DGRA – Jahreskongress

Implementation of the Review 2001

Impact on the pharmaceutical industry

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This presentation reflects the opinion of the author
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Review 2001 – Mission accomplished ?

"A compromise is the art of dividing a cake in such a way that everyone believes that he has got the biggest piece."

Ludwig Erhard, German Politician

Final **compromise package** does not fully meet the needs of the research-based pharmaceutical industry; yet it brings important improvements in Europe's regulatory structure (Source: EFPIA)

Review 2001 – Main Goals

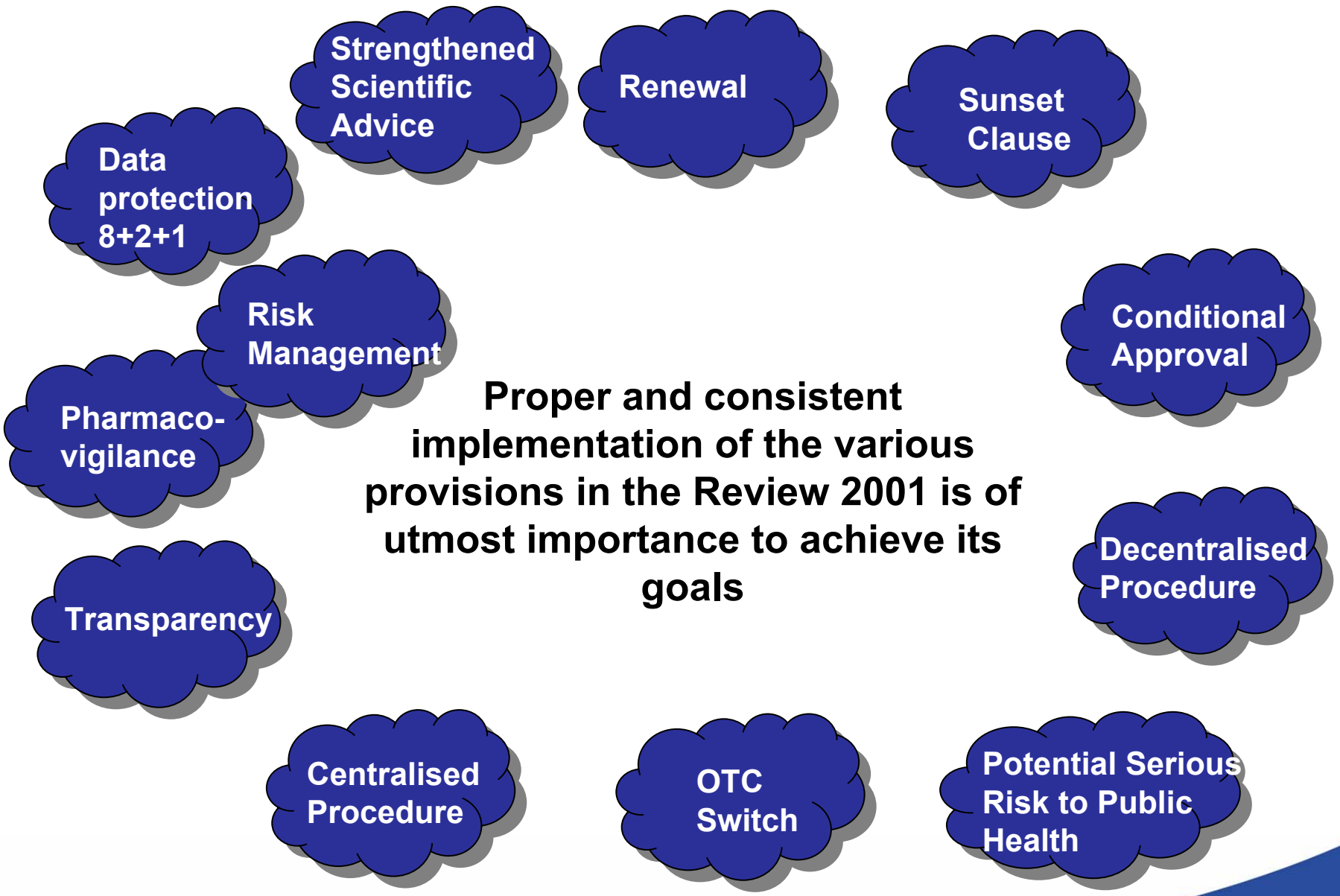
- *To guarantee a high level of public health protection by providing patients with safe and innovative medicines*
- *To strengthen pharmacovigilance procedures*
- *To rationalise and simplify the regulatory system*
- *To complete the Single Market for pharmaceuticals*
- *To strengthen the competitiveness of the pharmaceutical industry in an enlarged EU*

