BioRAM: connecting the drug product with the patient – from design to optimized product

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Aim

- Why is it important to link drug product to patients
- Discuss/illustrate what we mean by thinking differently as a system
- Describe BioRAM, the BioRAM Scoring Grid and integration of drug development

Disclaimer

- The views expressed in this presentation reflect my personal interpretation

- Conflict of interest: I own shares/stock in AstraZeneca and am a Director and owner of Seda which has a contract to deliver services to AstraZeneca. Prior to forming Seda I led the clinical pharmacology discipline for osimertinib
- All data discussed in this presentation is in the public domain

What is Biopharmaceutics Risk and the impact of therapy-driven drug delivery?

- The risk of **not achieving the intended in vivo Drug Product performance**

- the concept of a **therapy-driven drug delivery scenario** forces one to consider, at every stage of development, the clinical needs and the expected outcomes for a particular drug and how can the drug product be developed and optimized to meet those clinical needs and achieve desired outcomes

Can integrated risk assessment and development lead to more successful development?

Candidate Selection / GLP Tox → Phase 1 → Phase 2 → Phase 3 → Commercial

- Two camps

"A good drug declares itself big, early"

"Drug development is an iterative process following learn and confirm cycles"

Recent case studies imply that integrated thinking wins

- Case Study
  - Oct 2015 these two assets were neck and neck.
  - A lot of debate about which compound would create most value (meet patient need)
  - In Nov 2015 there was a net change in market capital value of:
    - **$11,000,000,000**

The Annals of Oncology 'Industry Corner' papers review both compounds and cite several key success factors for drug development

- key success factors include:
  - formulation
  - bridging
  - dose selection
  - patient selection

Aka: BioRAM

Data sources:

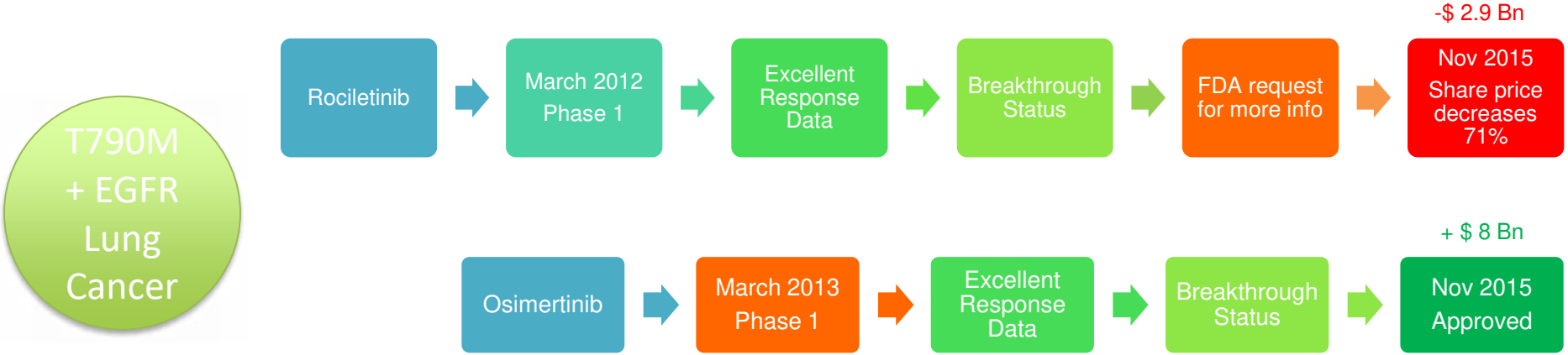
The Annals of Oncology 'Industry Corner' papers review both compounds and cite several key success factors for drug development

Yver, 2016: http://annonc.oxfordjournals.org/content/27/6/1165
Dhingra, 2016: http://annonc.oxfordjournals.org/content/27/6/1161

Osimertinib reviews:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208065Orig1s000SumR.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208065Orig1s000TOC.cfm
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004124/WC500202024.pdf

ODAC 12 April 2016 meeting for rociletinib:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm486395.htm

Recent case studies imply that BioRAM thinking wins



See also: **High-Tech Drugs in Creaky Formulations,** for wider review on formulations appropriateness in Oncology. https://link.springer.com/article/10.1007/s11095-017-2185

Quality Target Product Profile (QTPP): Defined in ICHQ8 R2:

"A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."

