Generalitat de Catalunya
Departament de Salut

CatSalut
Servei Català de la Salut

Challenges in medicines funding for rare diseases

ISPOR
Improving healthcare decisions

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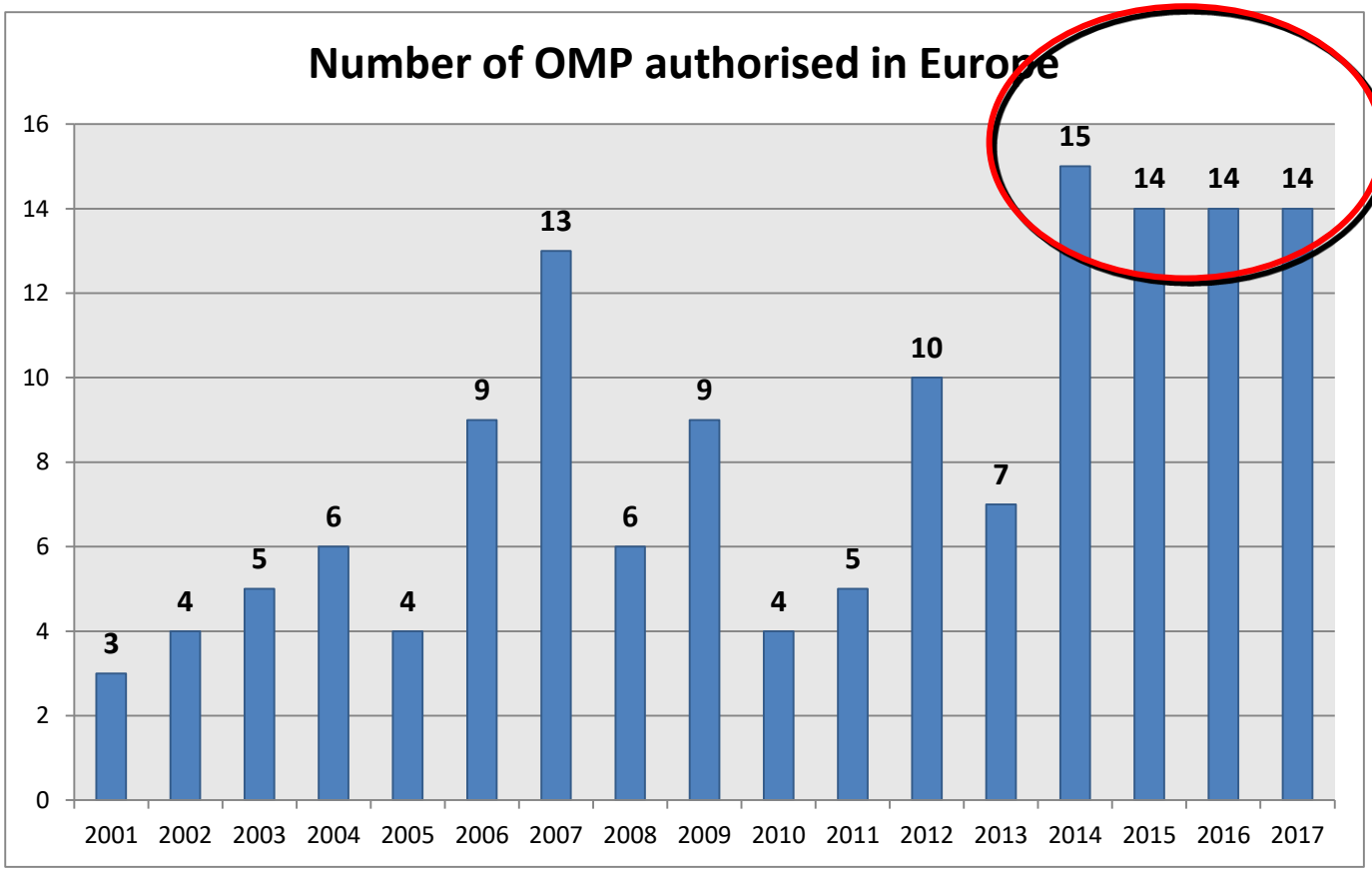
ISPOR Europe 2018
12th November 2018

Milestones of European Regulation: Increasing number of Orphan Medicinal Products in Europe



- **Up to 145** different OMP authorised in Europe till 2017
- **Higher number** of OMP authorised last 4 years (57 OMP, representing 39% out of all OMP)
- Up to date, **in 2018, 17 new orphan** medicines have been approved in Europe

