



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# The role of EMA in ensuring access to high-quality medicines in Europe

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EMSP Spring conference, Dublin, 9 May 2014

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An agency of the European Union





# Key Principles

- The EU is a Single Market for pharmaceuticals  
~ 0.5 billion people
- In order to market a medicinal product in the EU, a company needs a Marketing Authorisation
- There are different ways ('Procedures') for a company to obtain a Marketing Authorisation
- **The main scientific principle used in the evaluation of medicines is the benefit/risk balance, based on quality, efficacy and safety aspects**
- Economic considerations are excluded from the assessment



# A European agency and medicines system: How?

'One system, two routes for approval'

- **Centralised European route** - attracts nearly all innovative medicines
- **Mutual recognition + decentralised national routes** - mostly generics and some new indications for existing products



# European Medicines Agency: focal point of the centralised procedure

- 1 application
- 1 evaluation
- 1 authorisation for all EU
- 1 invented name
- 1 product information (SPC, Labelling, PL)
- All EU languages



The EMA is not responsible for pricing or reimbursement  
Marketing Authorisation is granted by the European Commission



# The various roles of the EMA

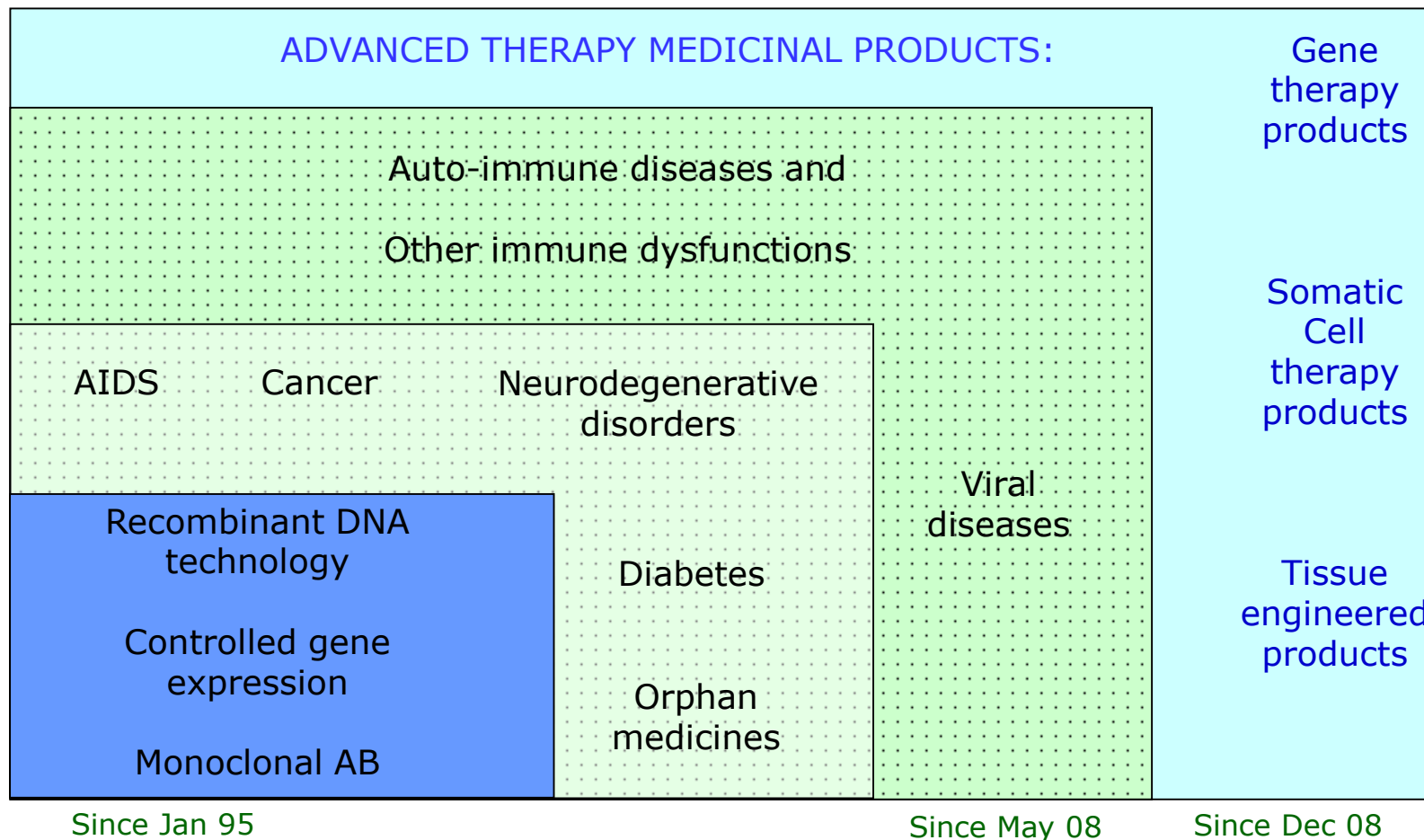


The Agency is responsible for:

- The **evaluation of marketing authorisation** for **human and veterinary** applications submitted by pharmaceutical companies
- The coordination of European **pharmacovigilance** (supervision of the medicines on the market)
- The provision of **scientific advice** on the development of medicines
- The evaluation of applications for **orphan** designation in EU
- The evaluation of **paediatric investigation** plans (or waivers)
- The evaluation of **arbitration** and **referral** procedures
- The provision of good quality and independent **information** on the medicines it evaluates to patients and health
- The coordination of Member States' **inspections** (*GMP, GCP, GLP*)



# Eligibility: "Mandatory Scope"





# European Regulatory Network

Member States have pooled their sovereignty for authorisation of medicines

- The Agency is designed to coordinate the existing scientific resources of Member States
- It is not intended to replace national authorities, but to be a partner in the system
- All parties linked by an IT network (EudraNet)
- Provide a platform of exchange between all partners and scientific community



# Challenges

**Distrust:** overall erosion of confidence in public service, governments and Europe

**Globalisation:** regulatory decisions scrutinised and compared in terms of outcomes and timing on both sides of the Atlantic  
Manufacturing sites/research outside Europe.

