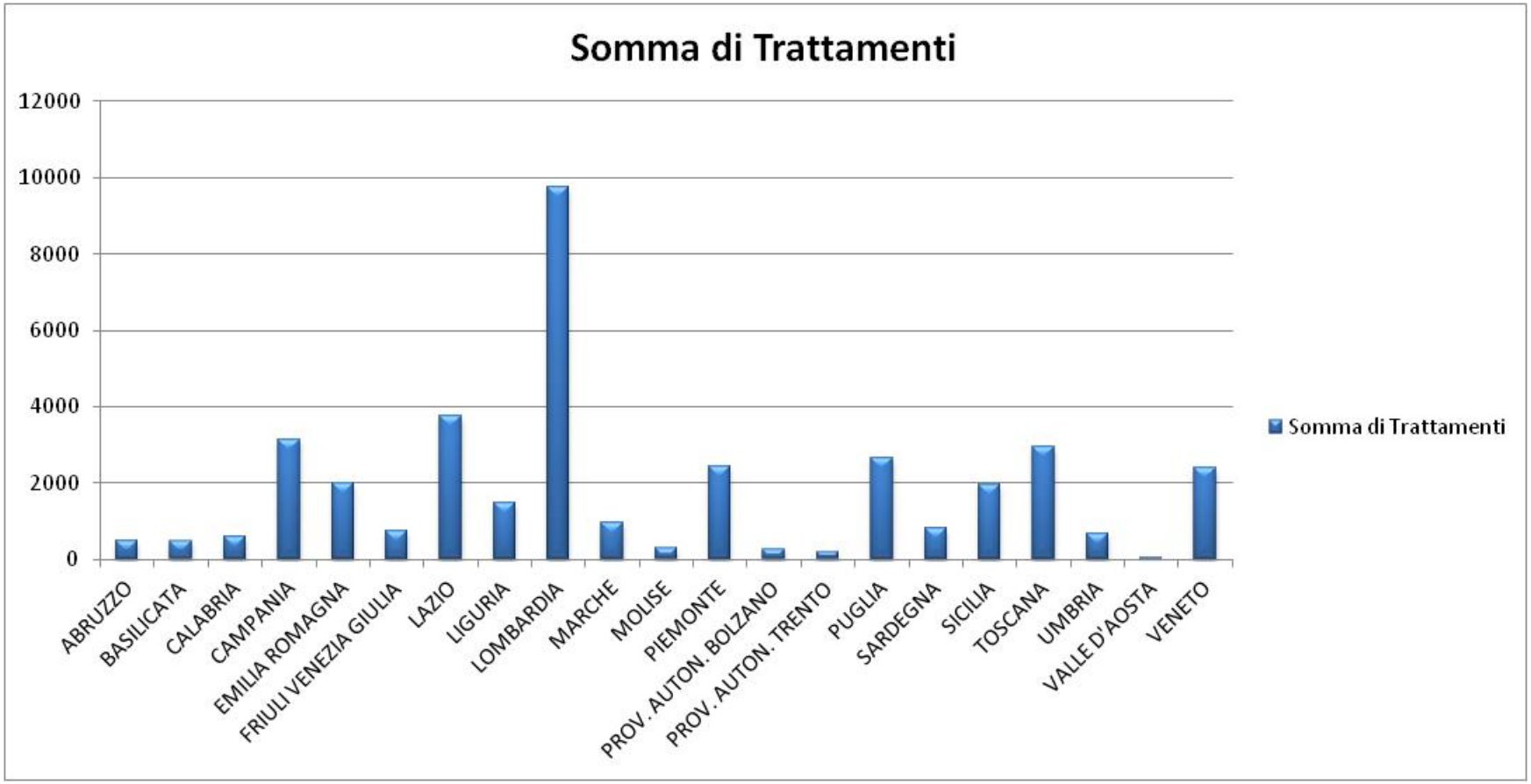
Medicines under monitoring	44
Therapeutic indications	71

