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Regulatory Comments: Pharmacometric principles in dose finding

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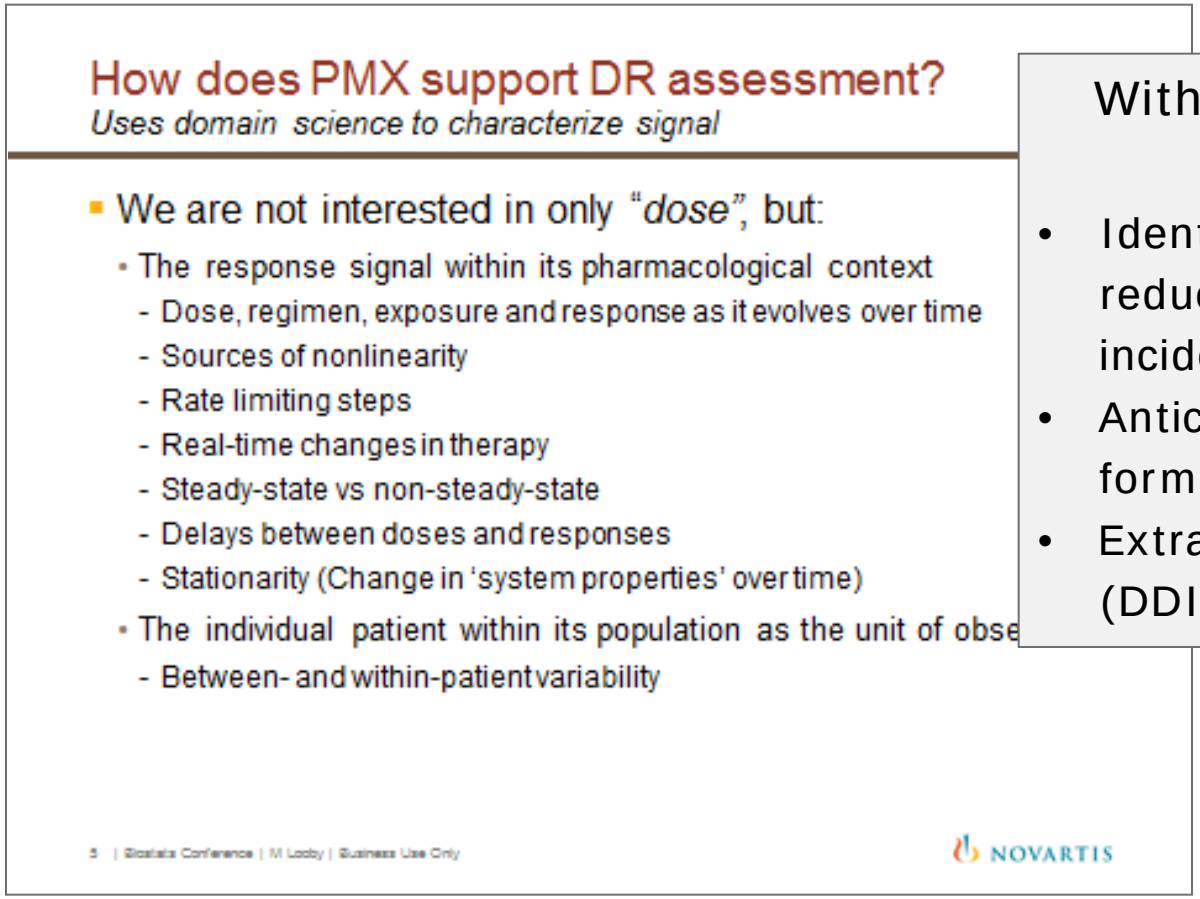
The views expressed in the following slides are those of the individual presenters and should not be attributed to their national agencies or EMA.