**Uncertainties:** all regulatory decisions taken in conditions of uncertainties and imply the management of risks

**Antagonism** between patients' demand for early access to medicines and society risk aversion

**Transparency and access to information/data:** increasing demand from civil society, academia leading to more engagement with the scientific community and the public

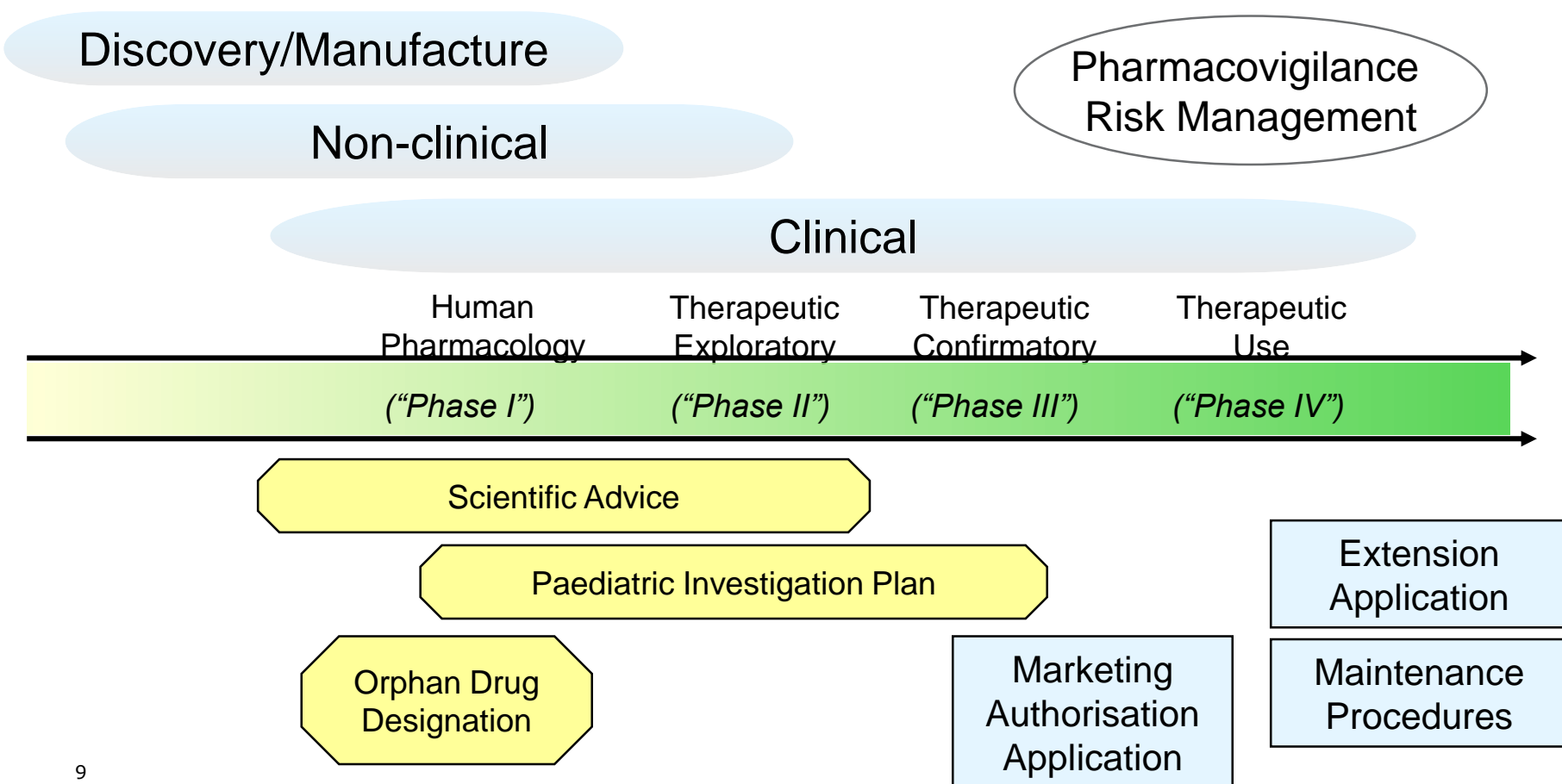




Access to high quality medicines is the result of a continuous collaboration between all partners all along the life cycle of the medicine from the development phase, through the evaluation to the post-authorisation monitoring.



# Drug Development Overview





Taking into account the challenges, regulators are now looking to bridge the gap between the clinical development of the medicines in a very controlled environment and the therapeutic use in an uncontrolled environment.

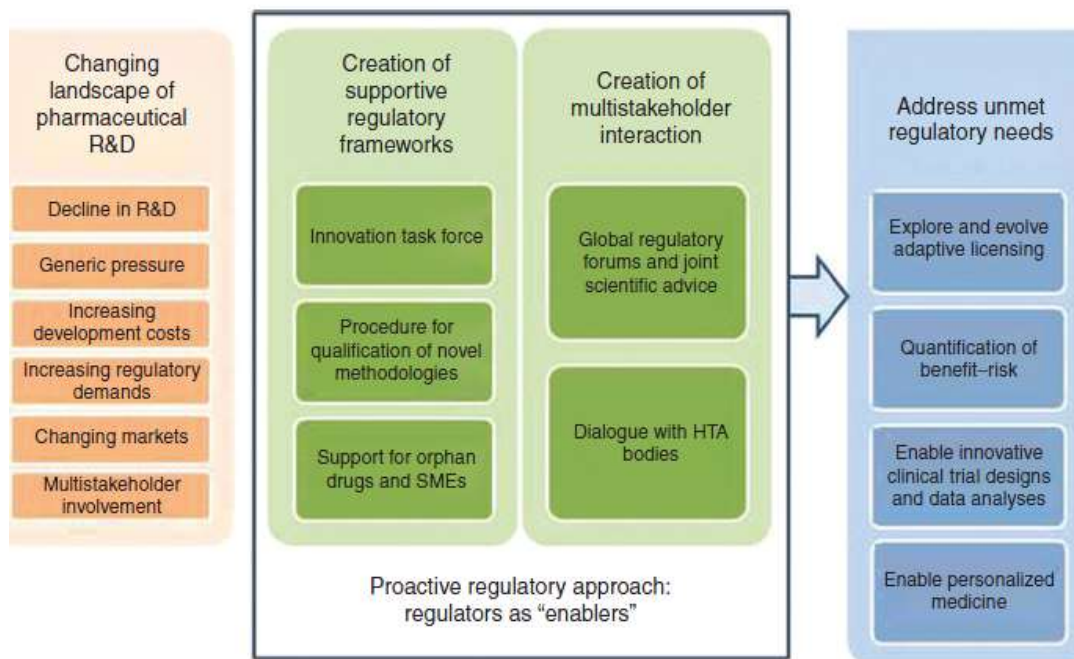
What are the tools?