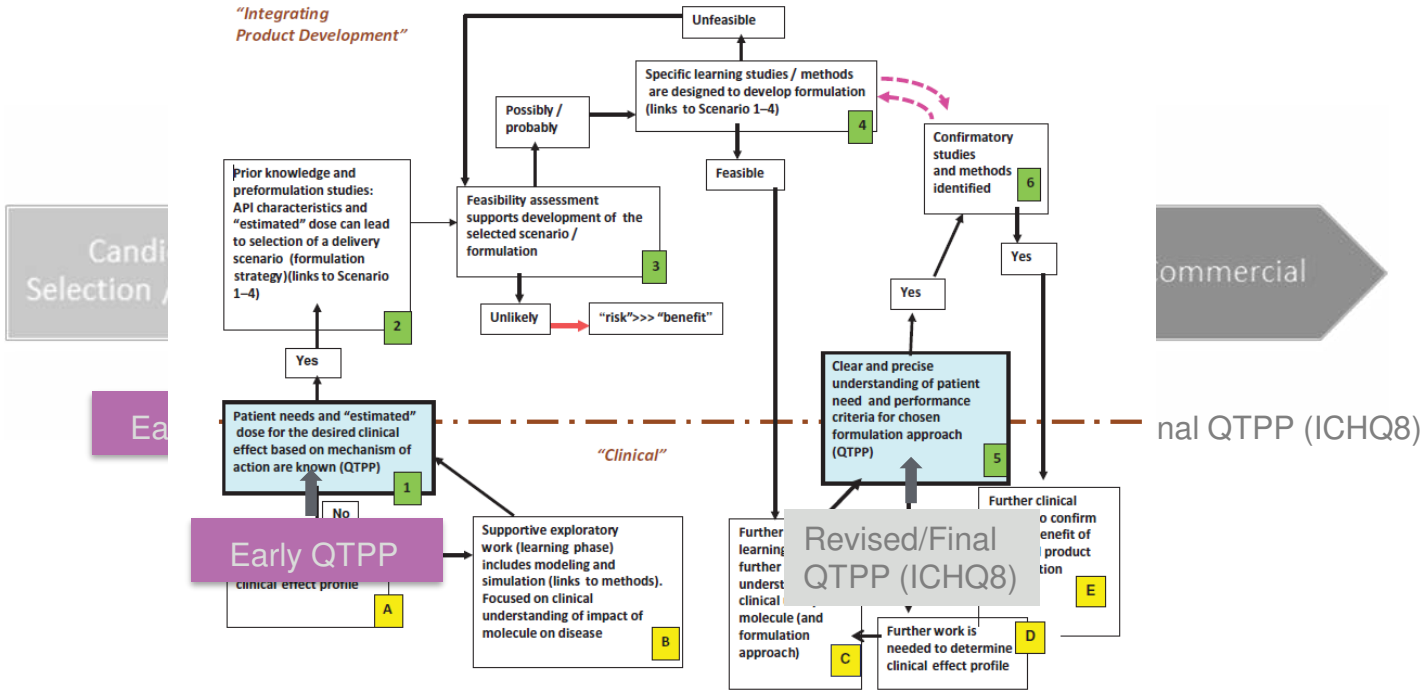
Systems Approach

- Recent BioRAM papers have suggested the concept of an early QTPP could be highly beneficial – links to blueprint meeting and systems thinking
- Along with blueprint meeting the foundation for developing critical questions and knowledge

A. Selen, P.A. Dickinson, A. Müllertz, J.R. Crison, H.B. Mistry, M.T. Cruañes, M.N. Martinez, H. Lennernäs, T.L. Wigal, D.C. Swinney, J.E. Polli, A.T.M. Serajuddin, J.A. Cook, J.B. Dressman (2014) The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance. J. Pharm Sci. 103: 3377–3397. http://dx.doi.org/10.1002/jps.24162

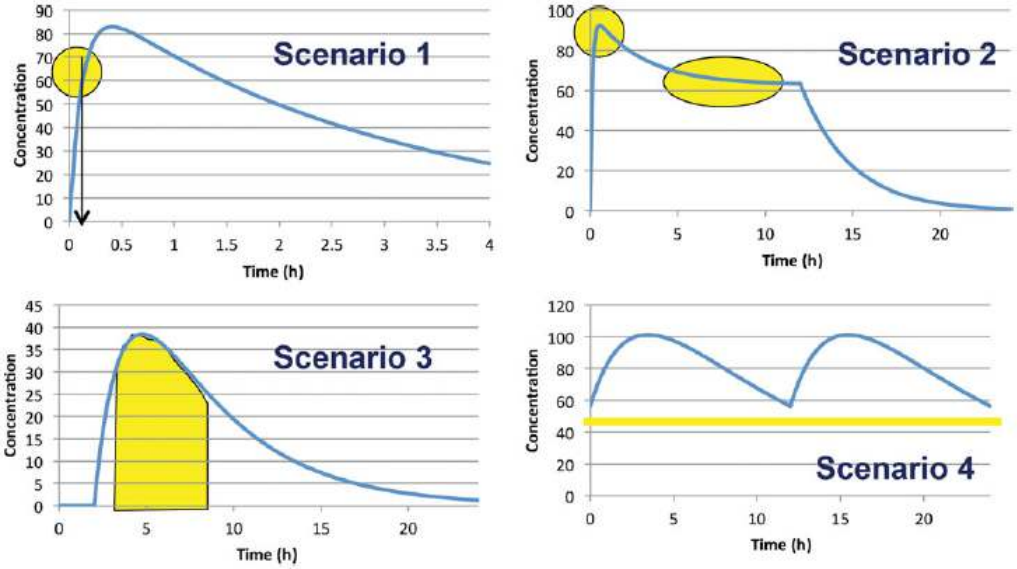
P.A. Dickinson, F. Kesisoglou, T. Flanagan, M.N. Martinez, H.B. Mistry, J.R. Crison, J.E. Polli, M.T. Cruañes, A.T.M. Serajuddin, A. Müllertz, J.A. Cook and A. Selen (2016) Optimizing Clinical Drug Product Performance: Applying Biopharmaceutics Risk Assessment Roadmap (BioRAM) and the BioRAM Scoring Grid. *J. Pharm. Sci.* 105: 3243-3255. http://dx.doi.org/10.1016/j.xphs.2016.07.024