Eligibles	38,009

Physians	2,821
Pharmacists	191

Updated 25/06/2013

New Registries



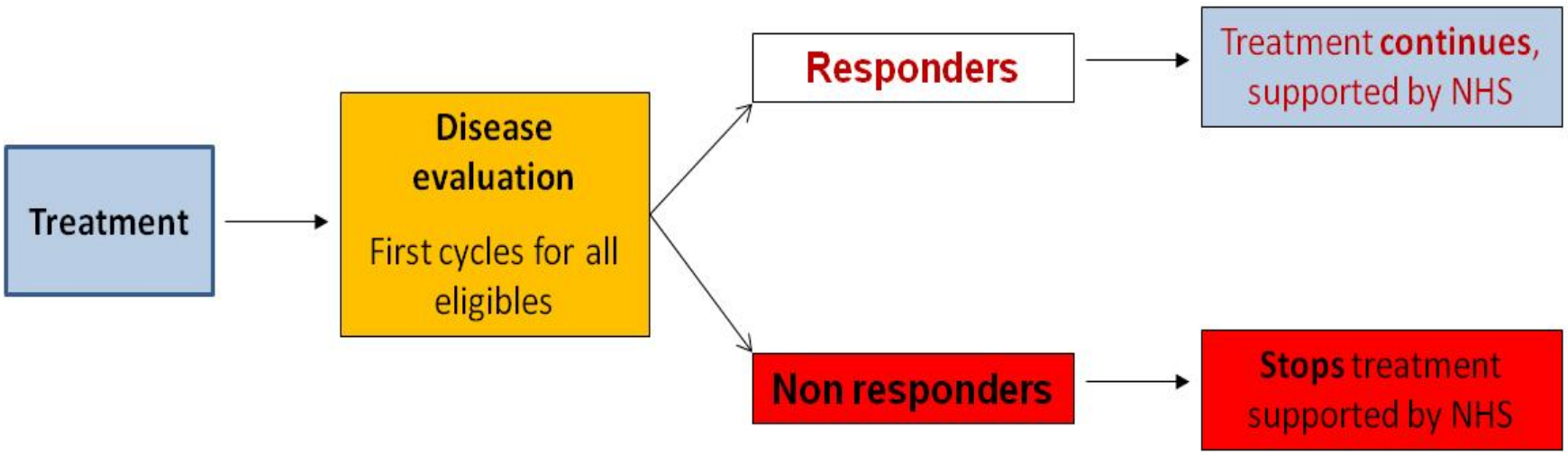
Updated 25/06/2013

Strategy based on simple principles

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.

Rules


Treatment
Disease evaluation
First cycles for all eligibles
Responders
Non responders
Treatment continues, supported by NHS
Stops treatment supported by NHS

Health Technology Assessment

Is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a HT in a systematic, transparent, unbiased, robust manner.

Its aim is to inform the formulation of safe effective, health policies that are patient focused and seek to achieve best value.

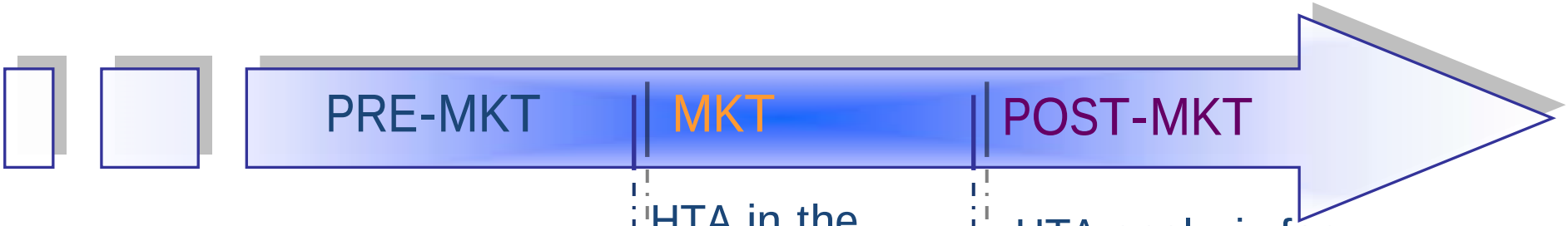
EUnetHTA , European network for HTA

HTA Evaluation

- Cost- effectiveness analysis (ICER);
- Cost- utilization analysis (QALY);
- Cost – benefit (critical: monetary value to a health condition)

Manuale di Health Technology Assessment, Cicchetti e Marchetti

AIFA e HTA!