# Gatekeepers and Enablers: How Drug Regulators Respond to a Challenging and Changing Environment by Moving Toward a Proactive Attitude

F Ehmman<sup>1,2</sup>, M Papaluca Amati<sup>2</sup>, T Salmonson<sup>3,4</sup>, M Posch<sup>5</sup>, S Vamvakas<sup>6</sup>, R Hemmings<sup>7,8</sup>, HG Eichler<sup>9</sup> and CK Schneider<sup>10,11</sup>

This article analyzes the role of regulatory authorities in facilitating innovation in the pharmaceutical sector. We describe how regulators are expanding their role to be not only gatekeepers but also enablers of development. They have already responded to the challenging and changing environment by moving toward a proactive attitude beyond evaluation of products, thereby more actively contributing to their development. Regulators have to continuously evolve their knowledge and standards alongside evolution in science. Creation of supportive regulatory frameworks and multistakeholder interaction will help address unmet regulatory needs.



**The proactive regulatory approach: "Be part of it and shape it together."**

8/clpt.2013.14



## During the development phase

- Qualification of innovative methods
- EMA/HTA scientific advice



## Examples

EMA has an advisory role in the Multiple Sclerosis Outcome Assessments Consortium (MSOAC):

MSOAC will develop and support adoption throughout the MS community (patients, clinical investigators, pharmaceutical industry, regulatory agencies, and advocacy groups) of a clinical outcome assessment tool for future MS clinical trials. This clinical outcome assessment tool will measure the impact of an intervention on the disability due to MS and will be qualified for use in registration trials. The tool must be acceptable to the patient, and will be: 1) multidimensional to reflect the principal ways that MS affects an individual; 2) highly reliable and valid – including meaningful to the patient; 3) sensitive to change over time to permit demonstration of a therapeutic effect; and 4) practical and cost-effective.



# Qualification of Novel Methodologies

- **Vision:** Speed up/optimize drug development and utilisation, improve public health
- Procedure to guide the development of new more efficient ways to develop drugs, e.g. development of new endpoints for clinical trials
- Started 2008: 60 procedures so far
- **Who can apply?** Consortia, Networks, Public/Private partnerships, Learned societies, Pharmaceutical industry.



## Scientific advice together with health technology assessment bodies

- Possibility for Applicants to discuss together with Regulators and Health Technology Assessment bodies (HTAs) early in development what is needed, not only for the benefit/risk assessment (Regulators) but also decide on the added value (HTAs) so that HTAs recommend reimbursement and the product gets to the patients.
- Started 2010: 30 procedures so far, HTAs from UK, Italy, France, Sweden, Germany, Spain, Netherlands, Belgium
- Workshop on the 26th of November 2013 attracted more than 300 participants: regulators, HTAs, Industry, SMEs, Academia, Health Care Professionals, Patient representatives, European Commission.





## Parallel HTA-EMA SA: Experience so far

- Diabetes, Heart Failure
- Alzheimer's, Depression
- Lung Cancer, Breast Cancer, Melanoma, Pancreas-Ca, Mesothelioma, Leukaemia, Cachexia in cancer
- Asthma, COPD, Rheumatoid Arthritis, Osteoporosis
- Multi-resistant Infections,
- Food Allergies, 2 Gastroenterology conditions
- Orphan conditions; Cell therapy; Ophthalmology

The majority are new mechanisms of action in the respective area, new monoclonal antibodies, new chemicals, tumour vaccines.



## Parallel EMA/HTA SA: Example

Questions for the HTAs only: Impact on the caregiver

- Do the Stakeholders consider the impact to the caregiver (e.g. time assisting or supervising patient) an important piece of the value proposition when evaluating a treatment for prodromal Alzheimer's disease?
- Do the Stakeholders agree with the selection of instruments in the clinical trial to capture the burden to the caregiver (Dependence Scale)? Are there any other data that should be collected?
- Overall cost-effectiveness of the product:
  - delaying progression may also extend life expectancy
  - Modelling is necessary to project out the implications of potential post-trial scenarios



Evaluation phase:  
regulatory pathways which facilitate market  
access



## Tools currently available

- Conditional marketing authorisation, approval under exceptional circumstances and accelerated assessment to facilitate access for medicines that fulfils unmet medical needs or when comprehensive data cannot be provided (very rare disease)

In 2013: 9 medicines for cancer, vaccines and rare diseases

- Compassionate use: access to treatment that are still under development to patients with life-threatening diseases with no available treatment options

In 2013: 2 medicines for hepatitis C virus infection

- Enriching scientific evaluation by listening to patients and healthcare professionals



# Adaptive licensing

Builds on existing regulatory processes including conditional authorisation and pharmaceutical tools.



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## European Medicines Agency launches adaptive licensing pilot project

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Press release

19/03/2014

### European Medicines Agency launches adaptive licensing pilot project

#### Improving timely access for patients to new medicines: pilot explores adaptive licensing approach with real medicines in development

The European Medicines Agency (EMA) is inviting companies to participate in its adaptive licensing pilot project. Companies who are interested in participating in the pilot are requested to submit ongoing medicine development programmes for consideration as prospective pilot cases.

