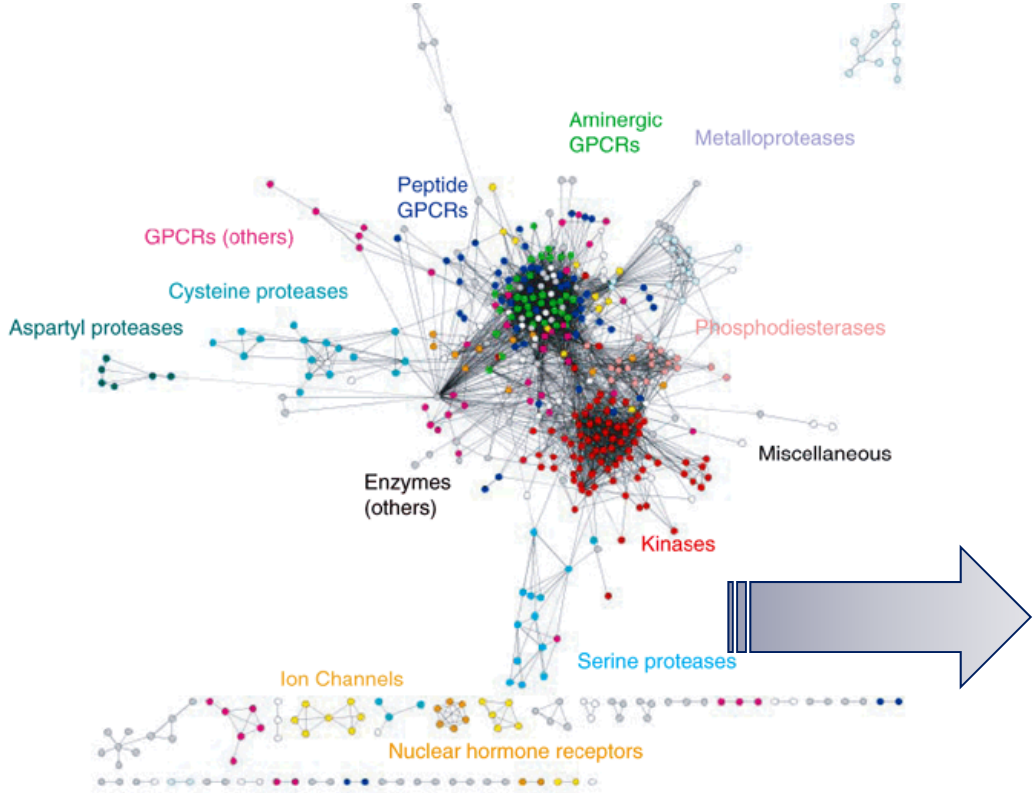
Workshop
Orphan Drugs & Personalised Medicine

Regulatory Perspective

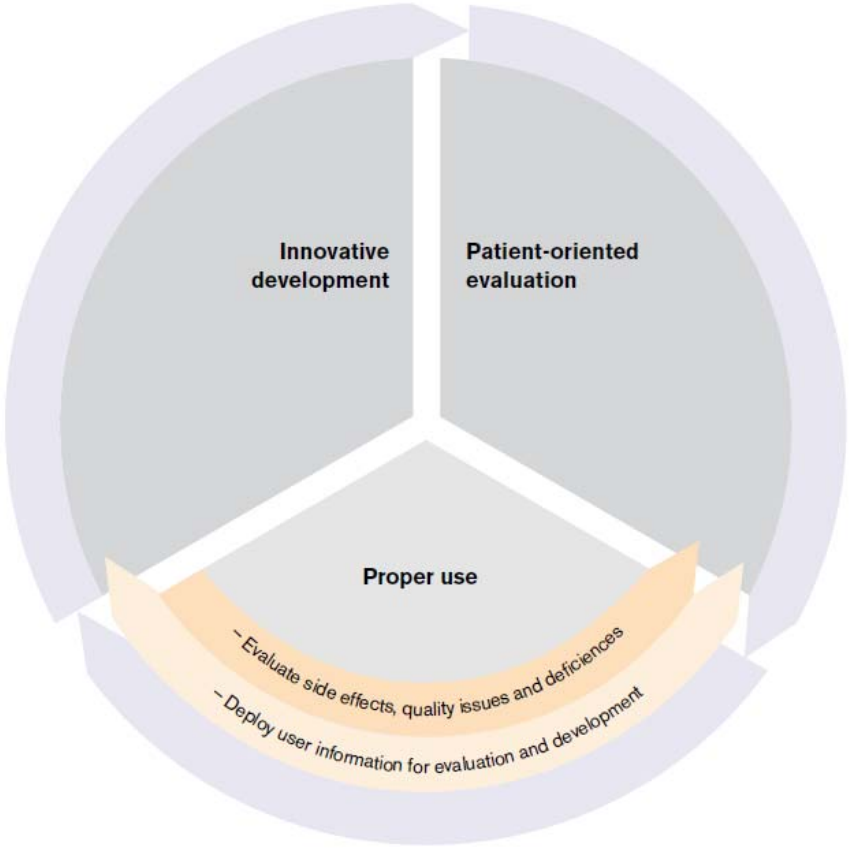
Marjon Pasmooij

MEB: connecting science, innovation and patient care



Paolini GV et al. Nat Biotech 2006; 24: 805-15.

MEB Strategic Business Plan 2014-2018



Patient-oriented evaluation of medicinal products. The patient's interests always come first in any activities concerned with the evaluation of medicinal products for human use.

Promoting the proper use of medicinal products. The benefit-risk ratio of a medicinal product depends strongly on the manner in which it is applied in clinical practice by the prescribing doctor and used by the patient.