HTA analysis for supporting P & R decisions

HTA analysis for evaluating risk-benefit profile

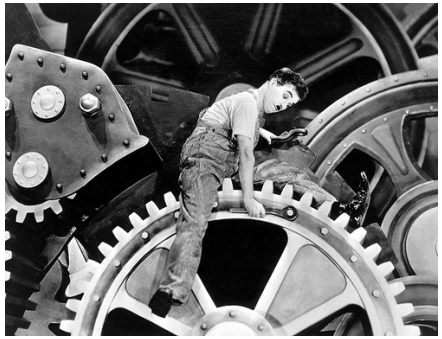
HTA in the appropriateness of utilization

HTA analysis for supporting P & R re-negotiation

HTA analysis for supporting decision of new therapeutic indications

HTA analysis for assessing risk-benefit profile following ADR signals

③ Managed Entry Agreements



About regulatory politic & money

- ✓ Cost of new drugs is prohibitive, and (sometimes) unrelated to benefit size

- ✓ At the level of EU member states, no or limited actions are possible
  - Registration is mandatory;
  - Reimbursment is the only field for actions.

To introduce “benefit size”...

NICE approach

- Cost-effectiveness analyses to assign economical value to innovative drugs;
- Need to define (and accept!) thresholds for reimbursment;
- Time-consuming, requires highly efficient and qualitative teams (with a lot of people);
- Might be unreliable when you have only (few) data on efficacy, none on effectiveness and need an overwhelming use of simulations and models .

A NICE-like approach

Is a pragmatic approach

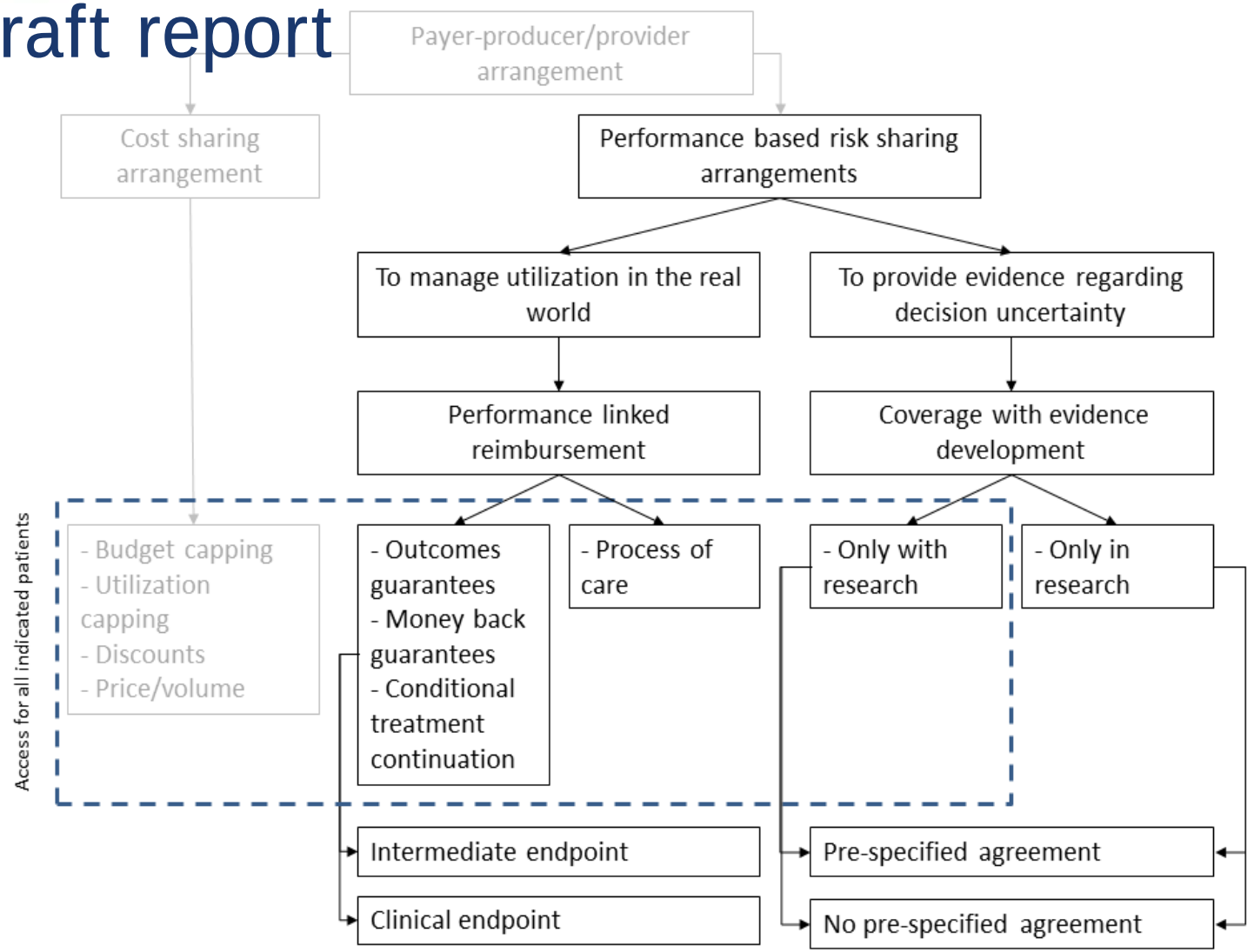
- Relying on measured activity of drugs in clinical practice;
- Not on cost-effectiveness analyses;
- Not requiring definition of thresholds;
- That could be decided within even only one agency/ industry meeting in the price commission;
- Only partially flawed by low amount and weakness of registrative data.