A framework to guide discussions of individual pilot studies has been published.

The adaptive licensing approach, sometimes called staggered approval or progressive licensing, is part of the Agency's efforts to improve timely access for patients to new medicines. It is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the [marketing authorisation](#) to expand access to the medicine to broader patient populations.

As a holistic approach, adaptive licensing requires the involvement of all stakeholders who have a role in determining patient access, including the EMA, the industry, health technology assessment (HTA) bodies, organisations issuing clinical treatment guidelines and patient organisations. All discussions will take place in a 'safe harbour' environment to allow free exploration of the strengths and weaknesses of all options for development, assessment, licensing, reimbursement, monitoring, and utilisation pathways in a confidential manner and without commitment from either side.

"With the adaptive licensing pilot project we intend to explore with real medicines in development a progressive licensing approach that would allow timely access for patients to new medicines that address serious conditions with unmet medical needs," explains Hans-Georg Eichler, the Agency's Senior Medical Officer. "The approach seeks to maximize the positive impact of new medicines on public health by balancing timely access for patients with the need to provide adequate evolving information on their benefits and risks."

Adaptive licensing builds on existing regulatory processes and intends to extend the use of elements that are already in place, including [scientific advice](#), centralised [compassionate use](#), the conditional marketing authorisation mechanism (for medicines addressing life-

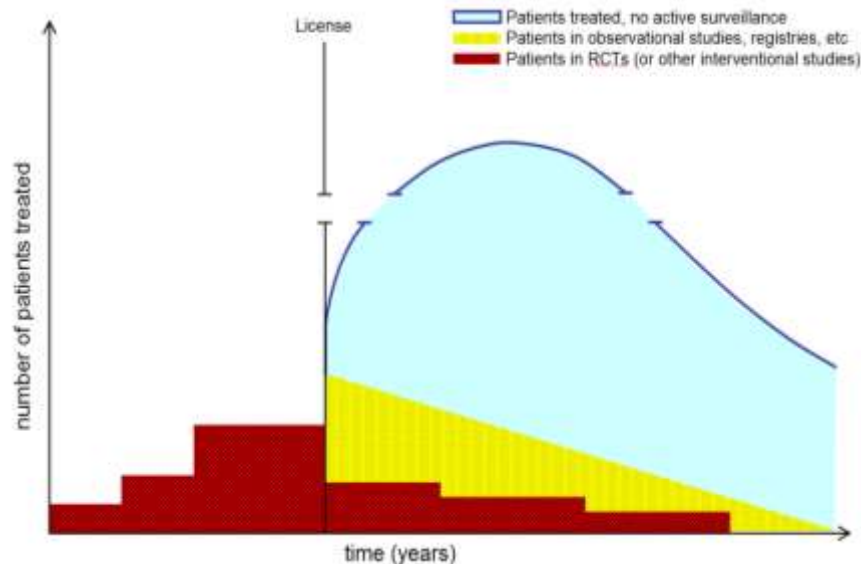
#### Related information

- Research projects
- Adaptive licensing: taking the next step in the evolution of drug approval [↗](#)
- Pilot project on adaptive licensing (19/03/2014)
- Pilot project on adaptive licensing Annex I – Framework for individual pilot studies (19/03/2014)

#### Contact point:

To initiate a pilot case:  
[adaptivelicensing@ema.europa.eu](mailto:adaptivelicensing@ema.europa.eu)

For media enquiries:  
Monika Benstetter or Martin Harvey  
Tel. +44 (0)20 7418 8427  
E-mail: [press@ema.europa.eu](mailto:press@ema.europa.eu)

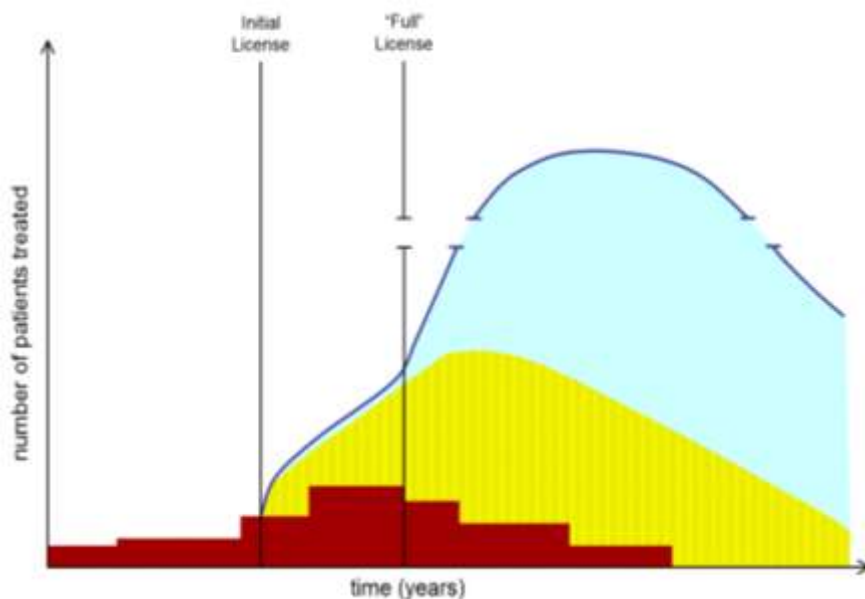


## Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

## Adaptive Licensing:

After initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information





Once the product has been put on the market:  
new pharmacovigilance tools





# From the first 12-months of operation of the Pharmacovigilance Risk-Assessment Committee

A major change has been delivered for better public health:

- Better public participation: increase of EU patient reports by 10,000 in first year; Patients and HCPs voting on PRAC
- Better planning – risk management plans now routine
- Better evidence – routine identification of data needs for referrals
- Faster decision-making
  - Referrals finalised in 1 to 8 months
  - PSURs directly lead to label changes
- Greater transparency – agendas, minutes, signals
- Better information – black triangle, ADR reporting, warnings

But there is still more to do:

- EudraVigilance, PSUR, Literature, Web-portal, Process improvements / simplifications



# New communication material on additional monitoring Q3 2013 Factsheet + Video

**What does the black triangle mean?**



The European Union (EU) has introduced a new way of labelling medicines that are being monitored particularly closely. These medicines have a black inverted triangle displayed in their package leaflet, together with a short sentence explaining what it means:

▼ **This medicinal product is subject to additional monitoring.**

All medicines are carefully monitored after they are placed on the EU market. The black triangle is an easy way to identify a medicine under additional monitoring. It means that the medicine is being monitored even more closely than others. This is generally because there is less information available on it than on other medicines, for example because it is new. It does not mean that the medicine is unsafe.