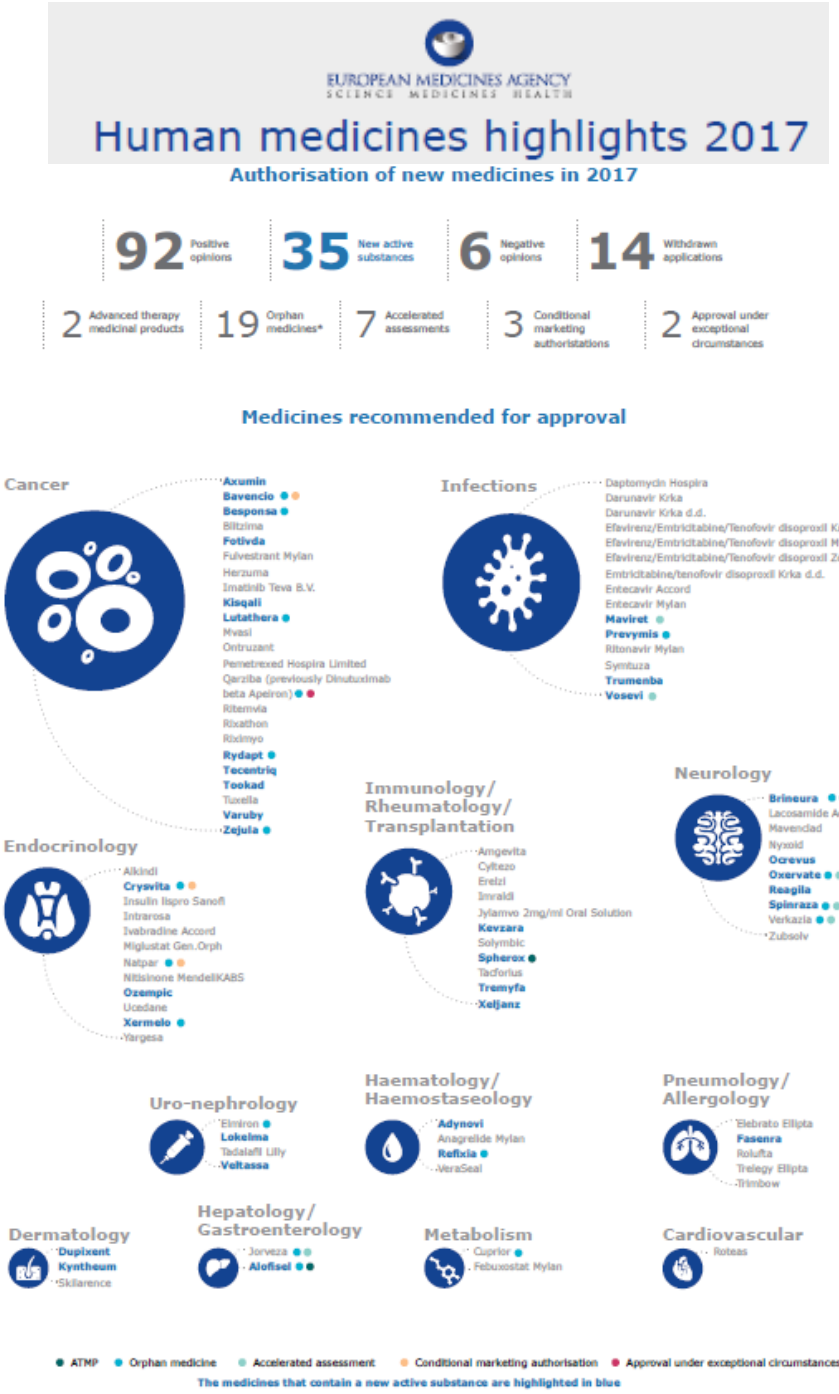
Innovation success

- EMA 2015, 2016, 2017
  - 93, 81, 92 positive opinions
  - 39, 27, 35 NCE
    - 13, 8, 11 oncology (~30%)

Uncertainty

- Conditional and exceptional approvals

	2015	2016	2017
Positive	93	81	92
CA	3	7	3
Exceptional	3	1	2
Accelerated	5	7	7



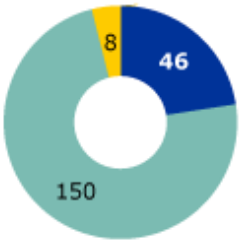
PRIME program

Recommendations adopted by 7 March 2018.

* Out of scope applications are not included in the detailed charts.