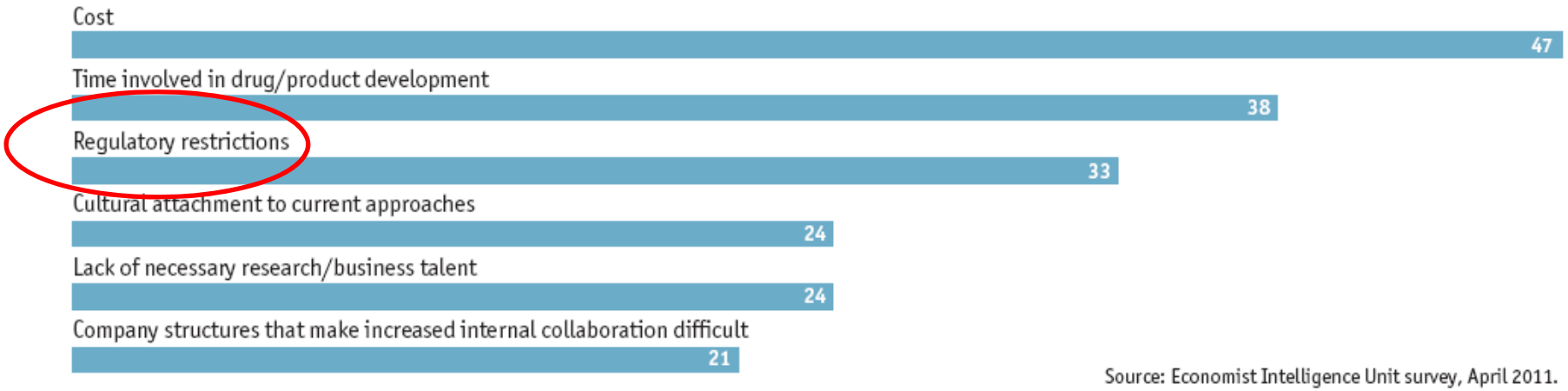
Promoting the innovation of medicinal products. The goal is to get new drugs available to patients as soon as possible by scientific advice of the MEB to companies and other regulations such as adaptive licensing.

Rechts en links ingehaald

https://www.youtube.com/watch?v=NqOZQpV9tgc

Barriers to innovation

Chart 2. **Top challenges to improving innovation record**
What are the biggest impediments to improving your company's product innovation? Select top three.
(% respondents)



Source: Economist Intelligence Unit survey, April 2011.

More transparency

OPEN ACCESS Freely available online

PLoS MEDICINE

Perspective

Open Clinical Trial Data for All? A View from Regulators

Hans-Georg Eichler[1]*, Eric Abadie[1,2], Alasdair Breckenridge[3], Hubert Leufkens[1,4], Guido Rasi[1]

1 European Medicines Agency (EMA), London, United Kingdom, **2** Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) Saint-Denis, France, **3** Medicines and Healthcare products Regulatory Agency (MHRA), London, United Kingdom, **4** Medicines Evaluation Board (CBG-MEB), Den Haag, The Netherlands

In this issue of *PLoS Medicine*, Doshi and colleagues argue that the full clinical trial reports of authorized drugs should be made publicly available to enable independent re-analysis of drugs' benefits and risks [1]. We offer comments on their call for openness from a European Union drug regulatory perspective.

For the purpose of this discussion, we consider "clinical study reports" to comprise not just the protocol, summary

Linked Policy Forum

This Perspective discusses the following new Policy Forum published in *PLoS Medicine*:

Doshi P, Jefferson T, Del Mar C (2012) The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med 9(4): e1001201.

research is a means to open health research.

Why Trial Data *Should Not* Be Open for All

There are indeed many good arguments for unrestricted and easy access to full RCT data. Yet, simply uploading all trial data on a website would entail its own problems.

PLoS Med 2012 Apr;9(4):e1001202. Epub 2012 Apr 10.

More transparency

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 October 2014
EMA/601455/2014
Press Office

Press release

Publication of clinical reports

EMA adopts landmark policy to take effect on 1 January 2015

The European Medicines Agency (EMA) has decided to publish the clinical reports that underpin the decision-making on medicines. Following extensive consultations held by the Agency with patients, healthcare professionals, academia, industry and other European entities over the past 18 months, the EMA Management Board unanimously adopted the new policy at its meeting on 2 October 2014. The policy will enter into force on 1 January 2015. It will apply to clinical reports contained in all applications for centralised marketing authorisations submitted after that date. The reports will be released as soon as a decision on the application has been taken.

Regulatory systems

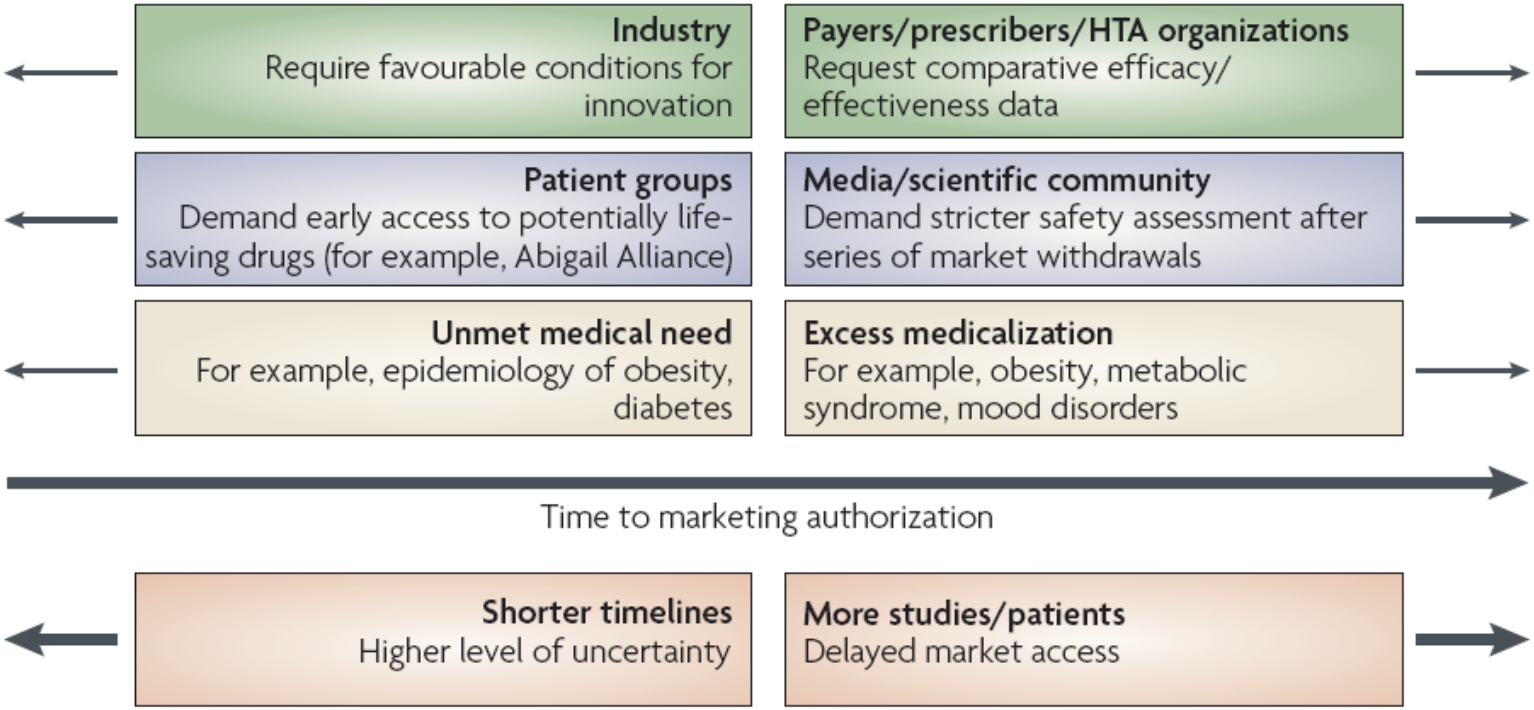
- Patient safety
- Public health
- Innovation

