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European Federation of Pharmaceutical Industries and Associations

EMEA/CHMP WORKSHOP
Draft guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products

THE EFPIA POSITION

EMEA Workshop

London – 12th June 2007

SOME BACKGROUND

- Multidisciplinary guideline released on 22nd March for a 2-month consultation
- Consolidation considered different disciplines, non-clinical safety, quality and clinical
- EFPIA position based on more than 120 pages of comments from >20 companies
- EFPIA supports the creation of this new guideline
  - good science and decision-making
  - good summary of what EFPIA considers to be standard good clinical practice in the conduct of CTs in early development

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EFPIA MAJOR ISSUE

- Definition of high risk versus non high risk compound
  - Risk is related in particular to dose selection and to the clinical trial (CT) design
- Currently proposed classification is not appropriate
- Guideline should preferably remain focused on risk mitigation principles and strategies through non-clinical data integration and appropriate CT design
  - To better ensure safety of subjects involved in ALL FTIH
  - To ensure good science is applied and the guidance is not seen as a check list
  - To avoid negative impact on clinical development in Europe

First Time in Human with High Risk Compounds - EFPIA View

- Proposal
  - EFPIA propose altering the guideline to “Guideline on risk management strategies and dose-setting for first-in-human clinical trials”
- Classification of some medicinal products as high risk medicinal products is inappropriate and unnecessary for the purpose of designing a safety evaluation programme

  In the early 1500s Paracelsus stated that "All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy"

  The general concept outlined in the draft guideline of taking account of both toxicological and pharmacological dose/concentration-response relationship is equally applicable to all IMPs

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Rationale for EFPIA Proposal

- Key to defining FTIH is risk assessment in the context of the proposed clinical trial
  - It is the clinical trial design that leads to acceptable or unacceptable risk to human subjects in first-in-human trials
  - The design of the trial is influenced by all available non clinical and human derived data
- The guideline should address risk mitigation principles and strategies. Integration of all preclinical data should influence appropriate design of clinical trials
  - No need for specifically defining high risk molecules
  - We already have extensive experience in dealing with ‘high risk’ molecules – e.g. oncology products
  - Clinical design and caution will differ on a case by case basis dependent upon knowledge of Biology, Toxicology and the confidence in predictive value of non clinical models

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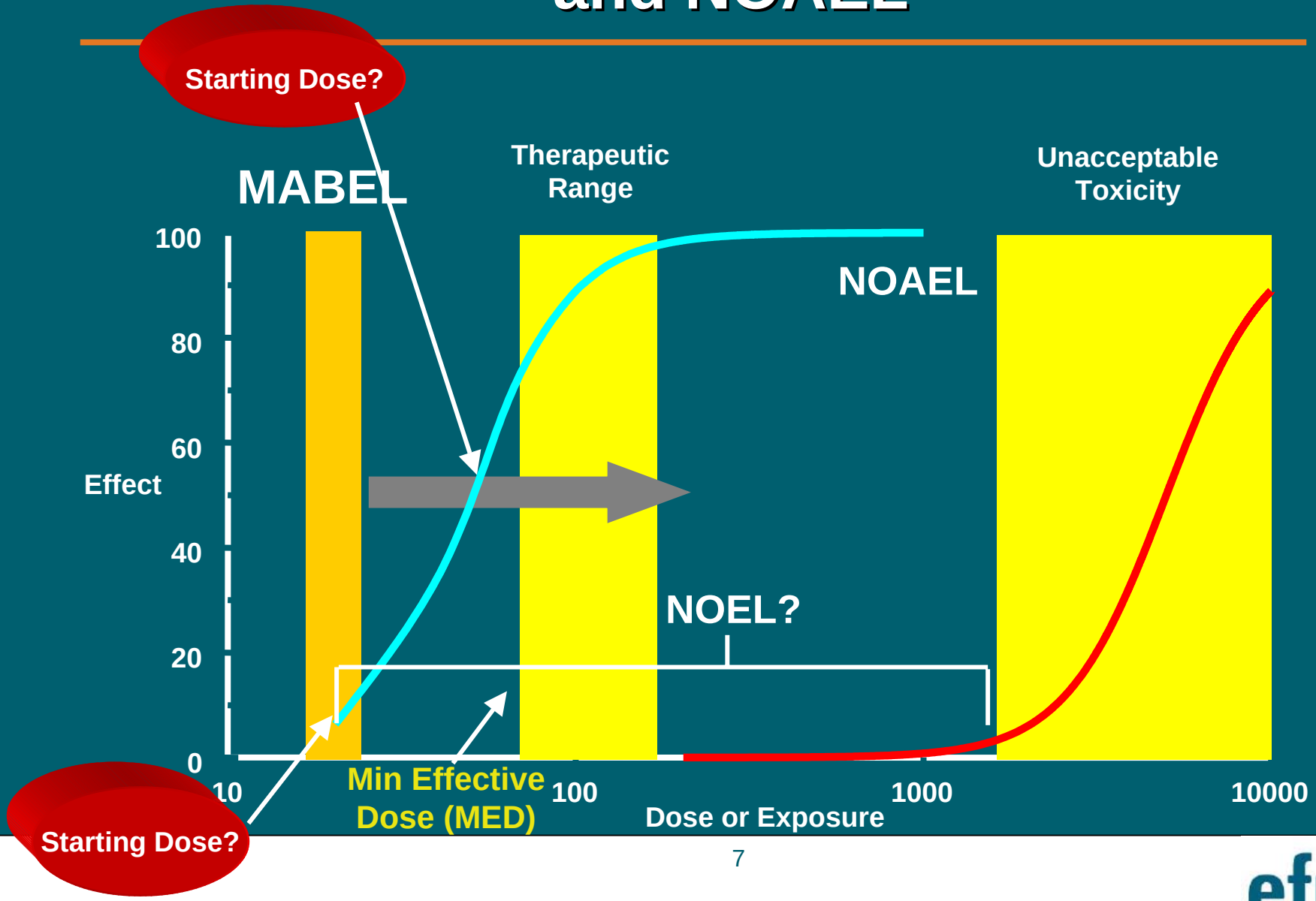
Rationale for Proposal
Principles of Risk Assessment