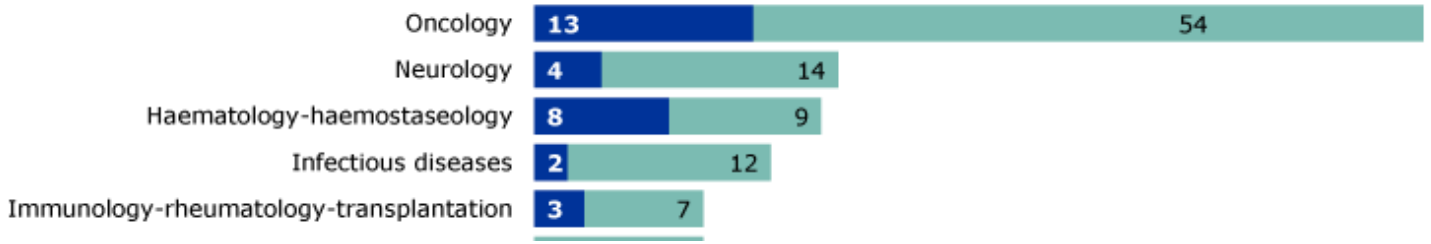
Granted Denied Out of scope*

Applications and eligibility decisions



Type of applicant

Therapeutic areas



36 products eligible to PRIME since launch

30 in rare diseases

16 for paediatric patients

15 advanced therapy medicinal products

PRIME/early access … Some potential concerns…

- PRIME should not compromise the generation of appropriate evidence-based data.
- Otherwise the PRIME is in risk to become a questionable shortcut.
- A reasonable compromise of patients and professionals expectations needs to be guaranteed.
- Connecting initial E data with RWD
- Minimizing tensions through HTA appraisals and early and equitable access.

Challenges to face up rare diseases uncertainties

High unmet medical needs

Scientific evidence not comprehensive

Serious diseases

High cost of orphan drugs

Reconciling patients/professionals expectations and needs

Affordability and sustainability

Risk of access inequities

BJCP British Journal of Clinical Pharmacology

Access to orphan drugs despite poor quality of clinical evidence

Alain G. Dupont[1,2] & Philippe B. Van Wilder[2]

EXPERT REVIEWS

Access to orphan drugs in Europe: current and future issues

Expert Rev. Pharmacoeconomics Outcomes Res. 12(1), 23–29 (2012)

The problems of clinical trials and registries in rare diseases

Maurizio Luisetti*, Ilaria Campo, Roberta Scabini, Michele Zorzetto, Zamir Kadija, Francesca Mariani, Ilaria Ferrarotti

Appl Health Econ Health Policy (2013) 11:1–3
DOI 10.1007/s40258-012-0004-y

EDITORIAL

Cost-Effectiveness Assessment of Orphan Drugs

A Scientific and Political Conundrum

Steven Simoens · Eline Picavet · Marc Dooms · David Cassiman · Thomas Morel

Picavet *et al. Orphanet Journal of Rare Diseases* 2013, **8**:157
http://www.ojrd.com/content/8/1/157

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Development and validation of COMPASS: clinical evidence of orphan medicinal products – an assessment tool

Eline Picavet[1*], David Cassiman[2], Bert Aertgeerts[3,4] and Steven Simoens[1]

Simoens *Orphanet Journal of Rare Diseases* 2011, **6**:42
http://www.ojrd.com/content/6/1/42

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Pricing and reimbursement of orphan drugs: the need for more transparency

Morel *et al. Orphanet Journal of Rare Diseases* 2013, **8**:198
http://www.ojrd.com/content/8/1/198

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries

Thomas Morel[1*], Francis Arickx[2], Gustaf Befrits[3], Paolo Siviero[4], Caroline van der Meijden[5], Entela Xoxi[4] and Steven Simoens[1]

Picavet *et al. Orphanet Journal of Rare Diseases* 2013, **8**:164
http://www.ojrd.com/content/8/1/164

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Clinical evidence for orphan medicinal products-a cause for concern?

Eline Picavet[1*], David Cassiman[2], Carla E Hollak[3], Johan A Maertens[4] and Steven Simoens[1]

Lower robustness in scientific evidence generated with orphan medicines

Picavet E, Cassiman D, Hollak CE, et al. (2013) Clinical evidence for orphan medicinal products-a cause for concern? Orphanet journal of rare diseases 8: 164.

Table 4 Study design of the pivotal studies (n = 108)

	Number of pivotal studies (%)
Control arm	
No control	34 (31.5%)
Controlled	74 (68.5%)
Historical control	2 (1.9%)
Different dosages of the OMP	11 (10.2%)
Placebo	49 (45.4%)
Active comparator (or standard of care)	17 (15.7%)
Similarity at baseline	
Yes, statistically verified	13 (12.0%)
Likely, but not statistically verifiable	41 (38.0%)
Not likely, but not statistically verifiable	4 (3.7%)
No, statistically verified	1 (0.9%)
Not reported	15 (13.9%)
Randomized allocation	
No	38 (35.2%)
Yes	70 (64.8%)
Valid method of randomization	25 (23.1%)
Invalid method of randomization	2 (1.9%)
Not reported	43 (39.8%)
Blinding	
No (open-label)	44 (40.7%)
No, but justified	10 (9.3%)
Yes	54 (50.0%)
Blinding of the care provider	53 (49.1%)
Blinding of the outcomes assessor	12 (11.1%)
Blinding of the patient	54 (50.0%)

Accurate estimation of effects pre-authorization?