Strengthening Competitiveness …

Commission Communication, July 2003: "A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient – A Call for Action"

Recommendations, e.g.:

- Developing a competitive EU- based pharmaceutical industry e.g. by improving access to medicines, speeding up negotiations on pricing and reimbursement, developing competitive generic and non-prescription markets
- Strengthening intellectual property protection in the new Member States
- Benefits to patients
  e.g. by improving patient information, strengthening the role of patients in public-health decision-making, reviewing national approaches to relative effectiveness, strengthening pharmacovigilance


Strengthened Scientific Advice
Renewal
Sunset Clause
Data protection 8+2+1
Risk Management
Conditional Approval
Pharmaco-vigilance
Proper and consistent implementation of the various provisions in the Review 2001 is of utmost importance to achieve its goals
Decentralised Procedure
Transparency
Centralised Procedure
OTC Switch
Potential Serious Risk to Public Health

Impact of the Review 2001 on the pharmaceutical industry

- Which of the provisions will ultimately strengthen the competitiveness of the pharmaceutical industry thereby fostering innovation ?
- Which of the provisions will increase the protection of public health ?
- Which of the provisions will rationalise and simplify the regulatory system ?

Scientific Advice

- **Different processes** for EMEA scientific advice to be established depending on the scope of the request, the type of products and their stage of development
- **Scope of scientific advice** to be extended to cover post-authorisation, pharmacovigilance and risk management/risk minimisation aspects
- Provision of scientific advice not to be limited to innovative medicines but also to address specific issues related to **generic medicines** and **OTC products**

Strengthening of scientific advice is good, however:

- Only when no guidance available ?
  Need for interpretation in the individual case
- Continuous dialogue throughout the development is crucial

Source: EMEA Road Map to 2010 – Preparing the Ground for the Future

Pharmacovigilance - Preapproval

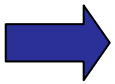
- Prospective pharmacovigilance planning to be included in applications:

  A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce

- Guidance: ICH E2E Pharmacovigilance Planning:

Safety Specification:
(based on available data)

- Identified risks
- Important potential risks
- Important missing information



Pharmacovigilance Plan:

To describe the appropriate plans and actions to proactively address the issues identified in the Safety Specification

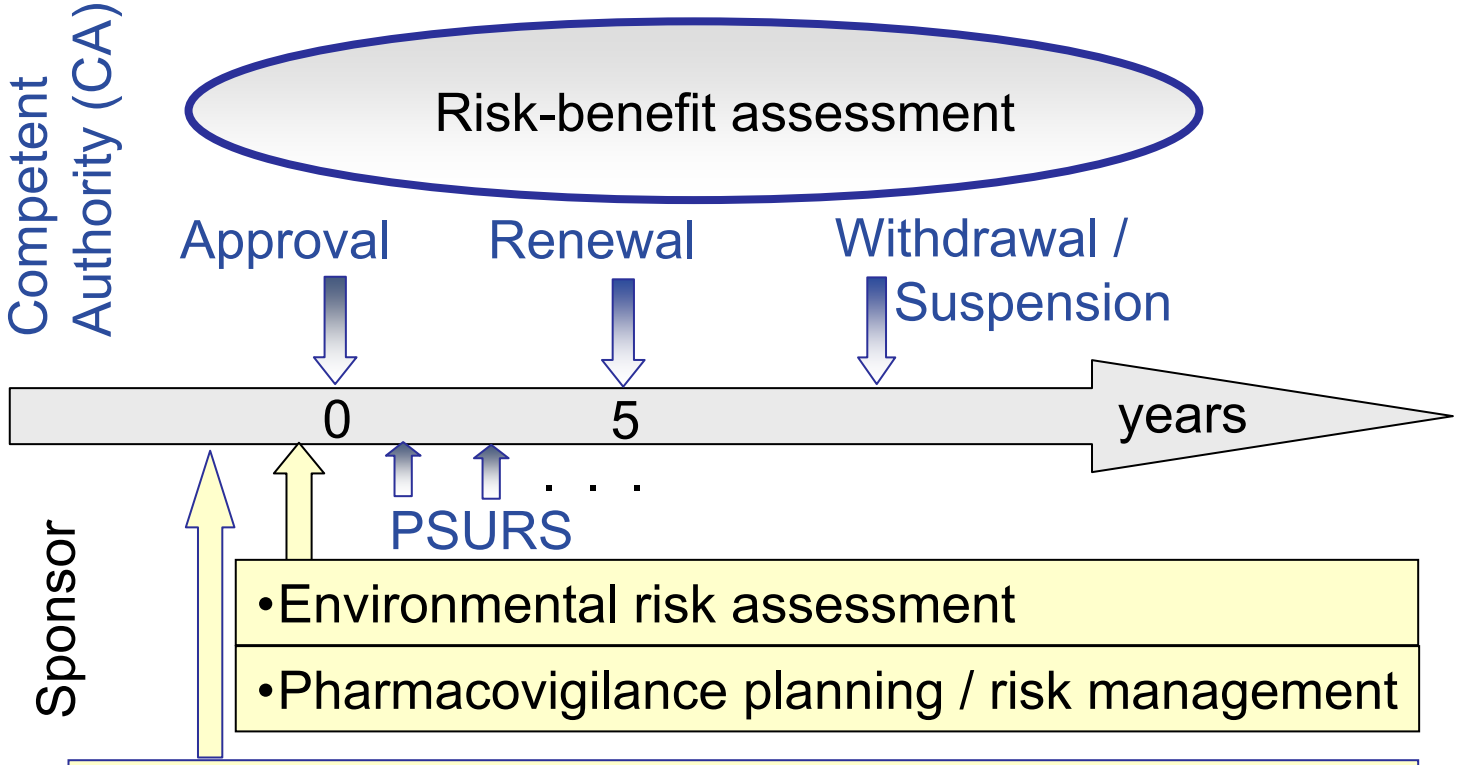
Pharmacovigilance planning as an important part of the application ultimately increasing the protection of public health