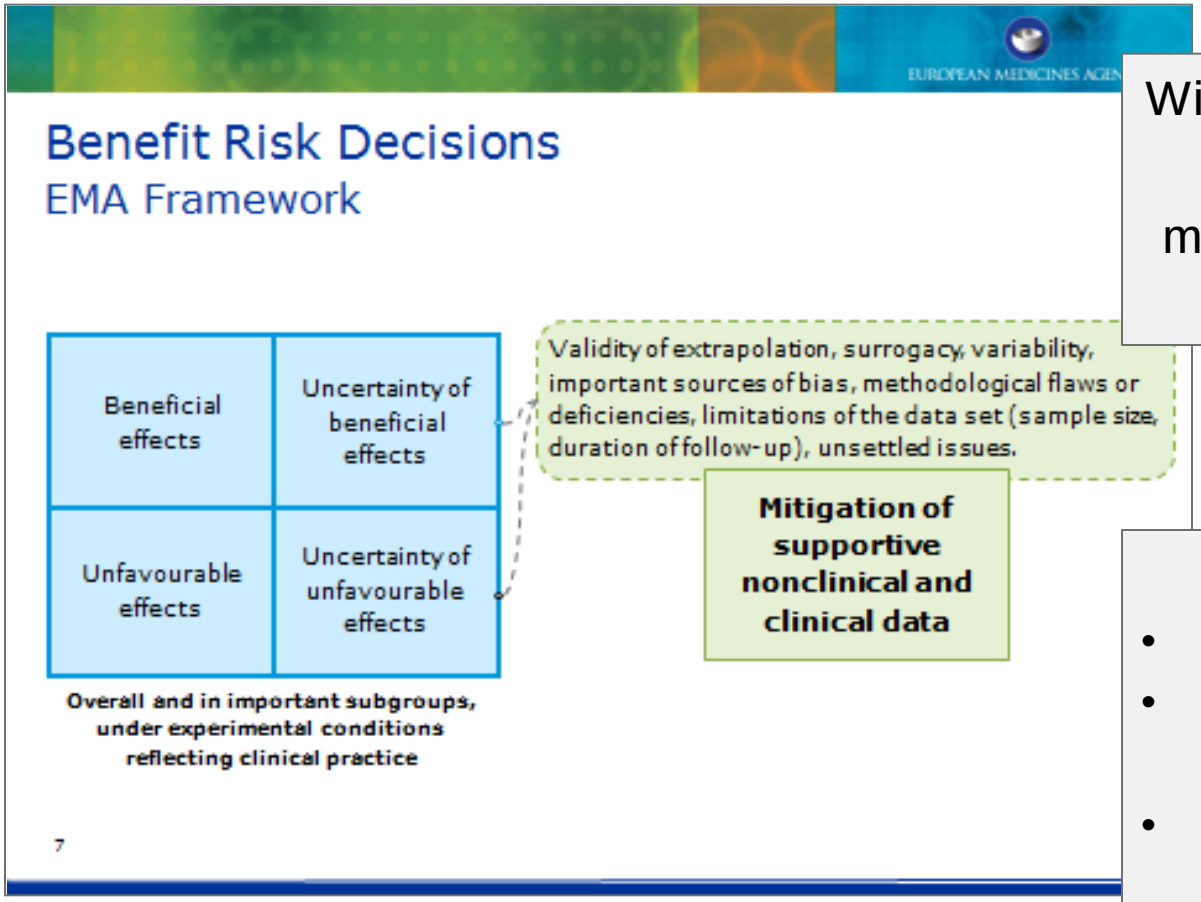
Regulators are interested in more than “dose”



Without this understanding, cannot

- Identify subpopulations at risk of reduced efficacy or increased incidence of adverse events
- Anticipate the impact of changing formulation, regimen
- Extrapolate to other populations (DDI, RI, HI, paediatric, elderly)

Implications of poor understanding of D-E-R



Without this understanding, miss the opportunity to mitigate uncertainty in the B:R decision

Implications:

- More conditions of approval
- More extensive RMP, PASS, PAES
- More extensive PIP commitments

To be covered in Session 5

RMP = risk management plan
PASS = post-authorisation safety study
PAES = post-authorisation efficacy study
PIP = paediatric investigation plan

