Regulatory vision of paediatric applications

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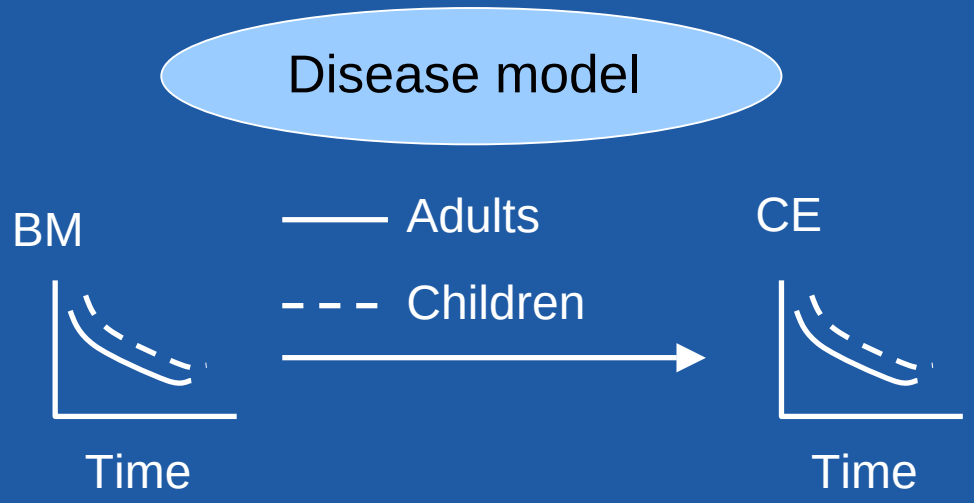
Overview

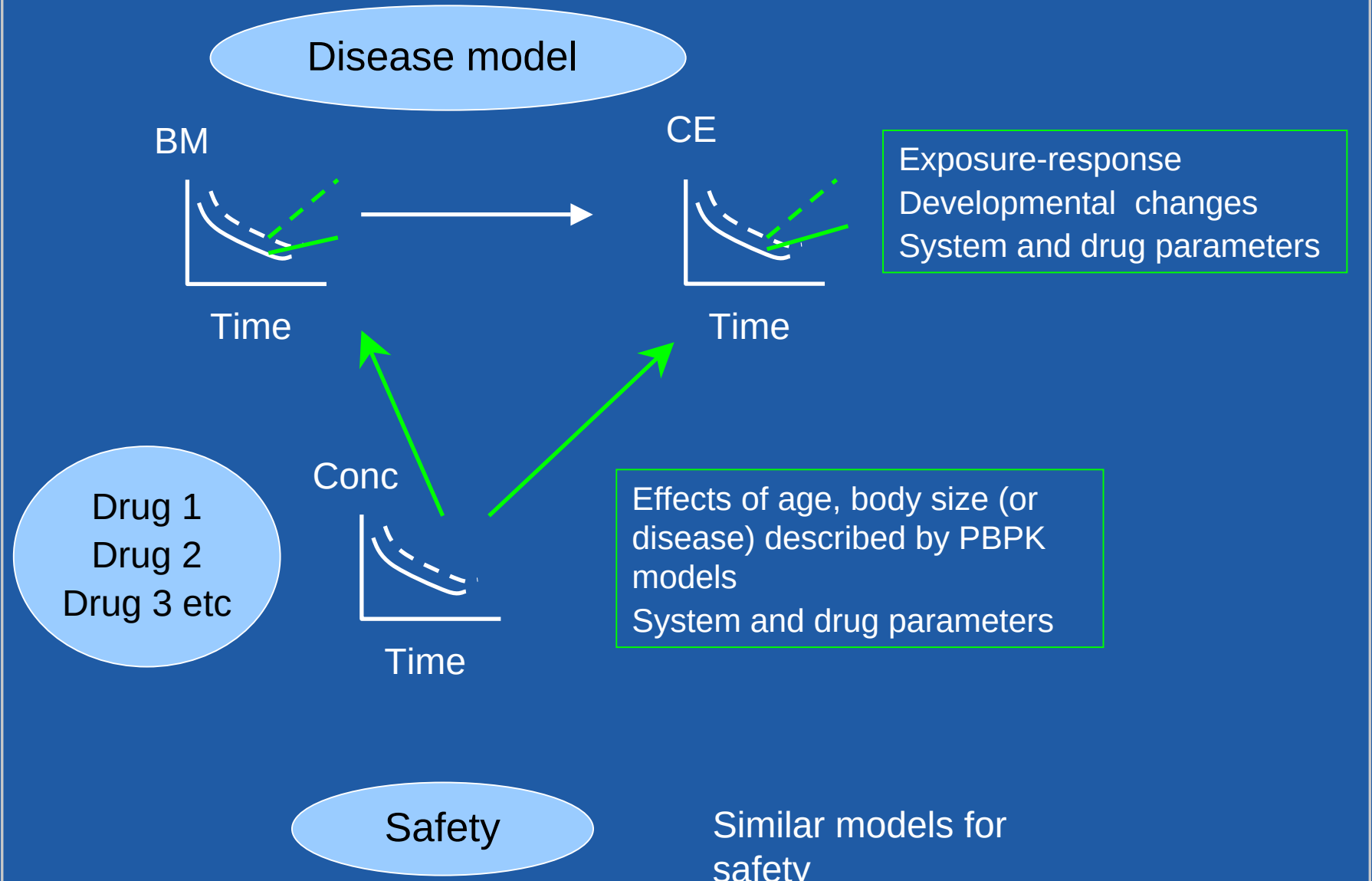
- Visions
  - Predictive models over large age span
  - Data share and collaboration
  - Adequate quality of M&S
- Hopes for near future
- Other thoughts