In addition, regulatory science should evaluate and study regulatory systems in terms of their ability to ensure patient safety, enhance public health, and stimulate innovation (*1*–*3*). During the past decades, the introduction of new innovative drugs has dropped, despite impressive investments and progress in biomedical research and development. Although the reasons for this innovation deficit are not fully understood, many observers see the increasing demands of the regulatory systems as one of the main drivers.

HUUB SCHELLEKENS[1,2]* ELLEN MOORS,[2]
H. G. LEUFKENS[1,3]

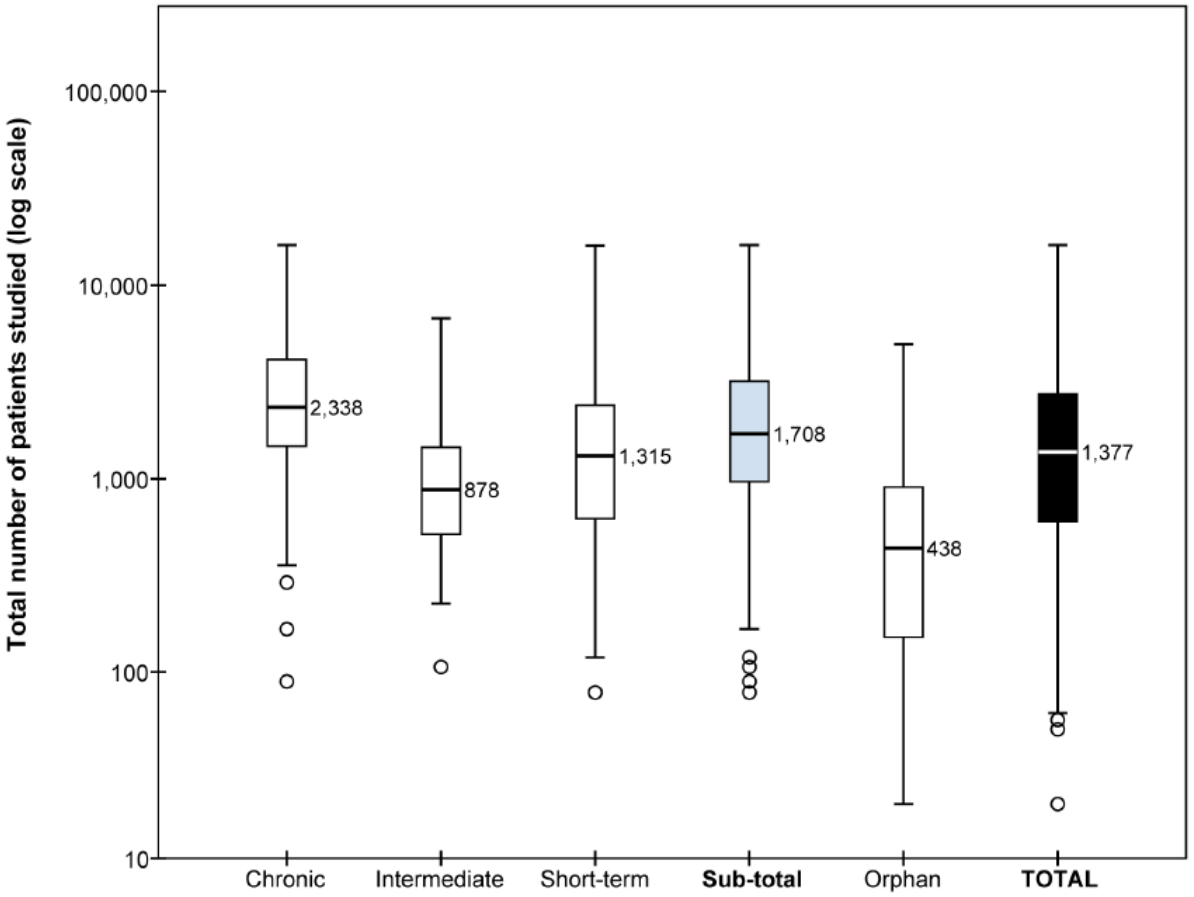
Drug regulatory systems must foster innovation. Science 2011 Apr 8; 332(6026): 174-5.

The best moment to bring a product to the clinic?



Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit-risk data. Nat Drug Discov 2008; 7: 818-26.

Number of patients studied prior to EU approval 2000–2010, 200 new medicines, 19.5% orphans



Duijnhoven RG et al. PLoS Med 2013; 10: e1001407.

Orphan drug regulation since 2000 - now

93 OMPs have been authorised for marketing

MEB contributions to orphan disease development

- Leading role in guideline development (i.e. PAH, Duchenne Muscular Dystrophy)
- Scientific advice (important challenges)
- Large proportion of NL driven European Rapporteurships Centralised Procedures

NL as Rapporteur/Co-Rapporteur for orphan drug dossiers

- Translarna (Duchenne Muscular Dystrophy)
- Cultured autologous oral mucosal epithelial cell sheet (Limbal stem cell deficiency)
- Cyramza (gastric cancer)
- Masitentan (pulmonary arterial hypertension)
- Adcetris (Hodgkin lymphoma and anaplastic large cell lymphoma)

NL as COMP Rapporteur Orphan Drug dossiers

- Adcetris (Hodgkin lymphoma and anaplastic large cell lymphoma)
- Pas-Gr and Delamanid (multi-drug resistant tuberculosis)
- Vantobra (cystic fybrosis)
- Holoclar (corneal stem cell deficiency)