Comparison of treatment effect sizes from pivotal and post-approval trials of novel therapeutics approved by the FDA based on surrogate markers of disease: a meta-epidemiological study

- FDA often approv
  trials using surrog
  risk making error
  the medical prod

- All novel drugs in
  FDA between 200
  surrogate markers as primary endpoints.
  - Comparison of treatment effects among pivotal trials vs post-approval trials for the same indication

- 88 novel drugs (90 indications) based on => 1 pivotal trials using surrogates.
  - Many post-approval trials not directly comparable to pivotals, particularly due to endpoint selection.
  - 27/88 novel drugs for 27/90 indications
    o at least one
    total of 43 matches.

    rrogates:

    al trials showed effects
    pproval trials (average
    ant differences)

    ates:

    tal trials showed
    post-approval trials (no significant average differences)

26/43 (60%) pivotal trials showed effects larger than post-approval trials

Wallach JD et al. BMC Medicine201816:45

Gathering evidence during early commercialization?

- **Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Ag… cohort study … 2009-13.**

- From 2009 to … approved the … drugs for 68 in…
  - **12% indicat… arm study**
  - **Survival dat…**
  - **Benefit on OS 1 to 5.8 months, median 2.7**
  - **QoL data available in 10%**

33/68 (49%) of authorised oncological indications remained uncertain after a mean of 5.4 years post-approval

- Post-marketing results …ut OS data in …
  …n QoL
  …ears, **…MA**
  …ad shown …nt in **OS or**
  …1 (48%) had …nent
  – 33 (49%) remained uncertain

Davis C, et al. BMJ 2017;359:j4530

High cost and buget impact of orphan drugs

"Most expensive drugs in the world"

Table 1 – The most expensive drugs in the world [1].

Drug	Indication	Annual cost	Company
Soliris (eculizumab)	Paroxysmal nocturnal hemoglobinuria	$409,500	Alexion
Elaprase (idursulfase)	Hunter's syndrome	$375,000	Shire
Naglazyme (galsulfase)	Maroteaux-Lamy syndrome	$365,000	BioMarin
Cinryze (C1 esterase inhibitor)	Hereditary angioedema	$350,000	ViroPharma
Myozyme (alglucosidase alpha)	Pompe disease	$300,000	Genzyme
Arcalyst (rilonacept)	Cryopyrin-associated periodic syndromes	$250,000	Regeneron
Fabrazyme (agalsidase beta)	Fabry disease	$200,000	Genzyme
Cerezyme (imiglucerase)	Gaucher disease	$200,000	Genzyme
Aldurazyme (laronidase)	Hurler syndrome	$200,000	Genzyme, BioMarin Pharmaceutical

Note. From 2010 data provided by *Forbes* and *Pharmaceutical Commerce* (all prices in US dollars).

All of them intended to treat Rare diseases

Winquist E, Bell CM, Clarke JTR, et al. (2012) An evaluation framework for funding drugs for rare diseases. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, Elsevier Inc. 15(6): 982–6.

Key considerations: Managing uncertainty with MEA

Limiting budgetary uncertainty

- Financial agreements can be useful
  - Relatively simple tools, such as caps or price-volume agreements
  - Only control budget impact, does not address uncertainty on value

Limiting uncertainty on evidence

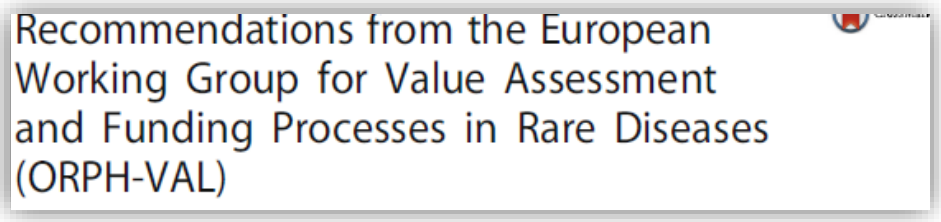
- Performance-based agreements can be useful
  - Implementation of studies or registries may be complex and costly in practice
  - Reliability of data, missingness
  - Definition of effectiveness based on surrogates of unknown clinical relevance as in trials – uncertainty may persist
  - Results available late – useful to reverse decisions?

- ***Management of stakeholders' expectations***
  - **Unfeasibility to conduct further controlled clinical trials**
    - Physicians' and patients' reluctance to enrollement into randomized controlled studies if product is commercially available
  - **Thus, difficult to gather robust risk/benefit evidence**
    - Bias of observational data (RWD), overestimation of effects
  - **Authorization reversal may be not feasible**
    - Patients on treatment requiring continuation
    - Treatment availability becomes SOC
  - **Difficulties for pricing revisiting**
    - Negotiation with MAH difficult since most eligible population already treated and product considered SOC

Exploring new solving-pathways

- Alternative and robust methodological designs on RD clinical trials.