Reporting side effects

You should report any suspected side effects with a medicine you are taking, particularly if it displays the black triangle. If you get any side effects, talk to your doctor, pharmacist or nurse. You can also report side effects directly via the national reporting system in your country. Information on how to do this is included in every medicine's package leaflet. By reporting side effects, you can help provide more information on the safety of your medicine. Medicine regulators look at reports of side effects alongside the existing information on each medicine. They monitor all of these data to make sure the benefits of medicines remain greater than their risks.



## ¿Qué significa el triángulo negro?



La Unión Europea (UE) ha introducido una nueva forma de identificar aquellos medicamentos que están siendo sometidos a un seguimiento particularmente riguroso.

Dichos medicamentos muestran en su prospecto un triángulo negro invertido, así como la siguiente frase:

▼ "Este medicamento está sujeto a seguimiento adicional."

Una vez comercializados en la UE, todos los medicamentos se someten a un seguimiento riguroso. Sin embargo, los medicamentos con el triángulo negro son controlados aún más que los demás.

Esto sucede generalmente porque hay menos información sobre ellos en comparación con otros, por ejemplo porque son nuevos en el mercado.

No significa que el medicamento sea menos seguro.

### Cómo notificar efectos adversos

Como paciente, usted debe informar de cualquier efecto adverso del que sospeche tras tomar un medicamento, sobre todo si dicho medicamento presenta el triángulo negro.

Puede notificar los efectos adversos a su médico, farmacéutico o enfermera.

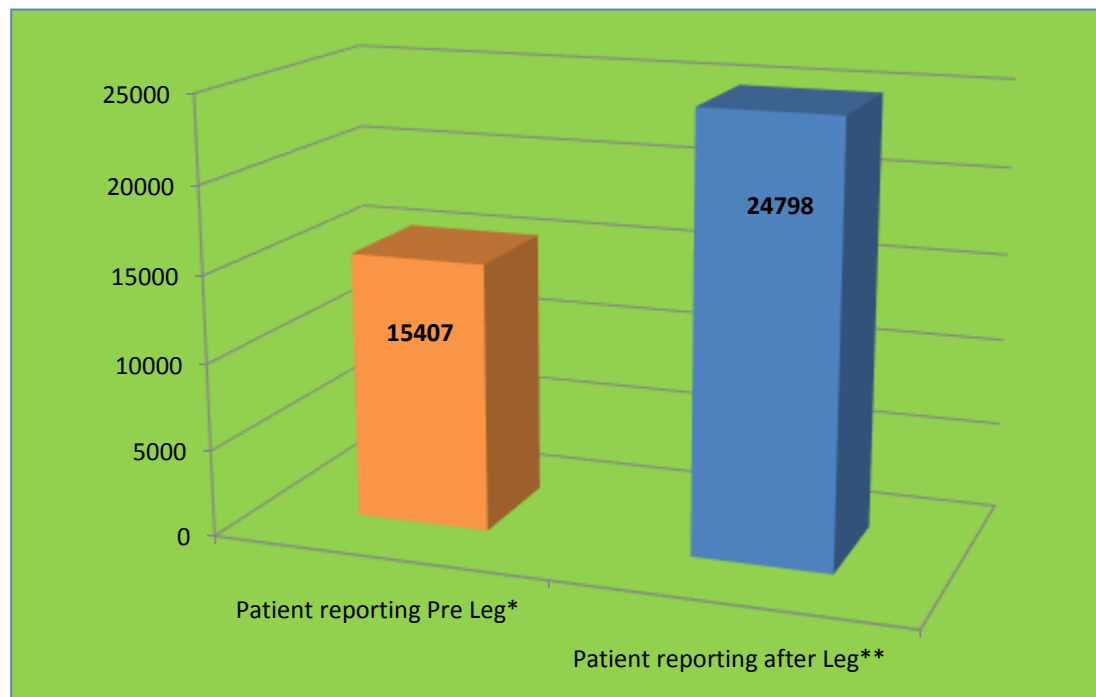
También puede notificarlos directamente a las autoridades sanitarias de medicamentos en su país, utilizando el sistema de notificación vigente en dicho país. Puede encontrar información al respecto en el prospecto del medicamento o en la página web de las autoridades sanitarias de medicamentos en su país.

Notificando estos efectos, usted puede ayudar a las autoridades sanitarias a evaluar si los beneficios de un medicamento se mantienen mayores que sus riesgos.