Pharmacovigilance - Postapproval

- Increased frequency of Periodic Safety Update Reports: At 3-yearly instead of 5-yearly intervals (including risk-benefit balance evaluation)
- Obligation by the sponsor to notify the authorities of any information that may affect the terms of their marketing authorisation
- The Member States shall operate a pharmacovigilance system: database established by the Regulation (EC) No 726/2004 (EuroPharm) - accessible to all Member States and to the public
- Inspection of pharmacovigilance systems

A well functioning risk management system at the pharmaceutical industry as well as at the agencies is key for improving the protection of public health !

Continuous Risk / Benefit



- Continuous relative risk- benefit assessment
- Complying with new guidelines?

'Controlled clinical trials' if possible, randomised and as appropriate versus placebo and *versus an established medicinal product of proven therapeutic value*

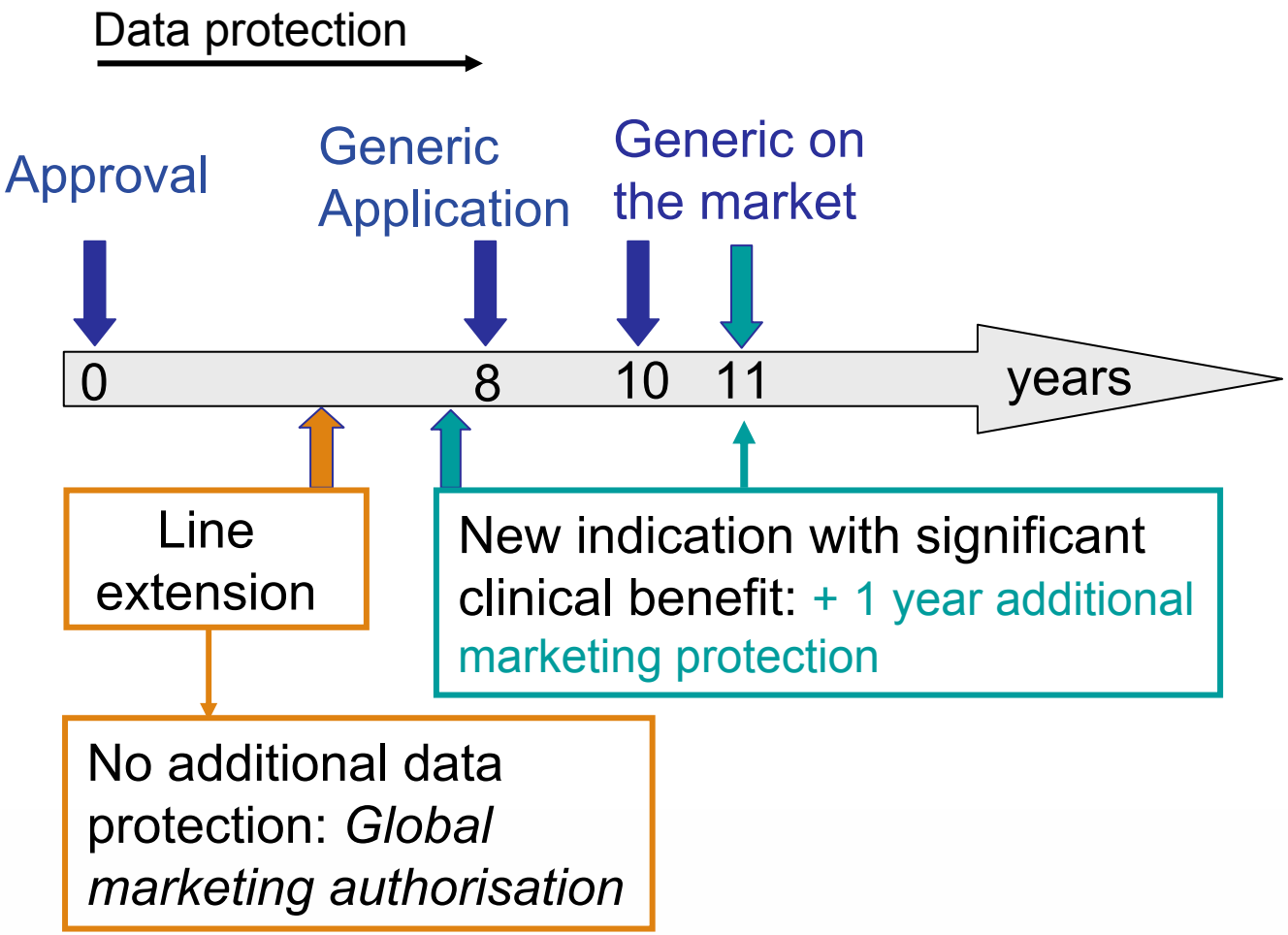
(Commission Directive 2003/63/EC, point 5.2.5.1.)

Renewal

- Why is a renewal necessary ?