NL as COMP Rapporteur Orphan designation dossiers

- Neuromuscular disorders (DMD/BMD, Spinal Muscular Atrophy, Charcot-Marie-Tooth, Freidreich's ataxia, Myotonic Dystrophy, Myasthenia Gravis)
- Neurodegenerative (Huntington's disease, Amytrophic Lateral Sclerosis)
- Neurodevelopmental: Fragile X syndrome, Dravet syndrome; Familial Cerebral Cavernous Malformations)
- Ophthalmology (Limbal Stem Cell Deficiency, Leber congenital amorhosis, neuromyelitis optica, choroideremia, non-infectious uveitits)
- Infectious diseases (polyomyelitis, MDR-TBC, malaria, CMV viermia post transplantation, trypanosomiasis)
- Cystic fibrosis
- Cycle cell anemia

Scientific Advice – some examples

- Neuromuscular disorders (DMD/BMD, SMA, CMT, Freidreich's ataxia)
- Neurodegenerative (Huntington's disease, ALS)
- Developmental: Fragile X syndrome,
- Ophthalmology (LSCD, Leber congenital amorhosis, neuromyelitis optica)
- Metabolic disorders (Gaucher, Pompe, familial hypercholesterolemia)
- Infectious diseases (Hepatitis C, MDR-TBC)
- Graft versus host disease
- TTR amyloidosis
- Pouchitis
- Cystic fibrosis
- Oncology (MDS, Hodgkin lymphoma)

- Example Familial Hypercholesterolemia
  Lojuxta (lomitapide)
  Rapporteur: NL, Co-Rapporteur: UK

- Scientific Advice on n-of-1 trials

- Adaptive Licensing

EMA guideline on Lipid lowering agents - EMA/CHMP/3020/2003-

- The primary goal of treating lipid disorders is to **prevent cardiovascular morbidity and mortality** associated with disturbed lipid levels

- **LDL-C is accepted as a surrogate marker** for CV risk prevention

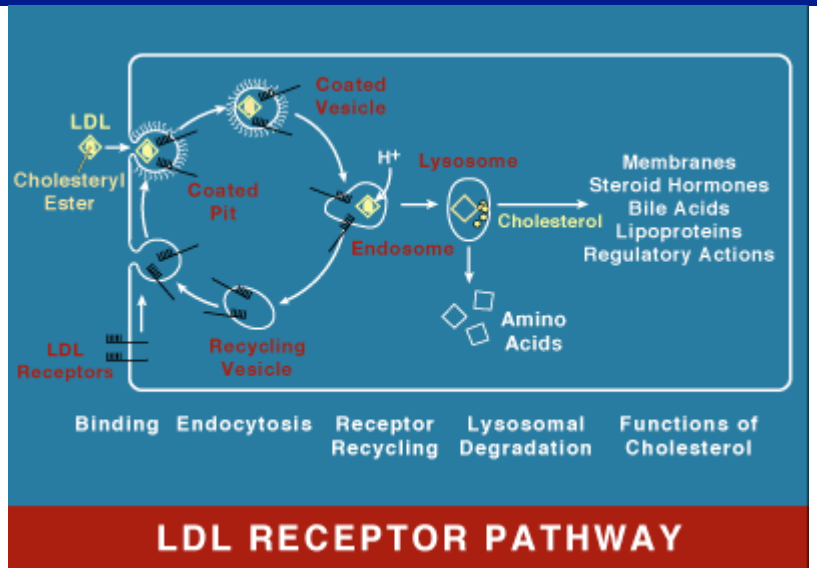
- A new lipid-modifying agent is only acceptable for registration when there is **no suggestion of a detrimental effect on both cardiovascular and non-cardiovascular mortality and morbidity**

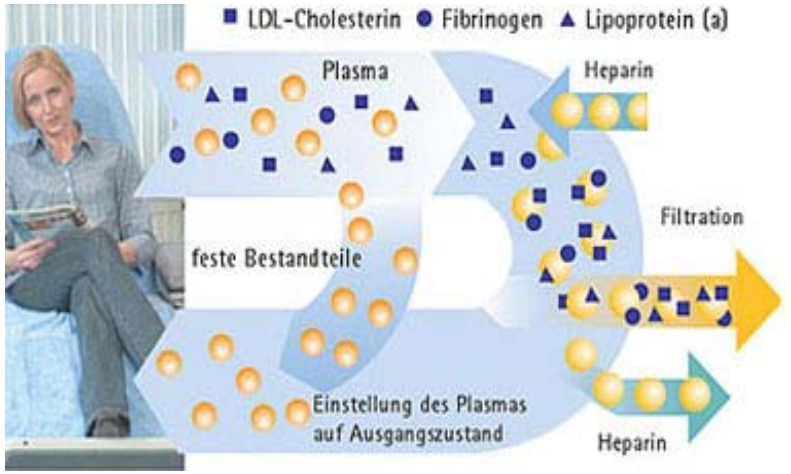
- Initial support for a lipid lowering indication should however **post-approval** be followed by a **cardiovascular outcome study** which would support a possible beneficial effect on CV morbidity and mortality

Familial Hypercholesterolemia

College ter Beoordeling van Geneesmiddelen

- Homozygote and heterozygote
- Homozygote (1:1.000.000)
  - LDL-Receptor dysfunction (about 98%)
  - Extremely high cholesterolvalues
  - Cardiovascular problems at a young age
  - Treatment options limited
    - statins are effective to a limited extent
    - LDL apheresis as alternative, only limited availability
- Heterozygote (1:500)
  - LDL-Receptor function is limited (about 60%)
  - Treatment options are better



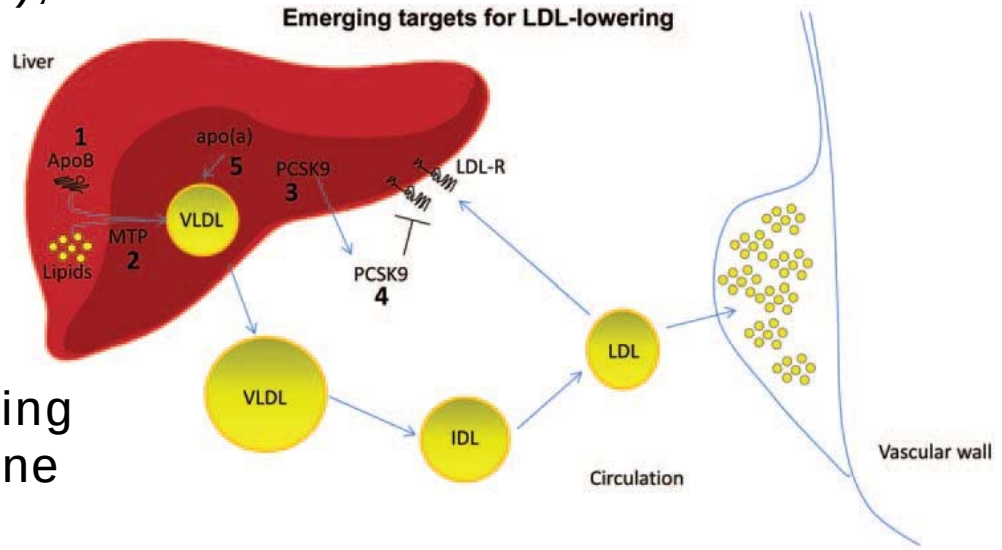


Lojuxta (lomitapide)