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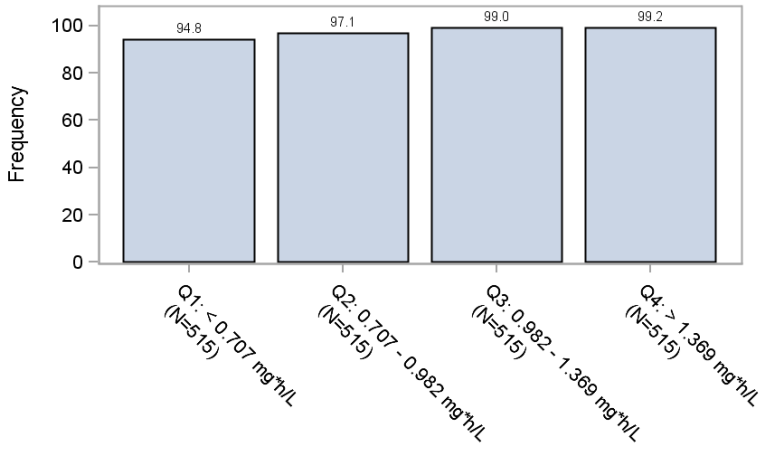
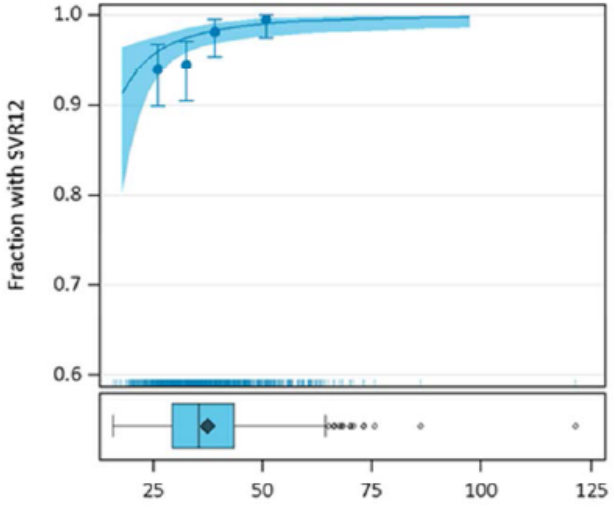
E-R analysis as presented in Marketing Auhorization Applications – often not as informative as it could be