- Tailoring the appraisal of OMP: MCDA


Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL)

- Following up real data of patient and treatment: MEA (Risk-sharing and financial agreements); Patient Outcome Registries; favouring PROMs / PREMS.

Drug access in Catalonia

Spain ~46,6 M
19 regions
Catalunya ~7.4 M

- Authorization and price& reimbursement at national level
  - P&R supported by national reports on therapeutic positioning
  - Reports coordinated, contributions of 17 regions
  - P&R decision binding for all regions
- Budget allocation at regional level

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- Catalan Harmonization Program
  - Therapeutic positioning:
    - Drug technical appraisal
    - Catalan Pharmaco-therapeutic Committee
    - Prioritization and clinical criteria for use
    - Invoicing system and requirements
  - Budget allocation
  - Managed access
  - Real world data collection and analysis
  - Tools for implementation

How to balance medical needs with uncertainties Initiatives developed in Catalonia

Steps taken to improve the assessment of **clinical added value** of orphan medicines

Steps taken for HTA appraisal to minimize the **budget impact** on OMP and reconciling the cost with the **outcomes achieved**

MCDA methodology

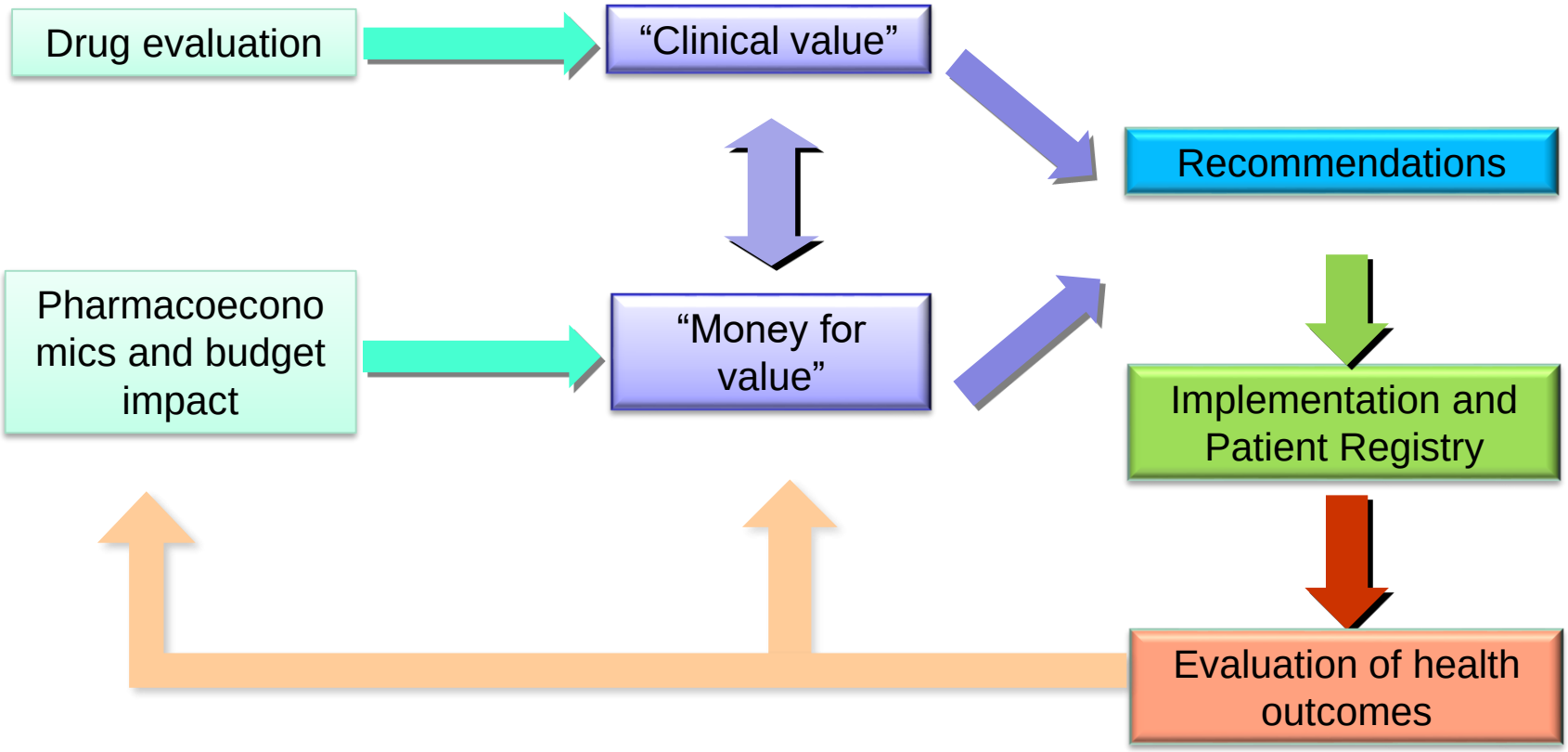
Patient participation in drug evaluation