Mechanism of action

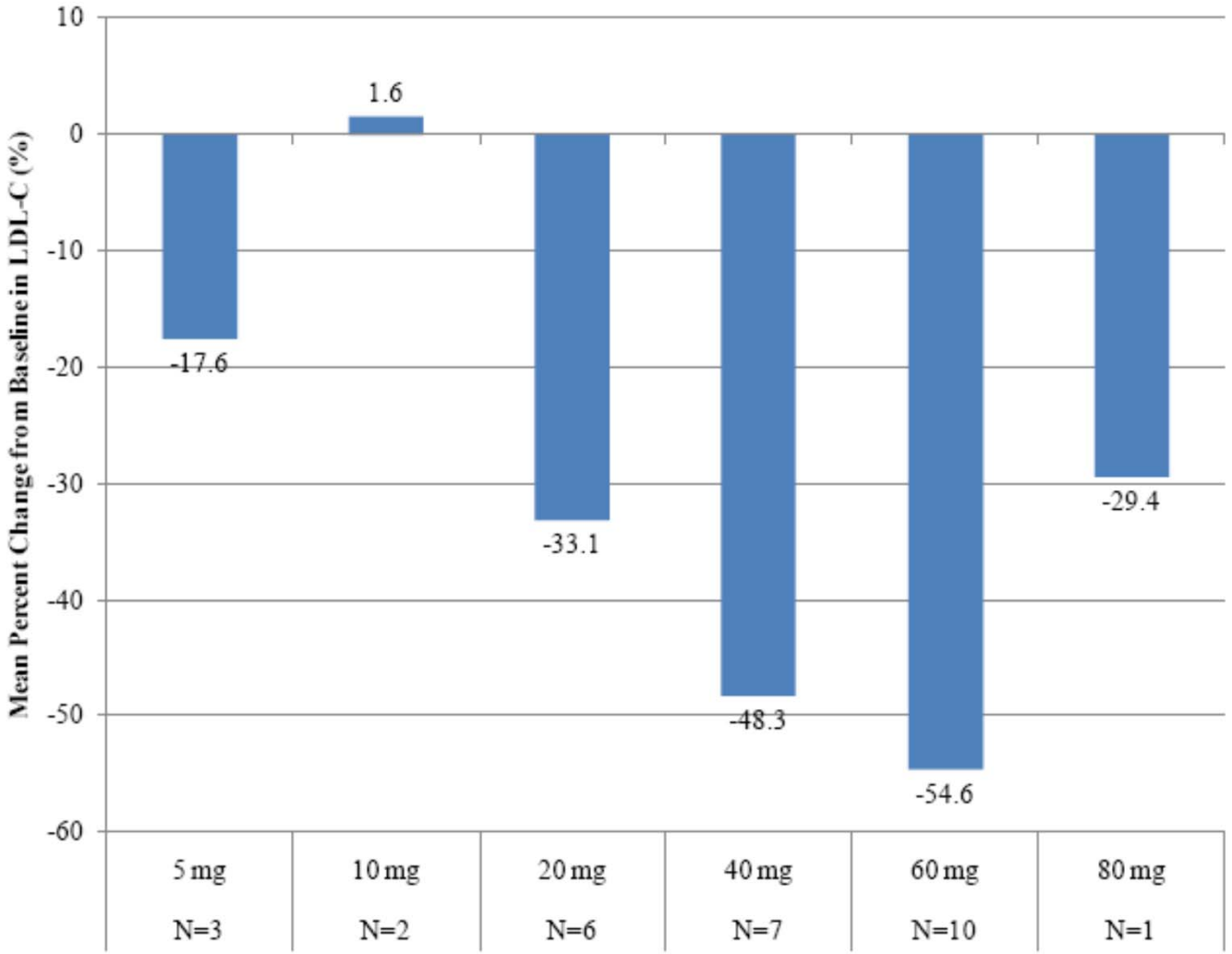
- Lomitapide is a selective inhibitor of Microsomal transfer protein (MTP), wich plays a key role in the assembly of apo B containing lipoproteins in the liver and intestines.

- Inhibition of MTP reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.