Graphical evalutation – exposure grouped into quartiles

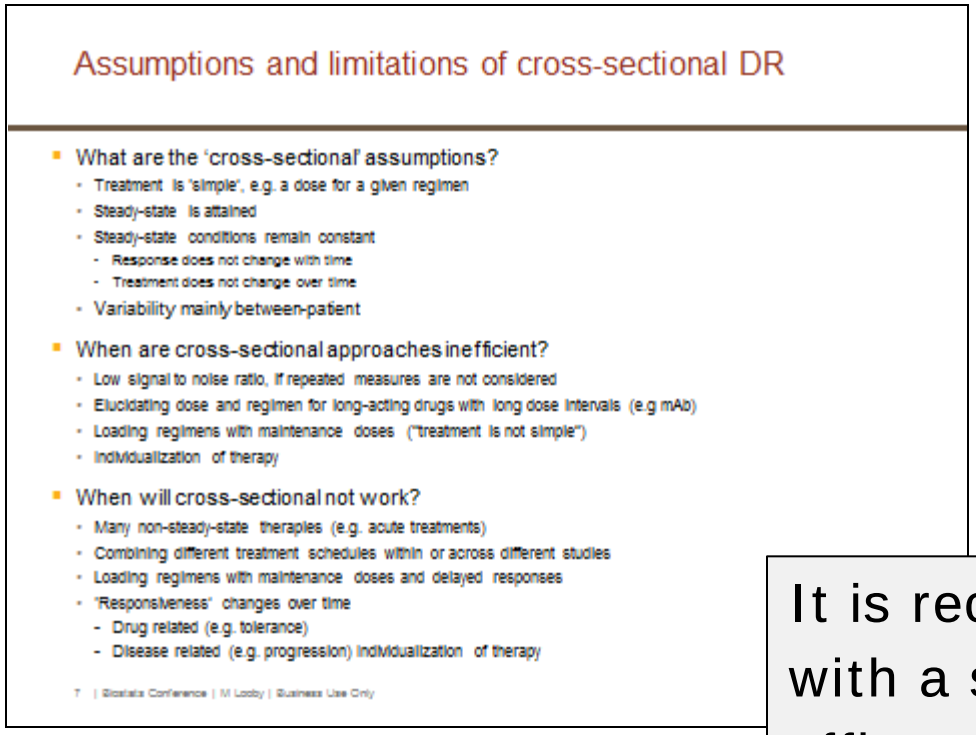


Logistic regression



- Exposure is estimated from the PopPK analysis and only includes Phase III patients – modest variability in exposure, AUC and Cmax/Ctrough are highly correlated
- Almost exclusively based on initial dose, i.e. dose reductions are not accounted for

Importance of D-E-R



Assumptions and limitations of cross-sectional DR

- What are the 'cross-sectional' assumptions?
  - Treatment is 'simple', e.g. a dose for a given regimen
  - Steady-state is attained
  - Steady-state conditions remain constant
    - Response does not change with time
    - Treatment does not change over time
  - Variability mainly between-patient
- When are cross-sectional approaches inefficient?
  - Low signal to noise ratio, if repeated measures are not considered
  - Elucidating dose and regimen for long-acting drugs with long dose intervals (e.g mAb)
  - Loading regimens with maintenance doses ("treatment is not simple")
  - Individualization of therapy
- When will cross-sectional not work?
  - Many non-steady-state therapies (e.g. acute treatments)
  - Combining different treatment schedules within or across different studies
  - Loading regimens with maintenance doses and delayed responses
  - 'Responsiveness' changes over time
    - Drug related (e.g. tolerance)
    - Disease related (e.g. progression) individualization of therapy

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It is recognized that many factors with a significant impact on efficacy or safety in individual patients are not readily detectable in standard Dose-Response studies, such as genetic variability resulting in altered PK and/or PD.

Regulators see value in PKPD model-based methods

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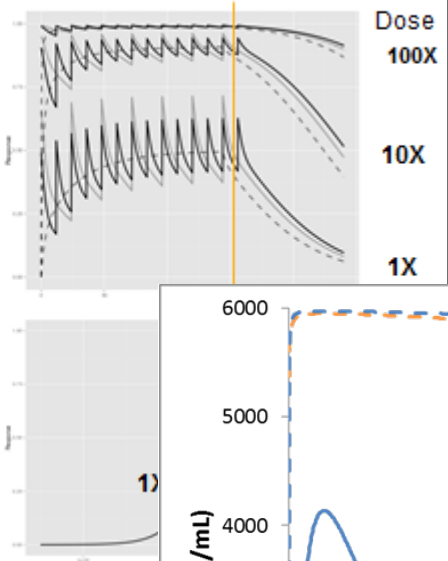
Response usually longitudinal, DR assessment usually cross-sectional

Fixed treatment & steady-state assumption in most DR analyses

- Pharmacological drug responses are usually longitudinal and very often a continuous measurement
- Pharmacostatistical PMX model based methods can account for longitudinal response across a wide range of different doses and regimens.
  - Heterogeneity, in input signals, if appropriately designed, increase overall understanding of system response properties
- However, traditionally DR is usually assessed cross-sectionally at a given point in time (e.g. a specific study visit), for a given regimen, and often transformed to a dichotomized variable



