EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Assessing benefit/risk of medicinal products

## Regulatory framework and legal implications

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# Acknowledgment and disclaimer

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The EMA paladin of RE BR assessment*

The views expressed in this presentation are those of the author only and do not necessarily reflect and cannot be quoted as the views of the European Medicines Agency

* Eichler et al., **Relative efficacy of drugs: an emerging issue between regulatory agency and third-party payers**, in *Nature Reviews| Drug Discovery, vol. 9|April 2010|277*

# The EMA remit

- EMA is a decentralised Agency of the EU
- It is not part of the Commission
- A decentralised body of the EU with its own legal personality
- Advisory role (assess QSE medicinal products)
- Risk assessment ⇒ Risk management

# Legal framework

- Centralised procedure
  *Reg.(EC)726/2004*
- Referral procedures
  *Reg.(EC)726/2004, Dir.2001/83/EC*
- Paediatric medicinal products
  *Reg.(EC)1901/2006*
- Orphan medicinal products
  *Reg.(EC)141/2000*
- Advanced therapies medicinal products
  *Reg.(EC)1394/2007*

# The advantage of the centralised approach

One R-B assessment
valid throughout
27 EU+3 EEA countries

Similar legislative principles
applicable to R-B assessment
within DCP/MRP

# The regulatory challenge

- The role of a drug regulatory agency
- Balancing early access with the need for comprehensive data
- From one-off licensing to “live licence” The way forward?

# The drug regulator's role…

…to protect public health

- against unsafe or ineffective drugs
- against the consequences of untreated disease

This role translates into a mandate to support the development of beneficial drugs

# The regulator's dilemma

"…it has been said that the FDA has just two speeds of [drug] approval – too fast and too slow."

Hamburg MA & Sharfstein JM. NEJM 360;24: 2493-5; 2009

# Walking on a tightrope

against negative consequences from unsafe or ineffective medicines

When in doubt, be negative, "we need more information"

Worry about false-positive decision "Type-1 error"

... against negative consequences from failing to meet unmet medical need

When in doubt, be positive, "it might be a patient's only hope"

Worry about false-negative decision "Type-2 error"

# … protecting public health

against negative consequences from unsafe or ineffective medicines

When in doubt, be negative, "we need more information"


… against negative consequences from failing to meet unmet medical need

When in doubt, be positive, "it might be a patient's only hope"

no penalty for being negative!

# R-B communication

"The emotional epidemiology of flu vaccination"*

Patients in summer 2009: "When will there be a vaccine?"

(Same) patients in late 2009: "It's not tested", "I'm not putting that in my body"

The media in summer 2009: "What are health authorities doing to protect us?"

(Same) media (and government) in late 2009: "Vaccines are unsafe, were rushed to market"



* Ofri D: N Engl J Med 361:2594, 2009

# Risk/R-B balance - Definitions

**RISK RELATED TO USE OF THE MEDICINAL PRODUCT:**

- any risk relating to the **Q, S or E** of the MP as regard patient's health or public health

- any risk of undesirable effects on the environment

**RISK-BENEFIT BALANCE:**

An evaluation of the positive therapeutic effects of the MP in relation to the risks relating to the Q, S or E of the MP as regard patient's health or public health

***[Art. 1 point 28 and 28a of the Dir. 2001/83/EC]***

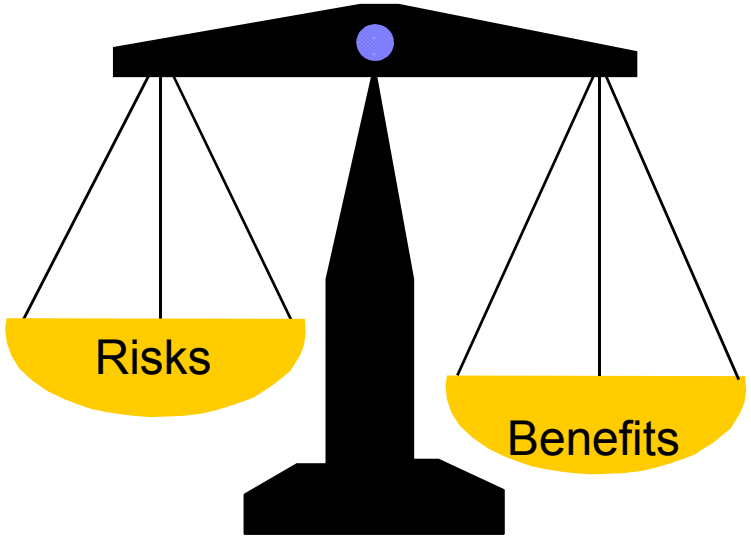
# Legal basis for EMA's R-B assessment

- *Reg.(EC)726/2004*

  *Recital(14):* provisions related to R-B assessment described in Dir. 2001/83/EC applicable:

  *"(…) it should be possible to assess the **risk-benefit balance** of all medicinal products **when they are placed on the market**, at the time of the **renewal** of the authorisation and at **any other time** the competent authority deems appropriate"*

# Criteria for authorising medicinal products




The main scientific principle used in the evaluation of medicines is the **risk/benefit balance** based on quality, safety, efficacy and risk management considerations.