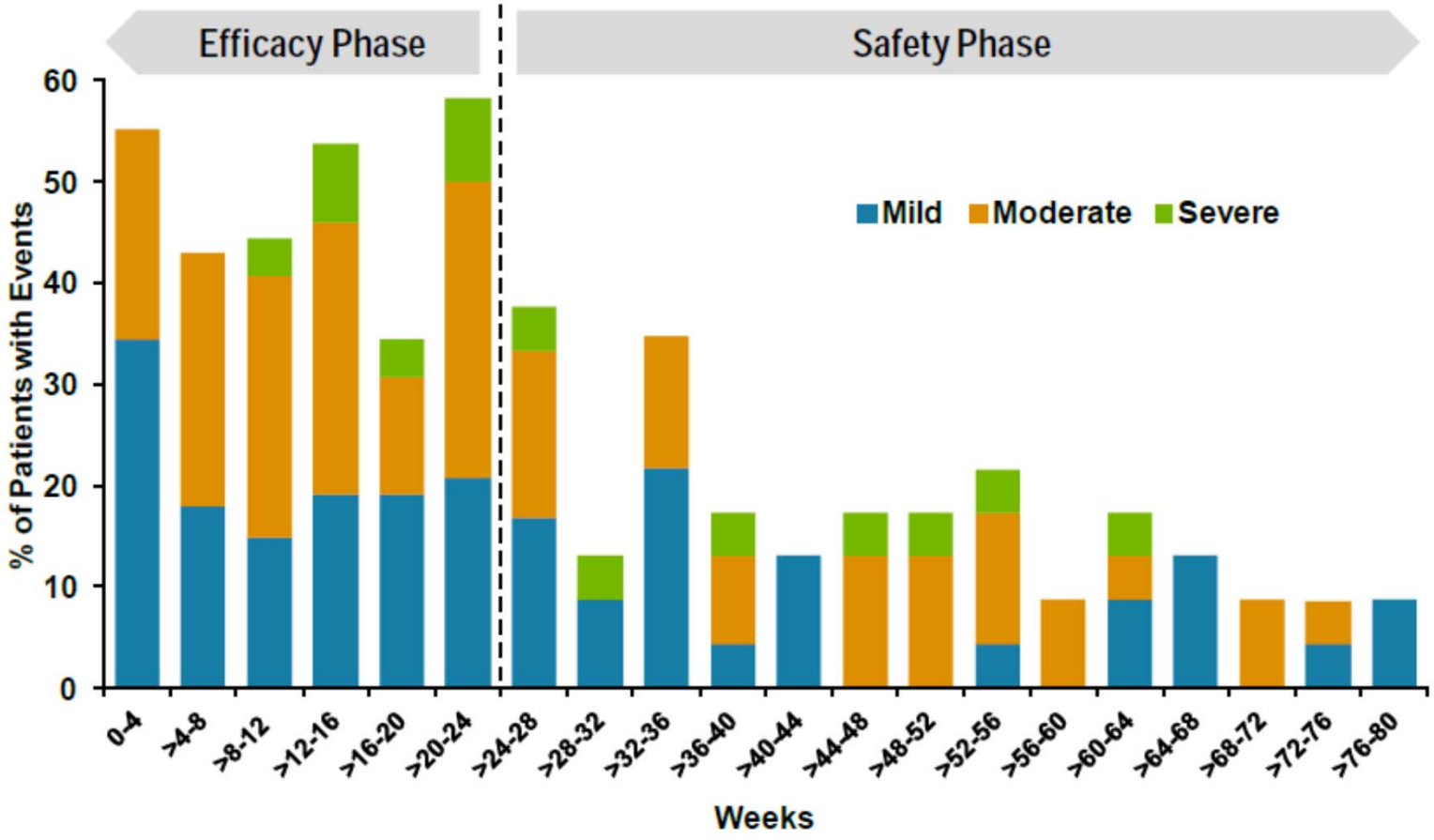
Lojuxta (lomitapide)

College ter Beoordeling van Geneesmiddelen



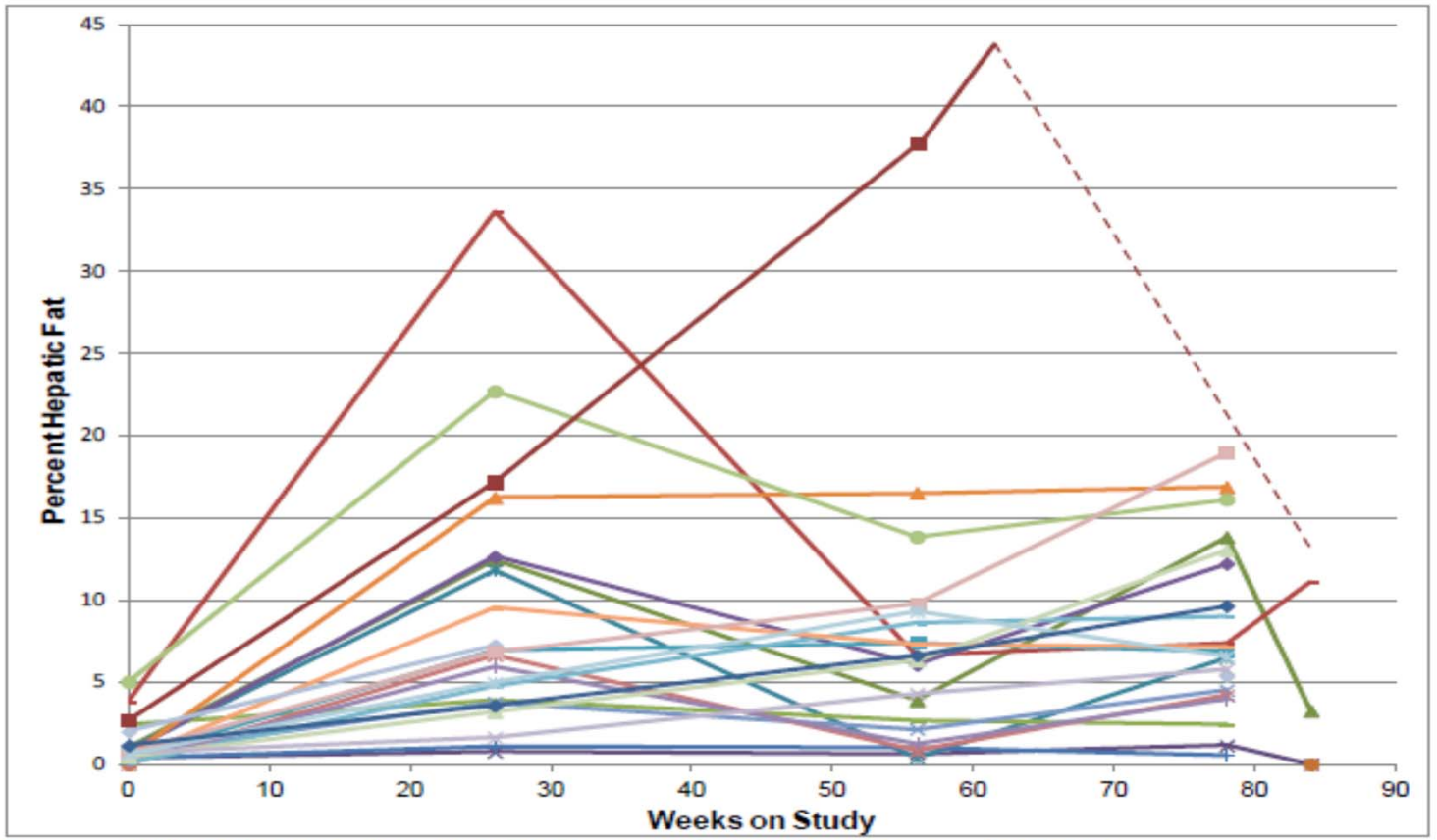
Lojuxta (lomitapide)

Figure 5: Patient Incidence of Gastrointestinal Adverse Events by Intensity Over Time on Treatment Through Week 78 in Study UP1002/AEGR-733-005 (Safety Population, N=29)



Lojuxta (lomitapide)

Figure 17: Percent Hepatic Fat Over Time by Patient Using Nuclear Magnetic Resonance Spectroscopy in Study UP1002/AEGR-733-005



Source: CSR UP1002/AEGR-733-005 Listing 16.2.8.14 and Listing 16.2.8.20
Note: Week 78 was end of treatment; Week 84 data presented are for patients off treatment who did not enter the extension study AEGR-733-012.
Note: dotted line represents levels obtained via CT scan; patient refused NMRS after Week 61 as he had metal implants.