MEAs: Performance - based risk sharing arrangements

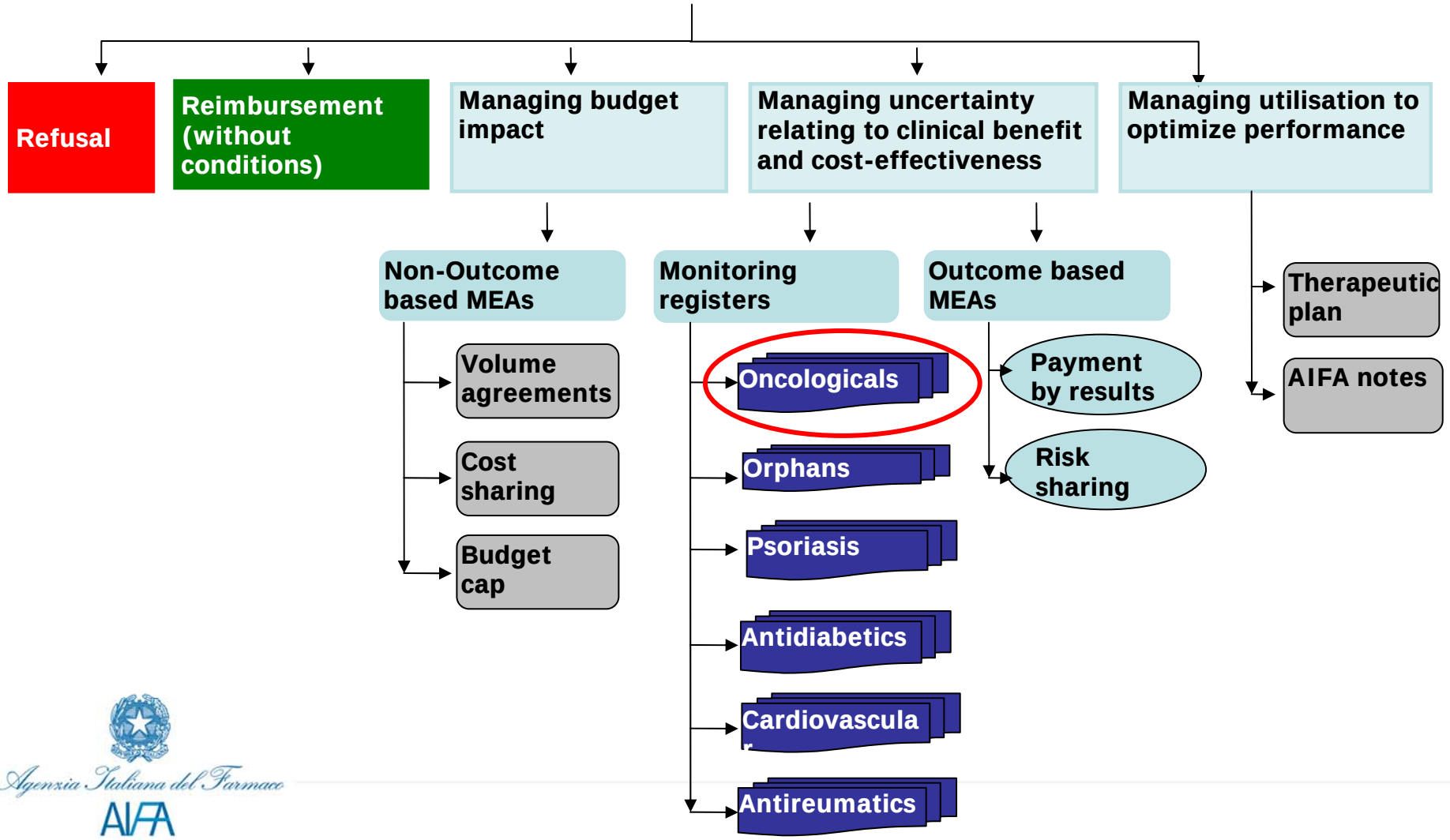
PBRSAs are payment schemes – they involve a plan by which the performance of the product is tracked in a defined patient population over a specified period of time and the level of reimbursement is based on the health and costs outcomes achieved.