# What falls within the scope of R-B assessment?

- Quality
- Safety
- Efficacy

of the concerned medicinal products for which the marketing authorisation is applied for

The MA is an administrative licence (which is granted when and if there are no public interest obstacles to exercise a regulated activity ⇒ i.e. placing the product onto the market)

# Stages of the R-B Assessment (1)

- **PRE-AUTHORISATION**

  - granting/refusing MA

The concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.

*[Recital(7) Dir.2001/83/EC]*

# Continuous R-B assessment (1)

- Obligation for MAH to inform the EMA, the EC and the MSs of any prohibition or restriction imposed by the CAs of any country in which the MP is marketed and of **any new information which might influence the evaluation of the benefit and risks** of the MP concerned
- In order that the risk-benefit balance may be continuously assessed, the EMA may at any time ask the MAH to forward data demonstrating that the risk-benefit balance remains favourable.

*[Article 16 point 2 Reg.(EC)726/2004]*

# Continuous R-B assessment (2)

- PSUR reports shall be accompanied by a scientific evaluation, particularly of the **risk-benefit balance** of the medicinal product

**QPPV obligations, *inter alia.:***

- ensuring that any request from the CAs for the provision of additional information necessary for the evaluation of the R-B of a MP is answered fully and promptly, including the provision of information regarding the volume of sales or prescriptions for the MP concerned;
- providing the CAs with any other information relevant to the evaluation of the R-B of a MP, particularly information concerning post-authorisation safety studies.

# The marketing authorisation shall be refused if:

[Article 26 of Directive 2001/83/EC]

- *the risk-benefit balance is not considered to be favourable; or*
- *its therapeutic efficacy is insufficiently substantiated by the applicant; or*
- *its qualitative and quantitative composition is not declared*

# Stages of the B-R assessment (2)

- **POST-AUTHORISATION**
  - **continuous R-B assessment,** if negative:
    - suspension,
    - revocation,
    - withdrawal or
    - variation of the MA
  - **MA renewal**

# Outcome of the negative B-R assessment

The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is **harmful under normal conditions of use**, or that it **lacks therapeutic efficacy**, or that **the risk-benefit balance is not positive under the normal conditions of use**, or that **its qualitative and quantitative composition is not as declared**. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

*[Article 116 Dir.2001/83/EC]*

# Renewal of the MA

- The MA may be renewed after five years on the basis of a **re-evaluation** by the Agency **of the R-B balance**.

- Obligation for the MAH to provide the Agency with a consolidated version of the file in respect of Q,S,E incl. all variations.

*[Article 14 point 2 Reg.(EC)726/2004]*

# REA – Legal question

For interpretation (with possible EC involvement)

**Does the EU legislation enable a MA to be refused (or revoked) simply because there are better products on the market?**

for further discussion and consideration, but…

# Relative efficacy assessment

- Evolving interface between MP regulators and Health Technology Assessment Bodies (HTA)
- High Level Pharmaceutical Forum Report conclusion – to request more often active comparator studies
- In general, clinical trials shall be done as "controlled clinical trials" if possible, randomised and as appropriate versus placebo and **versus an established medicinal product of proven therapeutic value**; any other design shall be justified"

  *[Dir. 2001/83/EC Annex I]*

- Exhaustive grounds for MA refusal in Article 26 Dir 2001/83/EC

# Can they be part of the R-B assessment?

- Costs
- Availability
- Promotion of innovation and development
- Effectiveness
- Alternative methods and health impact

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EMA has not NICE-like responsibilities

# Current legislative wording

- EU legislative regime does not provide a mechanism or system whereby a medicinal products can be denied an authorisation merely because other "better" products are available
- *Recital 13 Reg.(EC) 726/2004:* decisions should be taken **on the basis of the objective scientific criteria of Q,S and E of the medicinal product concerned**
- *Recital 34 Reg.(EC) 726/2004:* MSs do compare the E of MP with a view to ranking them as more or less effective than other products of the same therapeutic class and makes clear that **within MA framework there should be no such comparison** and that assessment should be confirmed to the fundamental criteria of Q, S, E

# *Thank you!*