Lojuxta (lomitapide)

Positive opinion of the CHMP (May 2013)

Authorisation under 'exceptional circumstances'

- The effect in reducing LDL-cholesterol levels was a benefit for patients with homozygous familial hypercholesterolaemia, who have an unmet medical need.
- However, the long-term benefit for the heart and circulatory system still needed to be confirmed.
- Side effects in the gut were noted in most patients, which caused some patients to stop treatment, and that it led to increased liver-enzyme levels whose long-term consequences are not known.

Lojuxta (lomitapide)

College ter Beoordeling van Geneesmiddelen

Positive opinion of the CHMP (May 2013)

Authorisation under ‘exceptional circumstances’

Every year, the European Medicines Agency will review any new information that becomes available.

Post-approval long-term study will be carried out in patients taking Lojuxta to provide further data on its safety and effectiveness, including its side effects on the liver, stomach, gut, and cardiovascular system.

Scientific advice on study designs

- Such as n-of-1 trials in which a single patient is the entire trial.

General methodological considerations

- As regulators, we get fewer data. Therefore, the main question is to which extent we want to use evidence depending on the context (need for medicine).
- Dealing with several n=1 trials is like dealing with a meta-analysis with patients instead of trials.
- A discussion of heterogeneity of the effect seen over patients
- A discussion why the treatment effect could be generalized to the population intended.
- Patient registries for future patients (in case of rare disease) and update of the evidence?

Adaptive licensing

College ter Beoordeling van Geneesmiddelen

1) Why adaptive licensing?

2) What is adaptive licensing?

3) Which actions are taken by the regulators?

4) Wat needs to be solved?

Why adaptive licensing?

Minister of Health, Welfare and Sport to Parliament (11 March 2014):

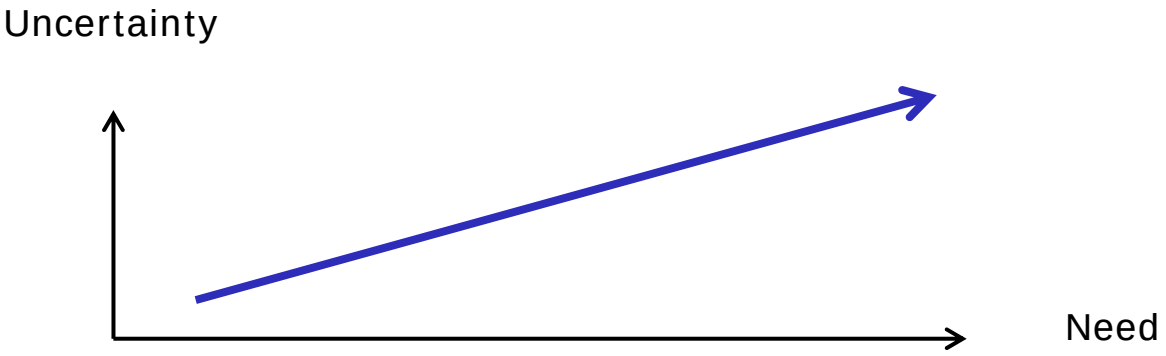
"If we manage to get drugs in a safe way faster to the market, patients need to make less frequently use of services provided by organizations like My Tomorrows. "

What is adaptive licensing? - 1

- The goal is to get good medicines to the patient as soon as possible
- Several synonyms, a.o. MAPP (Medicines Adaptive Pathways to Patients)

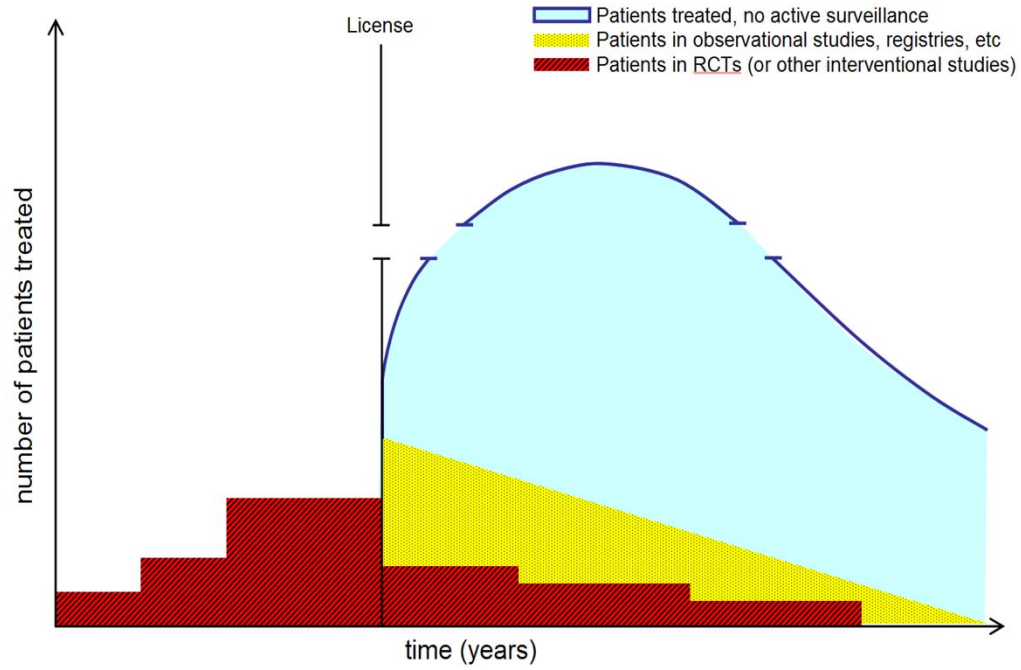
What is adaptive licensing? - 2

- Start with a specific patient group with a high unmet medical need
- Drug should met this medical need
- Uncertainty is accepted in the benefit and/or risk
- Uncertainty does not mean “bad data”
- No more data than necessary, but also no regulation light