# EudraVigilance reporting by patients in EU



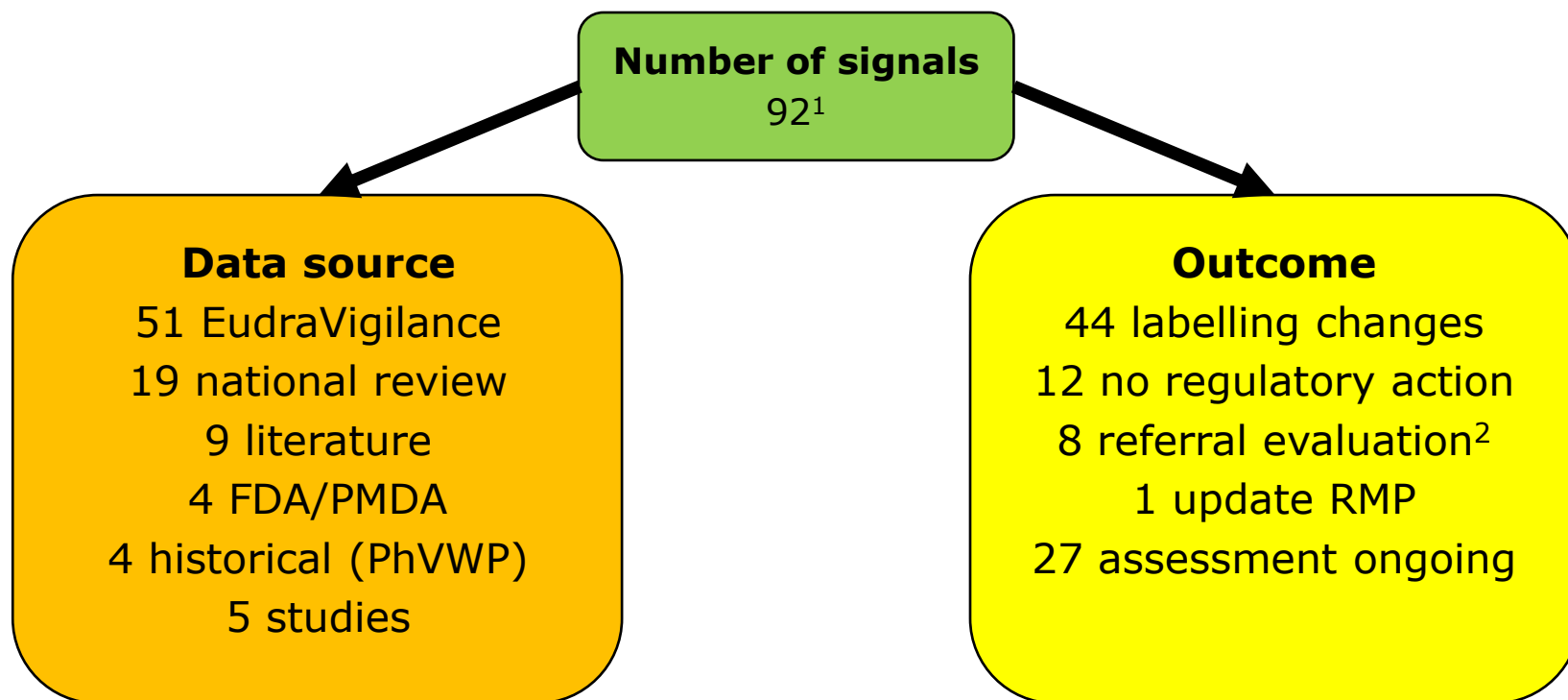
\* Pre legislation data period - 02/07/2011 - 01/07/2012

\*\* Post legislation data period -02/07/2012 - 01/07/2013



# Proactive pharmacovigilance – signal detection

July 2011 – July 2012 vs. July 2012 to July 2013



<sup>1</sup> 54 for CAPs (59%), 29 for NAPs (31%), 9 for both (10%)

<sup>2</sup> 6 referrals ongoing, 2 concluded: restriction of use (codeine) and suspension of MA (HES)



# Referrals: Outcomes

- Overview of finalised referrals:

Procedure name	Article	Finalised	Committee	Grounds	Outcome	EC Decision	Duration (calender days)
Tredaptive	20	Jan-13	CHMP	B-R	Suspension	Yes	1 month
Trevaclyn	20	Jan-13	CHMP	B-R	Suspension	Yes	1 month
Pelzont	20	Jan-13	CHMP	B-R	Suspension	Yes	1 month
Tetrazepam	107i	Apr-13	CMDh	S	Suspension	Yes	3 months
Cyproterone, ethinylestradiol - DIANE 35 & other medicines containing cyproterone acetate 2mg and ethinylestradiol 35 micrograms	107i	May-13	CMDh	S	Variation	Yes	3 months
Almitrine	31PhV	May-13	CMDh	B-R	Revocation	No	7 months
Codeine-containing medicinal products	31PhV	Jun-13	CMDh	B-R	Variation	No	8 months
Diclofenac-containing medicinal products	31PhV	Jun-13	CMDh	B-R	Variation	Yes	8 months
Flupirtine	107i	Jun-13	CMDh	S	Variation	Yes	6 months

- Time taken: 1 to 8 months
- High acceptance rate by CHMP/CMDh of PRAC outcome
- Compliance with legal deadlines



22 November 2013  
EMA/709120/2013

## Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation

Product information to be updated to help women make informed decisions

# CHCs and VTE

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### Combined hormonal contraceptives

Summary Key facts All documents

Procedure started → Under evaluation → PRAC recommendation → CHMP opinion → European Commission final decision

**Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation**

**Product information to be updated to help women make informed decisions about their choice of contraception**

The European Medicines Agency has now completed its review of combined hormonal contraceptives (CHCs), particularly of the risk of venous thromboembolism (VTE or blood clots in veins) associated with their use. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh these risks, and that the well-known risk of VTE with all CHCs is small.

The review has reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care.





## More transparency

- Improved EPAR to make decision making process more transparent
- Publication of agendas and minutes of scientific committee meetings since end of 2013
- Policy on access to clinical trial data
- Publication of risk management plan summary



# Access to high quality medicines: How to make it happen?

EMA mission statement:

Foster scientific excellence in the evaluation and the supervision of medicines for the benefit of public and animal health.