Vision: *Predictive models over large age span*

- Disease models
- Increased use of physiology based models
- Developmental changes for PD and PK endpoints
- PKPD for efficacy and safety
  - biomarkers
  - clinical endpoint
- Distinguish system parameters and drug parameters



- Mechanistic/Physiological models
- Established relationship between biomarkers (BM) and clinical endpoint (CE)
- Developmental effects taken into account

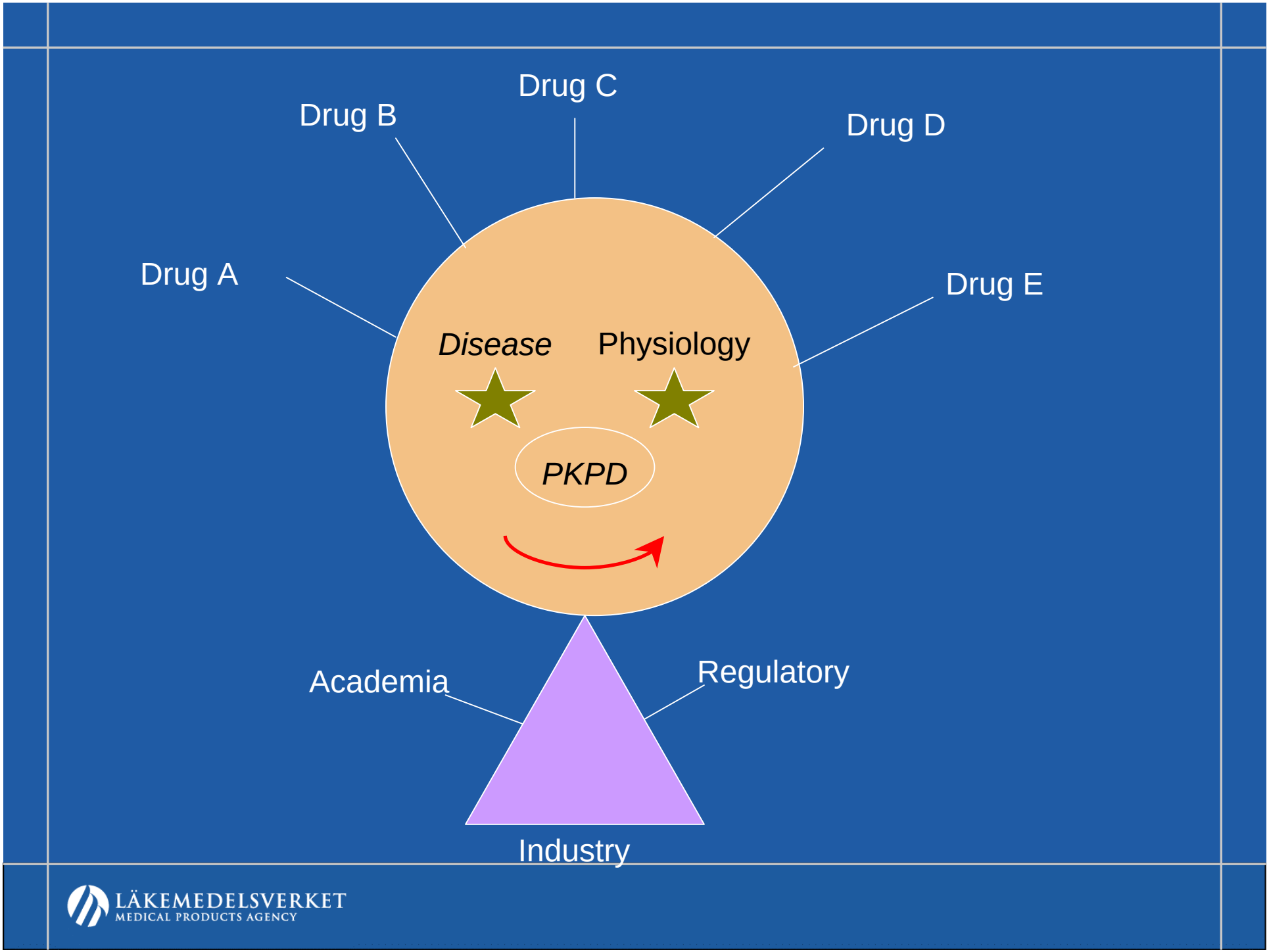

Disease model
BM
Time
CE
Time
Exposure-response
Developmental changes
System and drug parameters
Drug 1
Drug 2
Drug 3 etc
Conc
Time
Effects of age, body size (or disease) described by PBPK models
System and drug parameters
Safety
Similar models for safety

How can such vision become real?

More efficient usage of collected data

Vision: *Data share and collaboration*

- Continuous and structured collection of data
  - molecular structure
  - physiology
  - disease information
  - pharmacokinetics and pharmacodynamics
  - efficacy and safety
- Data bases to be shared between
  - industry, academia and regulatory bodies


Drug C
Drug B
Drug D
Drug A
Drug E
Disease
Physiology
PKPD
Academia
Regulatory
Industry

Vision: *Data share and collaboration*

- organised by
  - regulatory?
  - academia?
  - other???
- funding?
- confidentiality of data?

More needs to make the visions come true?

Vision: *Adequate quality of M&S*

- Training of pharmacometricians
  - industry
  - regulatory assessors
- Pharmacometric training
  - usually academia and/or industry based
  - graduate studies e.g. in Sweden, France, UK, USA
  - pharmacometric curriculum proposed[1]
  - e.g. new initiative in Germany[2]

[1]Clinical Pharmacology & Therapeutics (2007) 82, 103–105

[2] http://www.pharmacometrics.de

Vision: *Adequate quality of M&S*