- Sound Science – Aims of non clinical studies
  - Dose selection
    - Toxicological and pharmacological data define Hazard, and dose/concentration relationships
  - Species selection and extrapolation
  - Mechanistic understanding
    - Toxicology and Pharmacology seen in animals
- Recognition of the limitations of the test systems
    - Relevance of the toxicity seen in animals to humans
    - Ability of the non clinical models to predict effects in humans
- Risk Assessment
    - Utilising all available data – the dose makes the poison!

Relationships Between MABEL, NOEL, and NOAEL



OTHER EFPIA COMMENTS

- Considerations might be given to studies in patients, and the appropriate risk versus benefit evaluations in these populations *vis-à-vis* healthy volunteer
- Reference to existing oncology guidelines is recommended
- Considerations might be given to gender differences
- Final guideline is expected to ensure consistency within the EU Member States

SOME DETAILED COMMENTS

- **General aspects**
  - Trial design not used to identify the risks. It is the risk that define the design
  - Definition of 'high risk' may deter subject enrolment
  - Use of an Independent Safety Monitoring Board may be considered. The protocol should define clear processes and responsibilities for making decisions about dosing of subjects and dose escalation or any stopping criteria
- **Choice of subjects**
  - Targeted patient population (e.g. in relation to life expectancy, in oncology) should also be taken into consideration
  - Special considerations should be given to potential long-term consequences on physiological systems and potential long-term safety problems for agents anticipated to produce a demonstrable PD effect beyond the period required to fully assess PK

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Conclusion

- All IMPs should be considered using the same principles of safety
- Risk is a continuum and not a dichotomy (high versus low)
  - Related to dose and response
  - All available knowledge/data is pertinent to risk assessment
- Proposal
  - EFPIA propose altering the guideline to “Guideline on risk management strategies and dose-setting for first-in-human clinical trials”

Back ups

SOME DETAILED COMMENTS

- Scope
  - Helpful to have more explicit definition

- GLP – to greatest extent feasible
- ADME – where appropriate
- Vaccines - Exclude
- Micro dosing approaches - Impact

SOME DETAILED COMMENTS

- **Route and rate of administration:** infusion period should be justified but not unduly limited
- **Precautions within a cohort:** sequential dosing to be clarified
- **Dose escalation** would need clarification and rewording to avoid delay and lack of flexibility while ensuring subject's safety
- **Adverse events (AEs and SAEs)** : management and reporting to be clarified
- **Long term monitoring** may be necessary if the properties of the substance and the results of the trial suggest a particular need
- **Site of the CT:** preferably as a single protocol at a single site, however exception can be made on a case by case basis