## EMA – What we want to achieve

- Support the scientific work of the EMA committees
- Share the knowledge and information held by EMA throughout the EU medicines regulatory network
- Meet the need of our stakeholders and partners

*"My aim is to give our scientific committees the best possible support, alongside the expertise from the national agencies, to help them keep delivering high-quality, consistent opinions."*

*Guido Rasi, EMA Executive Director, Sept. 2013*



# EMA-EU Network

28 EEA Member States  
+ 4,500 European experts

EU institutions:  
Commission - Parliament

Committee for Human  
Medicinal Products  
(CHMP)

Management Board

Committee for Veterinary  
Medicinal Products  
(CVMP)

Paediatric Committee  
(PDCO)

EMA  
Secretariat

Committee for Orphan  
Medicinal Products  
(COMP)

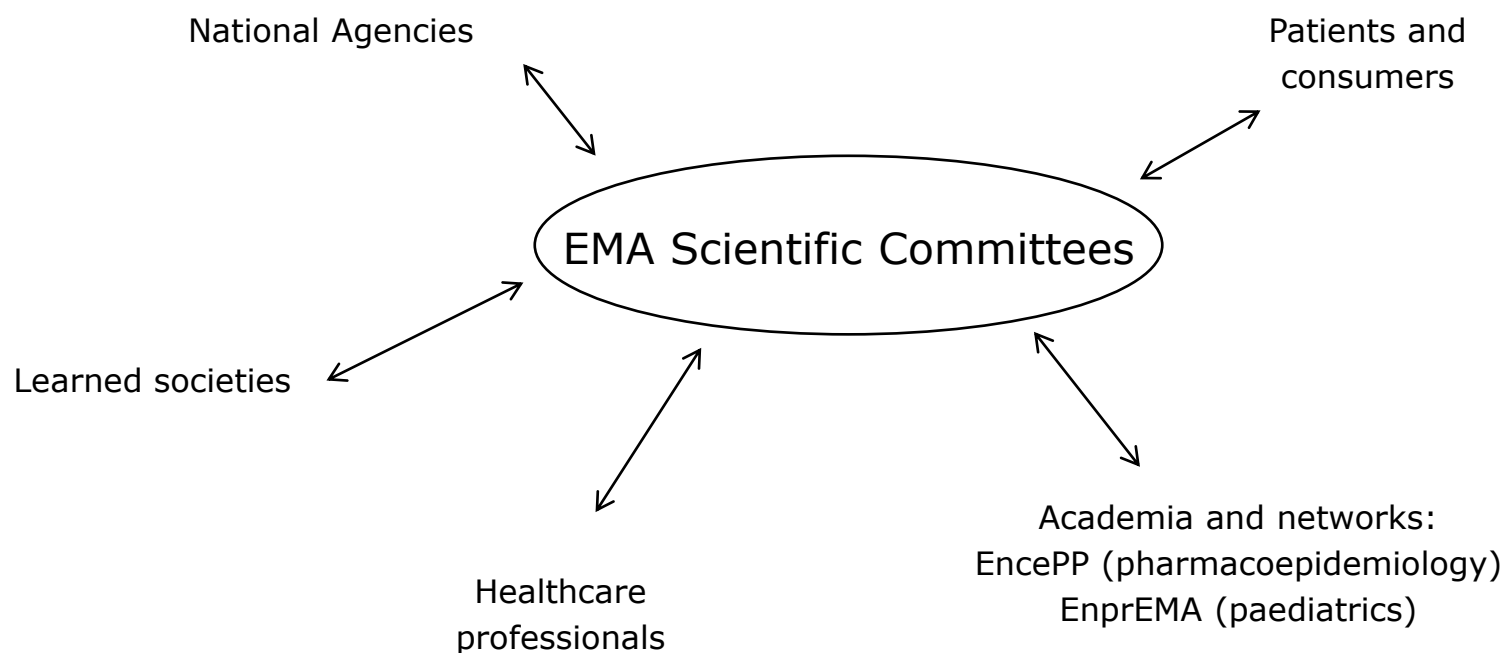
Committee for Herbal  
Medicinal Products  
(HMPC)

Pharmacovigilance Risk  
Assessment Committee  
(PRAC)

Committee for  
Advanced Therapies  
(CAT)



# Sources of expertise available to the scientific committees





## Independent expertise

All experts sign: . a declaration of interest  
. a confidentiality undertaking

The list of experts together with their declaration of interests and curriculum vitae is published on EMA website.