Managed entry agreements

Patient registries: real world data

Catalan Pharmacotherapeutic Harmonisation Programme

Developed to improve access to innovative medicines (including OMP)



2 (+ 2 alternates) patients out of 24 members participating in each committee

Catsalut: Real World Data collection

Ongoing for 7 years: ~200,000 treatments; ~125,000 patients; ~20,000 active; ~1,000 non-oncological OMP active

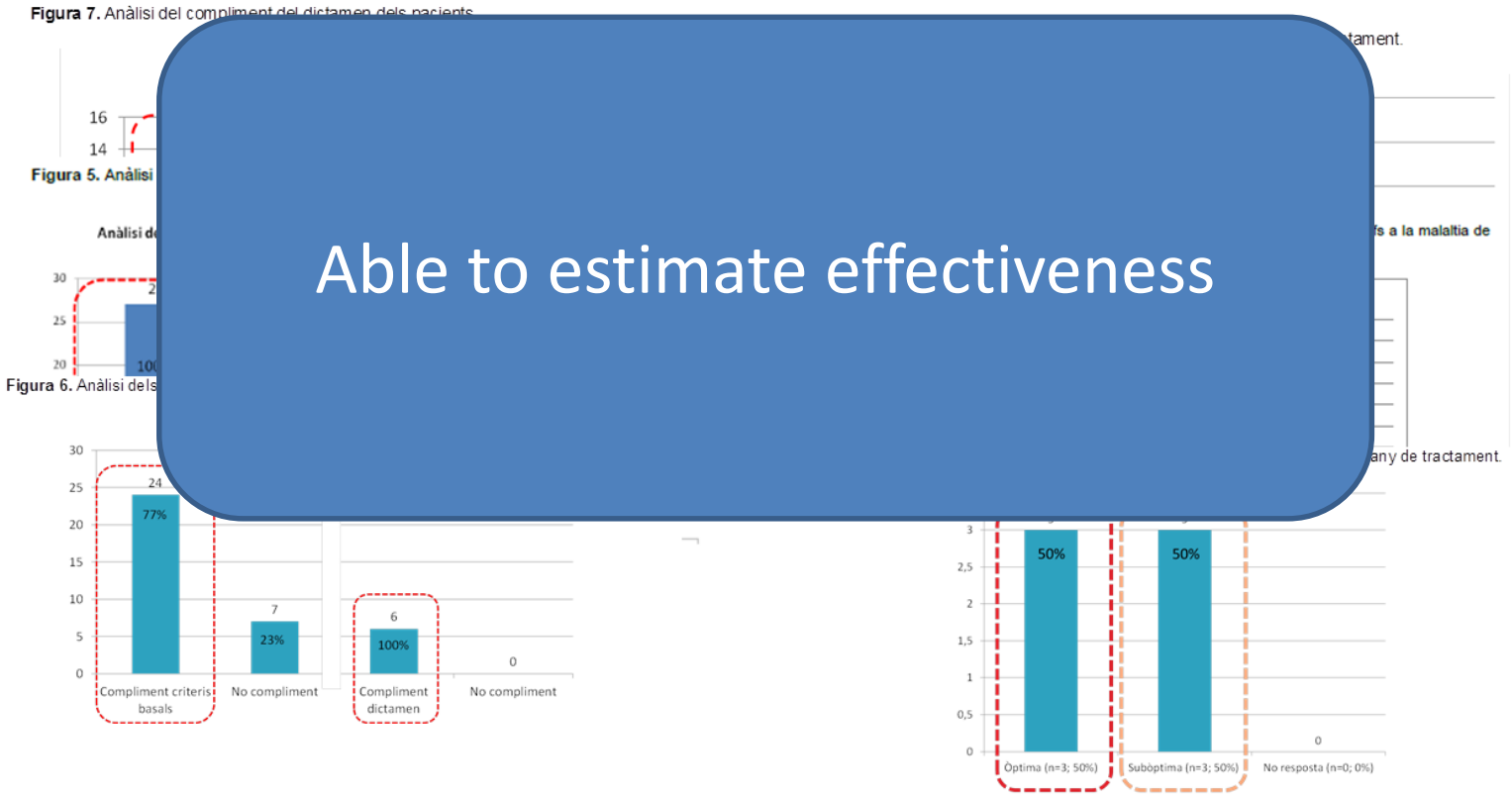
- Regional registry for high impact medicines
  - Involves OMP and non-OMP
  - Since 2011, requirement for invoicing since 2014
  - Data collected on:
    - Dates of treatment
    - Clinical indication criteria
    - Main effectiveness outcomes
    - Reasons for discontinuation
    - Invoicing
    - Linkable to other data sources