ISPOR performance based Risk sharing arrangements TF Report

ISPOR - draft report



Managed Entry Agreement (MEA)



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AIFA's MEAs rules

Eligible:

- Cost sharing (CR, special discount)

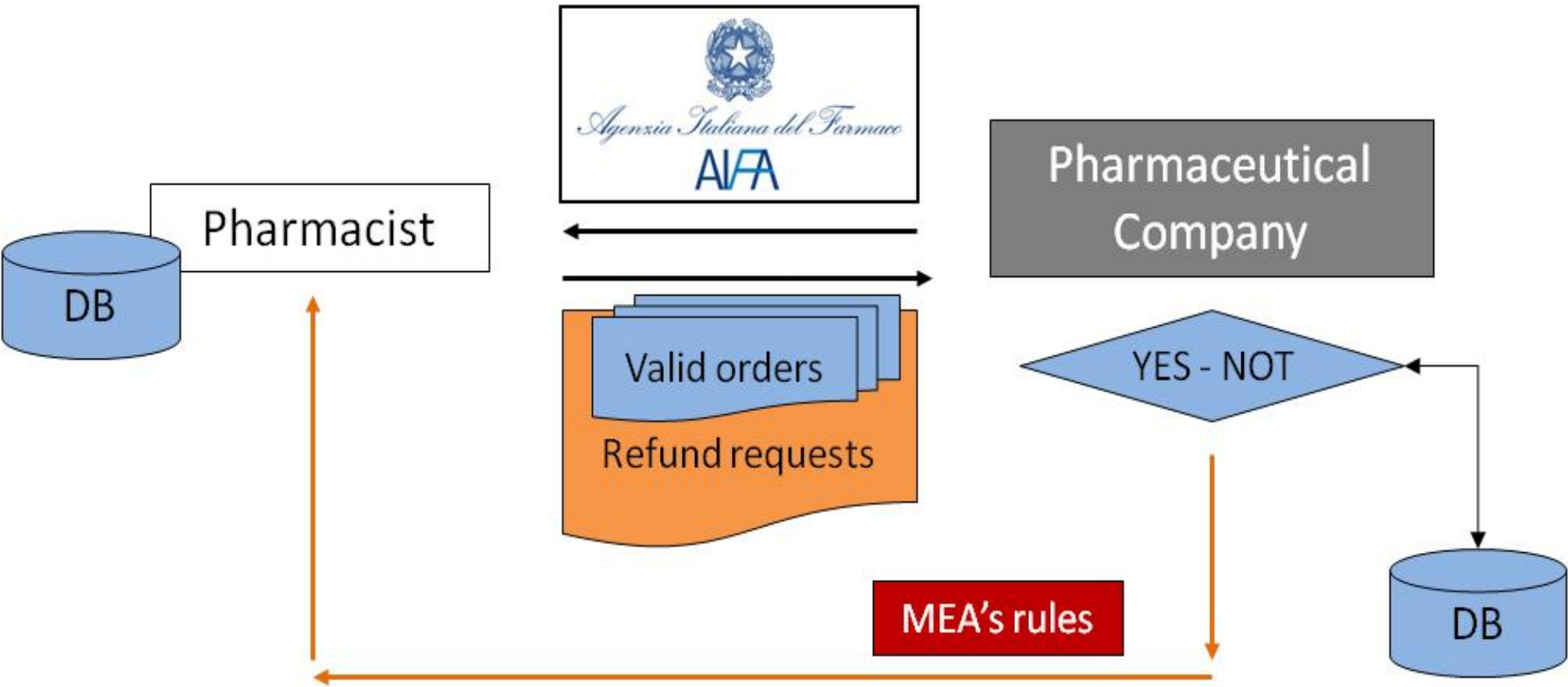
Non responder:

- Payment by results (PbR, total refund);
- Risk sharing (discount);
- Success fee (SF).

International approach & criticism

a. HTA model: UK, Germany, Sweden, Poland;
b. IQWiG, considers HTA in the context of the efficient frontier, while NICE uses cost per quality-adjusted life year;
c. HTA appraisal may over time reduce the importance of proving value at launch;
d. It is very costly and difficult to prove effectiveness at launch, not to mention raising ethical issues related to the use of non-approved medicines.

MEA's application



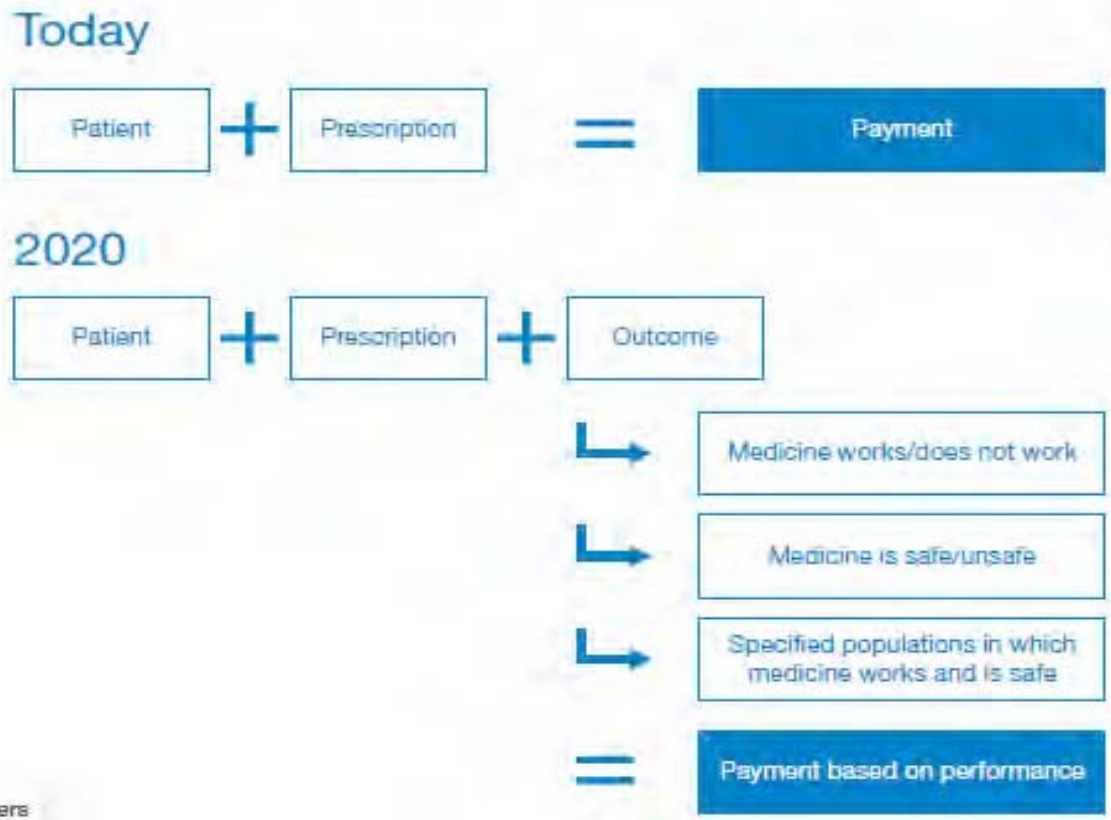
Criticals points

- ✓ Complexity in implementing Registers and related contracts with Companies and Hospitals;
- ✓ Homogenous Regional Access (a National problem!);
- ✓ Consolidation of a new model in monitoring innovative treatments and PBA contracting.