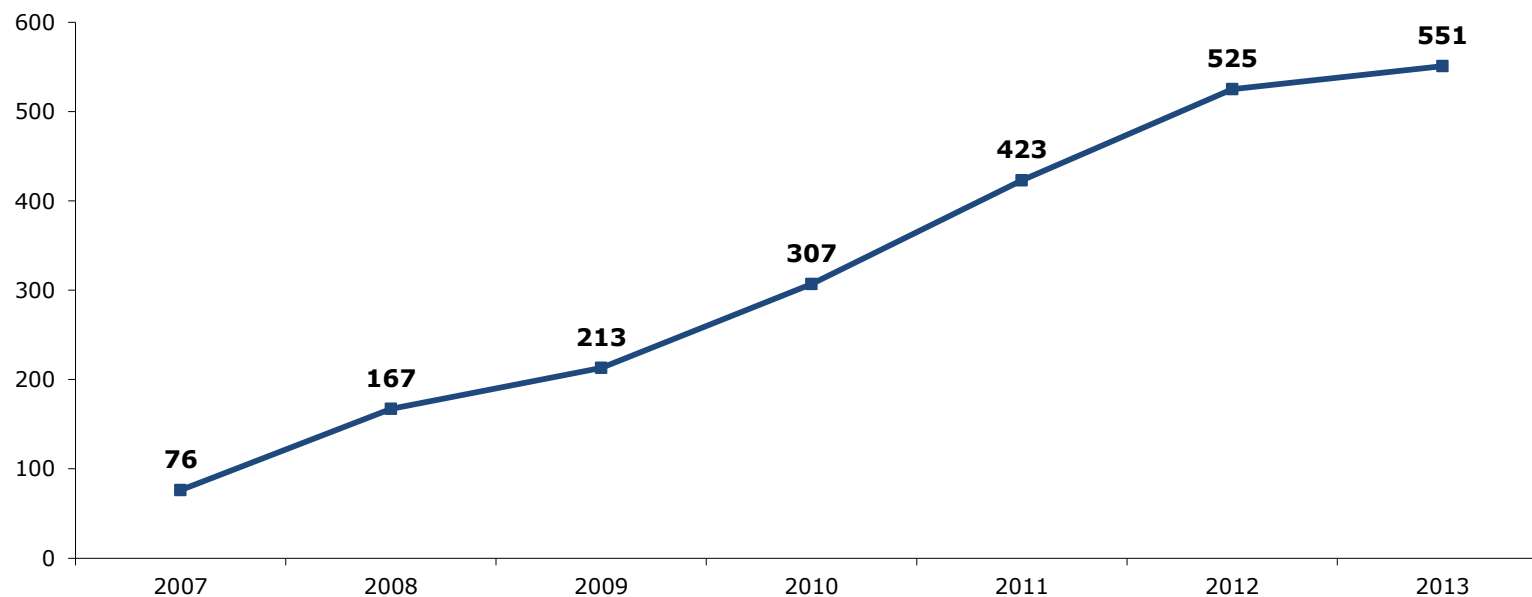


# Working with patients and healthcare professionals



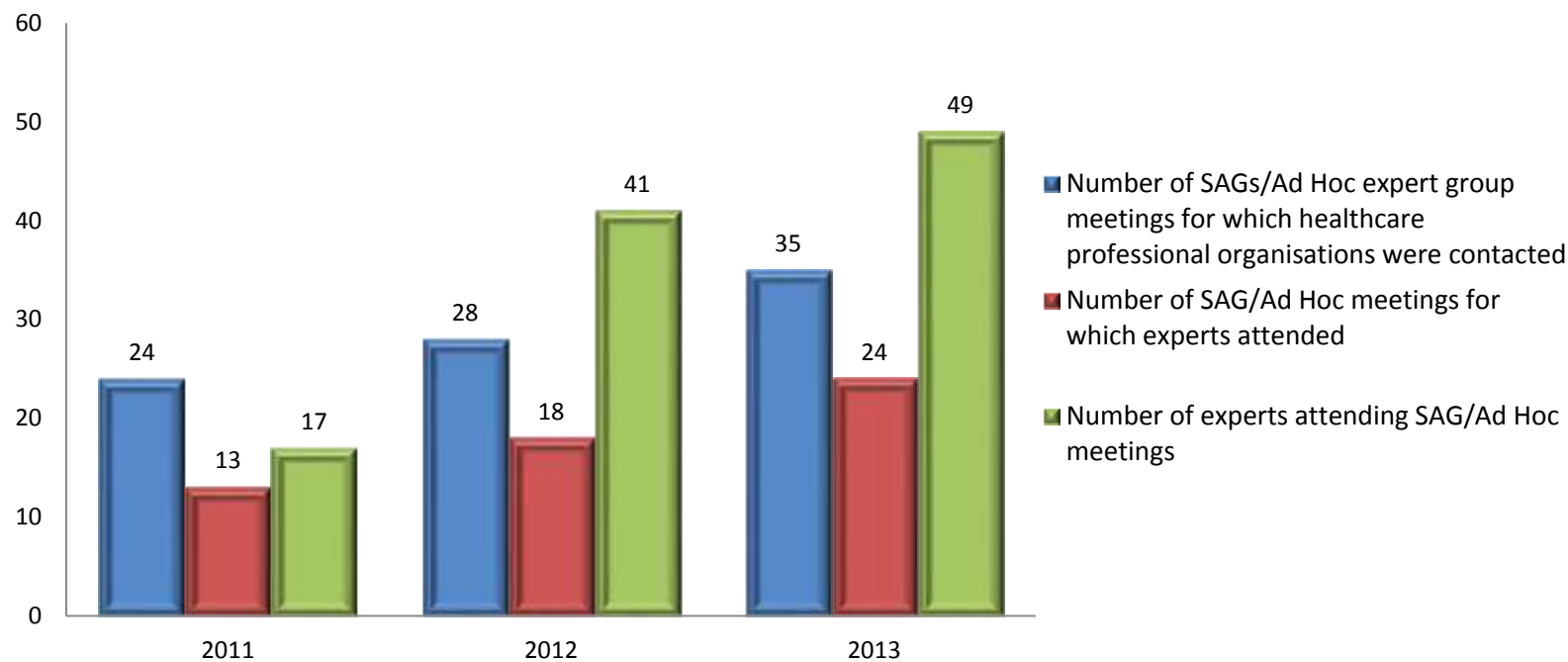
# Increasing number of patients involved in EMA activities

**Overall number of patients & consumers' involvement in EMA activities**  
2007-2013





# Healthcare professionals' involvement



- ✓ Clinical expertise in specific conditions (e.g.): Duchene's muscular dystrophy; severe primary insulin-like-growth-factor-1 deficiency; transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes; multidrug-resistant tuberculosis; sepsis; cognitive impairment no dementia
- ✓ Input from diabetologists; cardiologists; infeciologists; haematologists; oncologists; neurologists; endocrinologists; gynaecologists; rheumatologists; hepatologists; nephrologists; vascular surgeons; intensivists



## Patient centered regulatory science

“Because patient views of risk and benefit can differ from those of other stakeholders, and may vary between patients and at different stages of disease, this is an important and complex area that may require innovative methodologies”.

EMA workshop “[the patient’s voice in the evaluation of medicines](#)”, 18 October 2013.





## Conclusion

Providing access to high quality medicine is an objective which requires constant efforts and continuous improvement in drug development, evaluation and post-authorisation monitoring.

This objective can only be achieved through close collaboration between all partners, *i.e.* regulators, academics, Industry, learned societies, patients, healthcare professionals and also payers.



# Thank you

[www.ema.europa.eu](http://www.ema.europa.eu)

Acknowledgement for their contribution to:

- Ivana Silva
- Nathalie Bere
- Spiros Vamvakas
- Hans-Georg Eichler
- Anthony Humphreys
- Peter Arlett