- Some thoughts around pharmacometric training
  - takes time to learn
  - understanding of what modelling and simulations can be used for
  - understanding of the whole picture is important
  - easy to be critical when assessing, but difficult to evaluate importance of deficiencies – do they matter or not?
  - models do not have to be perfect to be useful

→ experience of usage of modelling and simulation is as important as the technical skills!

Vision: *Adequate quality of M&S*

- Spread knowledge, utility and possible gain of M&S among disciplines
  - upper management (maybe most important!)
  - physicians
  - statisticians
  - pharmacoligists
  - pharmacokineticists

Hopes for near future

- Increase focus on PD initially
- Utilise knowledge from
  - PD data for other drugs in same class
  - exposure-response in adults – prioritize!!!
  - in vitro PKPD and preclinical data
- Safety
  - Consider value of systemic exposure for safety, i.e. same safety limits (TW) for children?
    - e.g CNS – maturation of BBB and expression of efflux transporters?

Hopes for near future

- Initial dose choice in children
  - adequate scaling of size as an initial best guess
- Pilot PD and/or PK
  - measure PD and PK
  - get a rough idea if dose choice was appropriate
- Better study designs
  - design for modelling purposes "optimal design"
  - appropriate age range
  - simulations before study

Other thoughts

- Regulatory guidance – why so little in this area?
  - M&S is an evolving science
  - guidance will always be very general
  - guidance may be "old" when adopted
  - regulatory should not constrain science

Conclusions

- M&S efforts are appreciated
- Visions
  - Predictive models over a large age span
  - Collaboration and data share
    - Meaningful and ethical
  - Adequate quality of M&S