An impending problem

Growing regional autonomy reduces power and credibility of national negotiation

Pharma 2020: Marketing the future
Which path will you take?



Source: PricewaterhouseCoopers

④ Rheumatology area

The past

a) Psocare

b) Drug Registry

- Tocilizumab;
- Certolizumab;
- Golimumab

The future: Disease Registries

Rheumatoid arthritis

Juvenile idiopathic arthritis

Ankylosing spondylitis

Axial spondylitis

Psoriatic arthritis

⑤ New web platform

https://www.agenziafarmaco.gov.it/registri/

Nuovo portale di monitoraggio (Release 1)

Nuovo portale di monitoraggio (Release 2)

Nuovo portale di monitoraggio (Release 3)

Attori

- AIFA
- AIFA
- Medici
- Farmacisti
- Regioni
- AIFA
- Medici
- AIFA
- Medici
- Farmacisti
- AIFA
- Medici
- AIFA
- Farmacisti
- Regioni

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Processo di Pubblicazione di un nuovo Registro

Attori	CTS	AIFA	AIFA
			Regioni

Ciascuna Regione procede all'abilitazione del registro

⑥ Conclusions

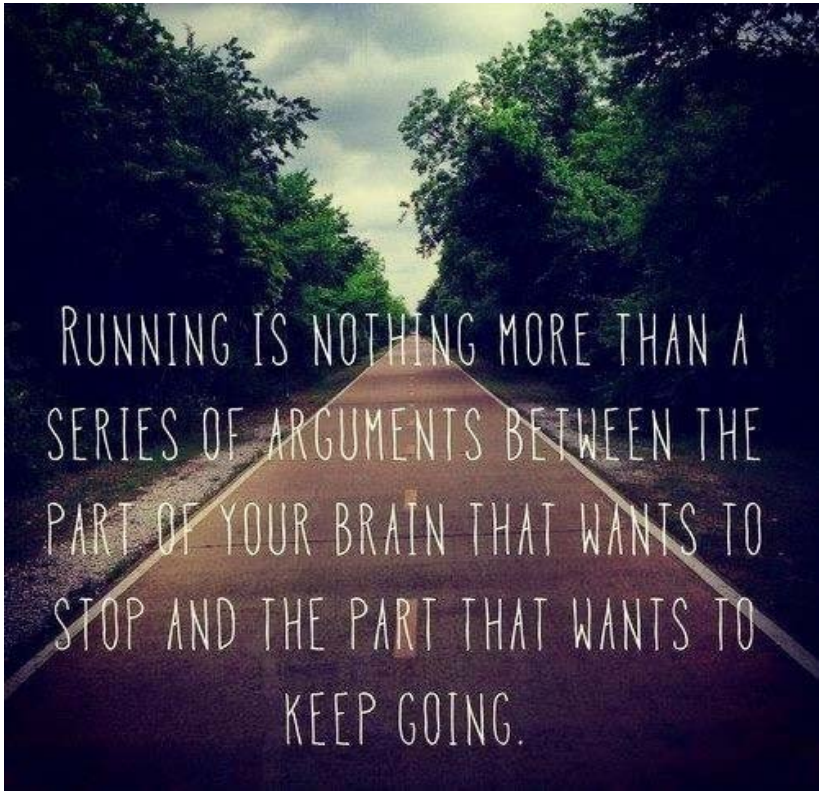
Exchange of data between:

- Clinicians;
- Pharmacists;
- Local healthcare units & Regions;
- Pharma companies;
- Regulatory;
- ePRO .. near future?

Properly managed registries can produce a wealth of valuable data about

1. Patients;
2. Institutions of health care, communities and payers;
3. Pharma Industry.

Grazie!



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http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottoposti-monitoraggio

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