- Analyzed yearly
  - By product or indication
  - Description of treated population
    - Adherence to harmonized clinical criteria
  - Main outcomes
    - As derived from trials supporting access decisions
    - Heterogeneity across sites
  - Impact in patients and €
  - Deviation from expectations

CatSalut: examples of RWD in OMP

- **HPN, Gaucher type I-III, Fabry's disease**

- Compliance with harmonised clinical criteria: in general 100% *(74% pre-treated)*
- Reaching of response according to main outcomes: 76%, 69%, 50%

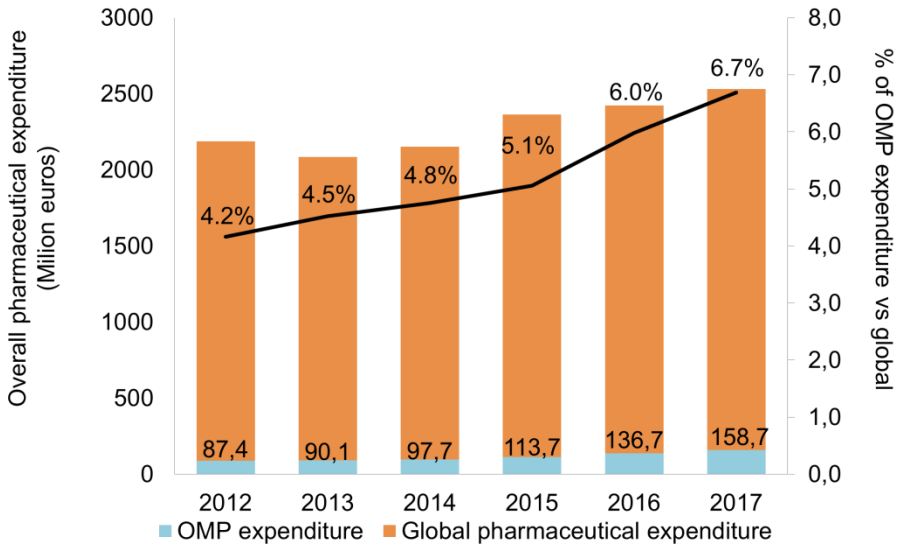


CatSalut: MEA in OMP (2018)

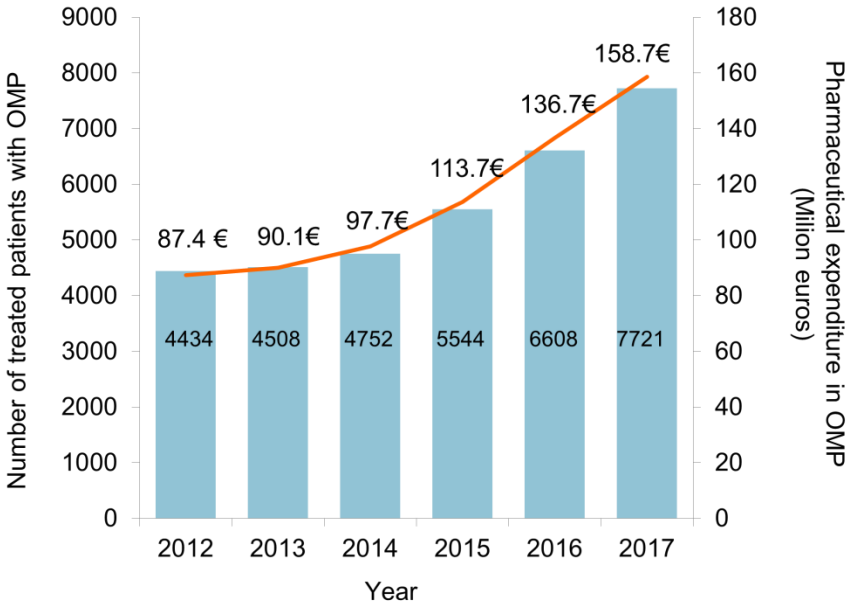
Area	Type of agreement	Description	Access
Pneumology	Financial (Price – volume)	Subgroup of patients + Volume discounts 4 years	Clinical criteria + registry Starting 2018
Nephrology	Financial (Cap)	Max regional invoicing 3 years	Individual authorization by expert group + registry Starting 2018
Gastroenterology	Financial (National budget Cap + Regional budget Cap)	Max national invoicing 2 years Max regional invoicing 2 years (NA if national cap reached)	Clinical criteria + registry Starting 2018
	Financial (patient cap + National budget Cap)	Discount (in product) + Max patient invoicing + Max national invoicing 3 years	Individual authorization by expert group + registry Starting 2018
Endocrinology	Financial (patient cap + National budget Cap)	Discount (in product) + Max patient invoicing + Max national invoicing 5 years	Individual authorization by expert group + registry Starting 2018
Neurology	Financial (National budget Cap)	Max national invoicing 5 years	Individual authorization by expert group + registry Starting 2018

Snapshot on Orphan medicinal products in Catalonia (preliminary data)