- Risk-benefit assessment should be done continuously by the applicant as well as by the agency independently from a renewal

There is no necessity for a renewal to trigger a risk-benefit assessment ; this should be done continuously !

Data protection
Global marketing authorisation



- Criteria for significant clinical benefit ? Consistent decisions?
- When will a generic MA be issued ?
- Who ensures no placing on the market before 10 (11) years ?
- High risk for lifecycle strategies

Additional Data Protection:
➢Well-established Use ➢Rx ⇨ OTC

Well-established substance: + 1 year for new indication(s)

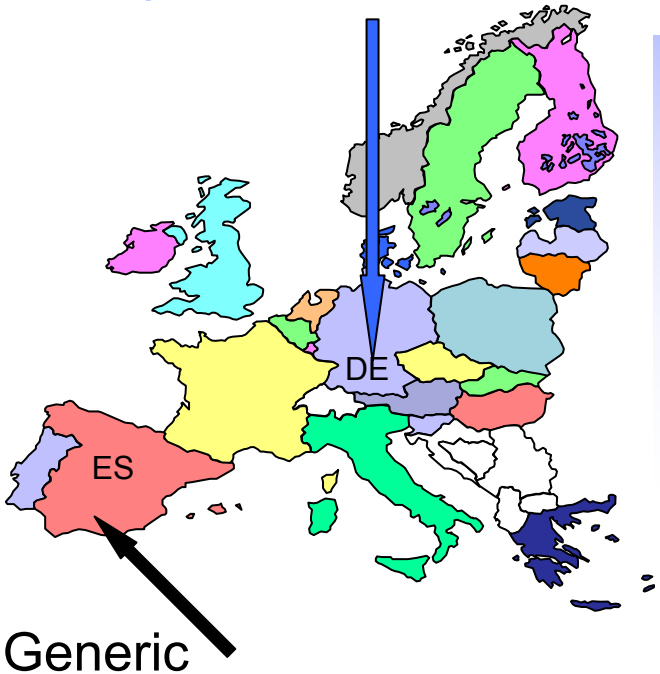
- Additional protection granted only once (non-cumulative)
- Prerequisite: significant pre-clinical or clinical studies in relation to the new indication

Rx ⇨ OTC switch: + 1 year protection

- Reclassification on the basis of “significant pre-clinical tests or clinical trials”
- Data protection for the OTC version
  - New guidelines expected this year
  - New brand should be used for the OTC version
  - Criteria for „significant trials“ ?
  - New opportunities for life-cycle management ?