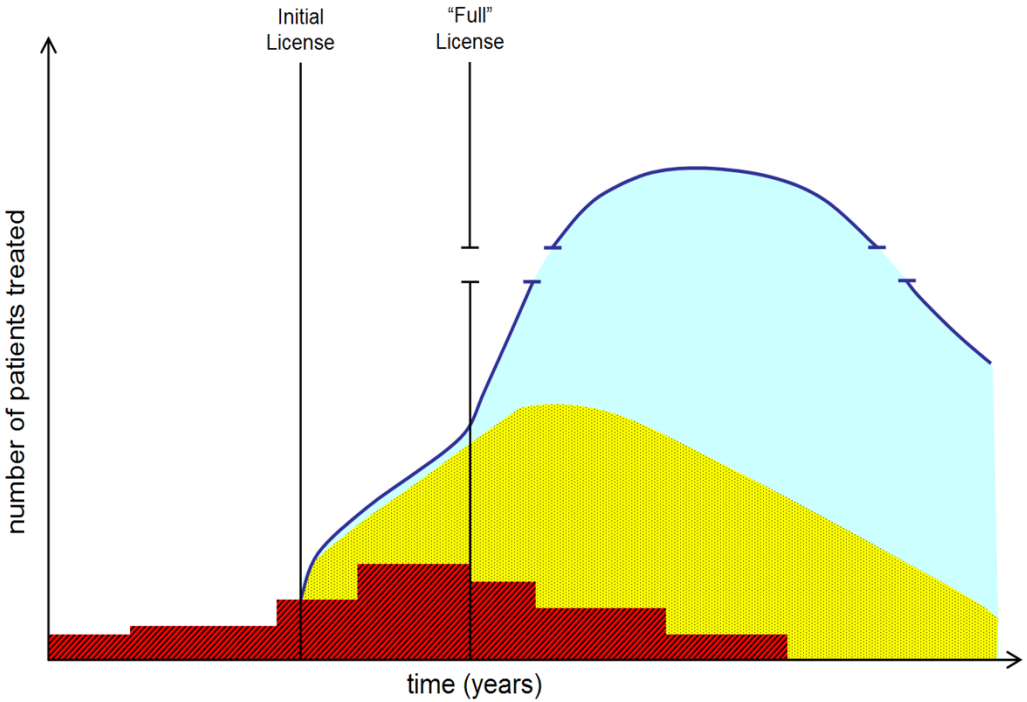
What is adaptive licensing? - 3

- Agreements on further data collection after registration
- Primarily in order to reduce uncertainties
- Data after registration can also contribute to widening indication
- Ultimately, more data are collected than in regular process
- Largely consist of real life data



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

What is adaptive licensing? - 4

- All disciplines, including quality (for example, dealing with not yet fully validated full scale)
- Patient, practitioner and other stakeholders directly at the table
- Every day life perspective of the patient (benefit & risk)
- Starting early in the developmental process, importance of good phase 1 and 2 studies.
- Adaptive pricing and reimbursement as part of adaptive licensing
- Discussing different scenarios developmental process
- Important role of scientific advice, but adaptive licensing concerns more than just advice

Which actions are taken by the regulators? - 1

- Collaboration with ZIN, CCMO en IGZ
- Tailored advice: early, multiple times
- Promoting innovation but also independent assessment

Which actions are taken by the regulators? - 2

- EMA pilot
- Companies submit applications for the pilot
- Active rol MEB in validation, prioritising and assessment pilots

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 March 2014
EMA/254350/2012
Senior Medical Officer

Pilot project on adaptive licensing

There is currently much debate about adaptive pathways for new medicinal products to come to the market. The terms 'staggered approval', 'progressive licensing', and 'adaptive licensing' have been used, often interchangeably, to describe the same broad concept. More recently, the term 'Medicines Adaptive Pathways' (MAPs) or 'Medicines Adaptive Pathways to Patients' (MAPPs) is discussed as potentially more appropriate terminology. For the time being, and in the interest of internal consistency, the term 'adaptive licensing' (AL) is used throughout this document.

AL can be defined as a prospectively planned, adaptive approach to bringing drugs to market. Starting from an authorised indication (most likely a "niche" indication) for a given drug, through iterative phases of evidence gathering and progressive licensing adaptations concerning both the authorised indication and the potential further therapeutic uses of the drug concerned AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.

In addressing the 'evidence versus access' balance, and consistent with a staged approach to collection of evidence and consequent licence adaptations, AL aims at a life-cycle approach to evaluation and licensing of medicines.

AL uses the regulatory processes within the existing EU legal framework, including scientific advice (with participation of HTA bodies and/or payers and/or other stakeholders), centralised compassionate use, the "standard" marketing authorisation, conditional marketing authorisation, marketing authorisation under exceptional circumstances, risk management plans, other provisions of the pharmacovigilance legislation, patient registries, etc.

The Agency is aware that representatives from different stakeholder groups, including patients, academicians, research-based industry, HTA experts, and regulators from several jurisdictions have expressed an interest in exploring how the concepts of AL could be further explored and developed.

The potential benefits and risks of AL, as well as the issues that need to be addressed have been discussed in publications[1] [2] [3] and at international conferences. Retrospective and hypothetical case

[1] Eichler HG et al. Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval. Clin Pharm & Ther 2012, Vol 91 (3), 426-437
[2] Woodcock J. Evidence vs. access: can twenty-first-century drug regulation refine the tradeoffs? Clin Pharmacol Ther. 2012 Mar;91(3):378-80
[3] Forda SR et al. Priorities for improving drug research, development and regulation. Nat Rev Drug Discov. 2013 Apr;12(4):247-8. doi: 10.1038/nrd3981.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8409
E-mail info@ema.europa.eu Website www.ema.europa.eu
An agency of the European Union

EMA pilot

- EMA press release 06/06/2014
- **European Medicines Agency selects first two medicines to be included in its adaptive licensing pilot project**
- The European Medicines Agency has received 20 applications so far as part of its adaptive licensing pilot project. Following an in-depth review of nine of these applications, the Agency has selected the first two medicines to be included in the pilot. A further four applications are potential candidates for the pilot and may be considered at a later stage. The other three applications were not considered suitable for the pilot and the remaining eleven are currently being evaluated.

Which actions are taken by the regulators? - 3

Adaptive licensing is a mindset, no additional regulations

Comprehensive range of legal options:

- Conditional approval
- Exceptional circumstances
- Compassionate use
- Hospital exemption
- Named patient
- Price- / reimbursement arrangements

What needs to be solved?

- Risk of off-label use
- Ten years of protection starts directly
- Communication and dealing with uncertainties
- Role as advisor versus regulator
- Successful adaptive licensing within framework of current regulations?
- Dominant focus on risk
- Pricing/reimbursement national concern
- Establish good patient registrations with stakeholders
- Common goal to do a step back when results from daily practice will be disappointing

Thank you!

Marjon Pasmooij
am.pasmooij@cbg-meb.nl