Percentage of OMP expenditure in relation to the total overtime



Number of patients treated with OMP and expenditure overtime

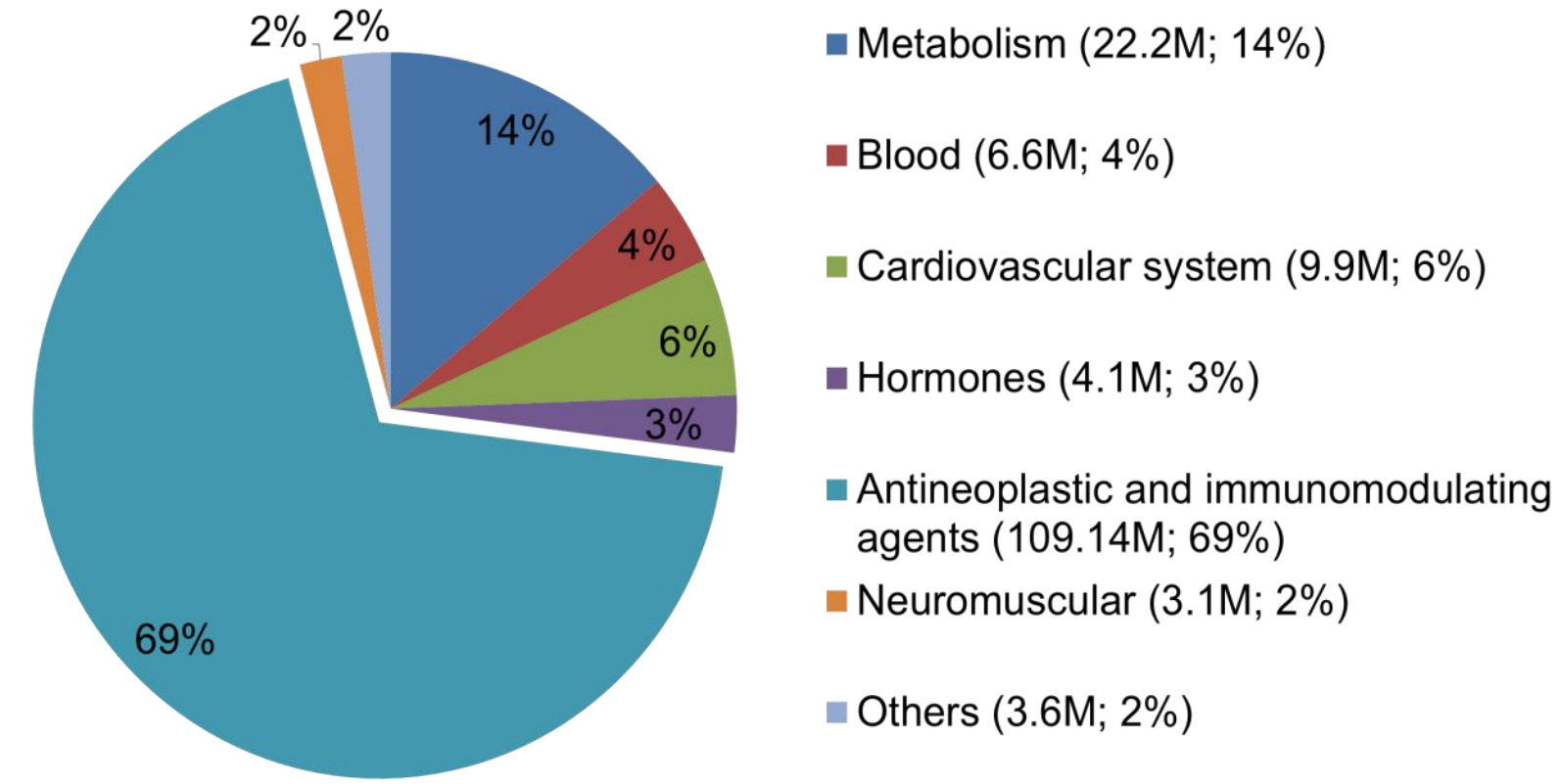


6,7% of the budget assigned to medicinal products

OMP used by 0,1% Catalan population

OMP - Catalonia

Percentage of OMP expenditure in 2017 per ATC



Lessons learned and take-home messages

- Positive 18-year- effects of the EU OMP policies on all stakeholders and for the patient's unmet medical needs.
- OMP displays unique features that needs to be properly addressed: new tools for clinical development and new methods for pricing, HTA appraisal and patients registries and follow-up
- Independent and industry-based research should be aligned with patients and societal needs
- Empowered patient's participation becomes a "must" in all orphan decision-making process

Dialogue-cooperation-collaboration-transparency-participation

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OUR WAY (1st Prize EURORDIS Photo Award 2018)

Thank you for your attention

http://canalsalut.gencat.cat