EU Reference Product

Reference product authorised for 8 (10) years



Which data exclusivity period applies to products submitted before 30 Oct. 05?

- of the reference product authorising state (e.g. 10 years)?
- of the generic authorising state (e.g. 6 years)?

Generic application possible where the reference product was not authorised – authorisation in any member state is sufficient!

Decentralised Procedure

For which products?

- New products not mandatory for the centralised procedure

Advantage to the Centralised Procedure?

- Choice of member states
- More complicated procedure as compared to the Centralised Procedure
- As for the MRP agreement by all member states necessary, otherwise forced arbitration
  (Centralised Procedure: Opinion is adopted by a majority vote)

- Mostly for generics ? New Active Substances - centralised
- A simplified regulatory system ?

New definition of "potential serious risk to public health" (draft Commission proposal; Feb. 05)

- **Risk definition:** *any risk relating to the quality, safety or efficacy of the medicinal product as regards to patients' health or public health*
- Examples that would not be considered as grounds for a serious risk to public health issue
  - The absence of an active comparator study
  - The absence of evidence demonstrating added therapeutic value of the new medicine in comparison to existing medicines
  - The lack of compliance with current Guidelines does not automatically result in a serious risk to public health issue

The right interpretation and implementation of this definition is crucial for the proper functioning of the MRP and DP in future.

Decentralised Procedure & MRP (1)

Forced arbitration in case of no agreement in the new co-ordination group (CMDh)

- Loss of possibility to withdraw to avoid arbitration
- Loss of business flexibility for industry

Possibility for MS to grant MA without waiting for the outcome of arbitration (at the request of the applicant)

- A significant advantage ?

Decentralised Procedure & MRP (2)

Following finalisation of the MRP/DP, national MA to be issued within 30 days

- Now legal requirement, not just “best practice”
- Faster granting of national MA ?
- Launch strategy and timing more predictable ?

Definition of deadlines for the issuing of MAs in the law is not new.

The compliance is the problem !!!

Centralised Procedure (1)

Mandatory use of the CP

- New active substances for the treatment of :
  - AIDS, cancer, neurodegenerative disorders, or diabetes
  - In 2008: Immune dysfunctions and viral diseases
- Orphan medicinal products
- Biotech products

Optional use of the CP

- New active substance (not included in disease categories above)
- Not innovative but may be “of interest to patients at Community level” (e.g. certain OTC products)
- Generics of centrally authorised products

A clear trend towards centralised

Centralised Procedure (2)

Conditional Approval

- Marketing approval based on predefined commitments
- Criteria: life threatening diseases, public health interest
- Essential to agree as early as possible on the use of appropriate surrogate endpoints
- Early consultation with relevant Working Parties / Therapeutic Advisory Groups crucial

Accelerated Assessment

- Shortens review time to a max of 150 d (active review time)
- Eligibility criteria “of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation” need further clarification

- New procedures offer new opportunities for innovative products
- Limited to the centralised procedure ?

Transparency (1)

The following information shall be made publicly accessible:

- The assessment report * + reasons for the opinion
- Information about all refusals + the reasons for them (CP)
- Withdrawals of applications + applicant´s reason for the withdrawal (CP)
- The marketing authorisation (MA) + SmPC (MRP/DP)
- Opinion of the Committee for human medicines in the case of an Article 29 referral (MRP/DP)

Who benefits from this transparency, the patient ?

* after deletion of information of a commercially confidential nature

Transparency (2)

Rapporteur / Co-Rapporteur appointment in the Centralised Procedure

- Lack of transparency regarding the CHMP decision on Rapp/Co-Rapp appointment
- Proposals by the applicant will be no longer considered

CHMP decision

- Without the presence of the applicant

Transparency – A one way road ?

Conclusion

- Some provisions like the conditional approval, accelerated assessment and strengthened scientific advice may support innovations
- In the major EU markets, data protection has been reduced from 10 to 8 years
- The provisions of the global marketing authorisation, the EU reference product and “Bolar” support the generics industry
- Whether the DP is going to be simpler, remains to be seen …
- It is crucial to harmonise the definition of potential serious risk to public health
- The adherence to timelines for issuing a MA by the competent authorities remains questionable
- Does the clinical trials directive really improve competitiveness of clinical research in Europe ?
- The EU paediatric regulation is in preparation for 6 years (!) and the outcome might not be competitive to the US !

Thank you for your kind attention !