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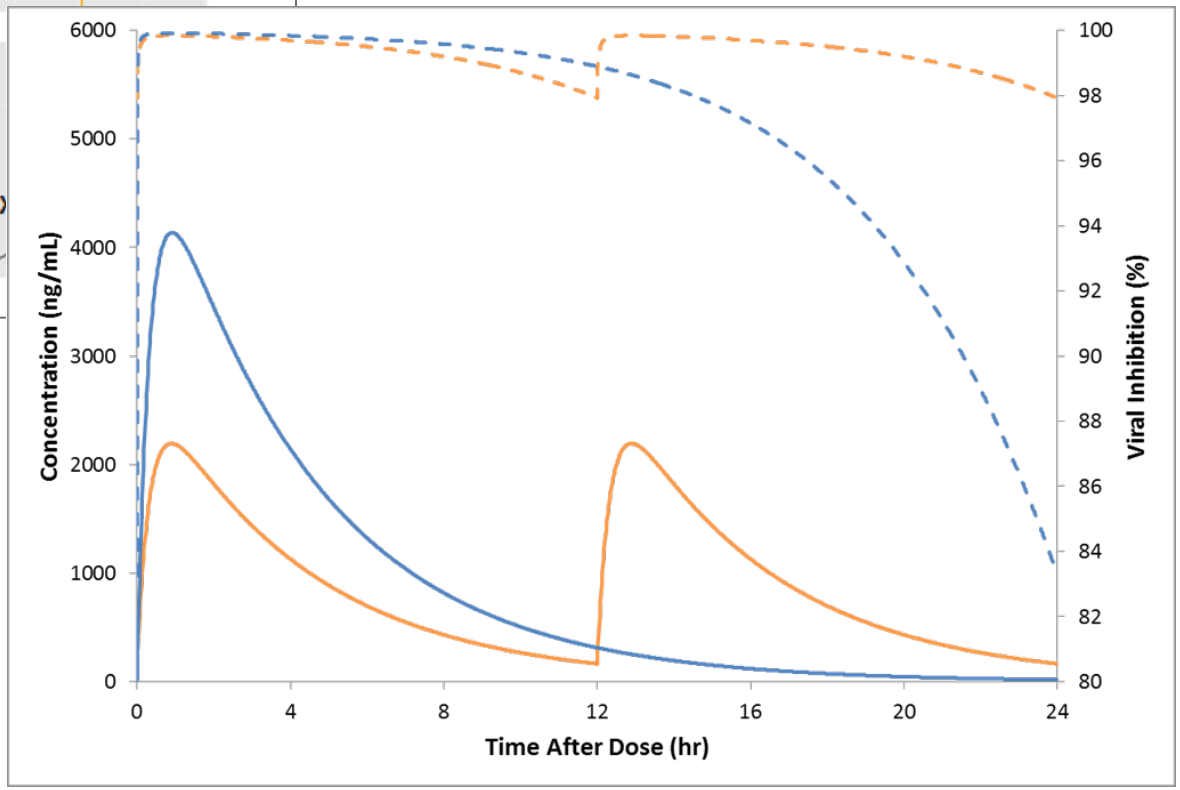
- Important dependence of efficacy on formulation, regimen
- Particularly important in paediatric population
- Does not fit traditional DR cross-sectional approach



Regulators endorse PMX methods in D-E-R

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Pharmacometric principles: why they are important

Integration of PMX methods can change how we develop some drugs

- PMX does not replace 'pharmacostatistics', it extends it.
  - To ensure optimal dose finding on each program, we must prospectively assess where:
    1. PMX may add little to aid program design and analysis
    2. PMX principles and methods may support traditional design and analysis planning
    3. PMX methods may be the most efficient means of addressing program needs.
- To improve dose finding, we need developers and regulators with
  - the knowledge to consider where PMX principles add value or not
  - the know-how to implement PMX methods when necessary
  - and the fortitude to continually evolve how we develop new drugs to meet real development and therapeutic needs

For Discussion at end of Session 2:

Implications of Proposed Prospective Assessment

1. Traditional cross sectional D-R and analysis
2. PMX-informed design, traditional cross-sectional D-R (or D-E-R) and analysis
3. PMX-informed design, PMX-based analysis

For Discussion at end of each therapeutic area (Session 3):

As a meeting outcome, assess the value of PMX (i.e., adds little, supports design, supports design and analysis) for each therapeutic area.

For Discussion (end of Sessions 2 and/or 3):

It could be argued that PMX is always expected to add value to design and analysis of D-E-R (and to regulatory review) and therefore should always be used. PMX only doesn't add value where we don't understand enough and therefore its use is even more important to facilitate continued learning.