Systems Approach: the roadmap



Dose in BioRAM: **drug delivery scenarios** / drug concentration-time profiles

- The BioRAM discusses four drug delivery scenarios / PK profiles that cover many of the potential PK considerations for therapy driven product performance
- These are not intended to be exhaustive or for classification of the drug
- Instead they serve as analogues which can act as learning tools for those trying to implement BioRAM and therapy driven product development



Scenario 1: Rapid therapeutic onset	Scenario 2: Multi-phasic delivery	Scenario 3: Delayed therapeutic onset (e.g. Chronotherapy)	Scenario 4: Maintenance of target exposure

The 2nd BioRAM paper

- The second BioRAM Paper introduced the:
  - **The BioRAM Scoring Grid**
- 12 Key Elements
- Facilitates Cross-disciplinary Thinking
  - functions as a translational tool to enable systems thinking across disciplines
- Translates Uncertainty Into Patient-focused Action
- Facilitates Phase-appropriate Development and Knowledge Generation
- Simple and Decisive
- Customized to Fit Each Individual Development Project
- Encourages an Entrepreneurial Mindset

Box 1 (starting point)

Patient needs and "estimated" dose for the desired clinical effect based on mechanism of action are known (QTPP)

Unless otherwise noted, score each response as: yes=1, otherwise=0

QTPP

1: Targeted Patient Population	Well characterized and "reasonably" homogeneous or if heterogeneous, distinct groups are well characterized
2: Indication	Indication and registrational endpoints are precedented (vs. novel), and duration of treatment known (acute or chronic)
3: Availability of prior knowledge on Drug Substance and / or Drug Product	There is prior knowledge about the DS (and DP, if applicable)
4: Pharmacology of DS	Based on available data and preliminary screens, there is adequate robust and favorable information on mechanism of action and systems pharmacology to warrant more definitive studies with the DS
5: Dose	Dose range can be estimated
6: Understanding clinical endpoints, disease progression and effect on clinical endpoints	Effect of disease progression on clinical endpoints can be identified
7: Bioavailability (BA)	Is BA estimable and if it is, estimated BA >5%
8: Solubility **Note: In subsequent boxes solubility becomes release / dissolution**	The solubility and precipitation characteristics are adequate to support feasibility of dose regimen (e.g. range in mcg or mg) and route of administration based on either early experimental data, prior knowledge (e.g.. previous drug product in same chemical space) and/or in silico modeling
9: Drug Delivery / Input Parameters	A) Given DS characteristics, and the estimated dose, and intended delivery characteristics, intended route of admin. can be further explored (0/1) B) in vitro methods that can link with in vivo drug release exist (0/1)
10: Stability	DS is stable in physiologic pH range (slow or no degradation)
11: Manufacturability	Not scored, Note: Manufacturability is scored in subsequent development stages boxes
12: IVIVR - the model building	Are there suitable techniques/methodologies for developing an IVIVR for the candidate drug product taking into account the intended drug delivery characteristics (release rate and pattern)

BioRAM Scoring Grid: Phase Appropriate

Talia Flanagan

- The questions are not generalised numerical criteria (e.g. is solubility greater than *x* mg/mL?)
  - Constructionist rather than reductionist
- Rather, the scoring criteria center around how well understood the indication, the patient population and the desired drug delivery profile are, and whether the API and formulation approach under consideration are able to reliably achieve this
- This means that the criteria applied will be customized to fit each individual development project, based on specific knowledge about the patient, therapy-driven drug delivery scenario, formulation technology and indication.
- Flexible enough to work across all disease areas and drug delivery routes.

BioRAM Scoring Grid: Scoring

Talia Flanagan

- For each question, answer either **yes** or **otherwise** (**not yes)**
- A **yes** score has an associated number of points (1, 2 or 3 depending on the element and stage of development)
- There are no intermediate values!
  - ‘maybe’ ‘almost’ ‘a little’ are not covered
- The simple binary nature of the scoring system encourages decisiveness, and focusses the team on actions needed to address critical knowledge gaps

BioRAM Scoring Grid: Entrepreneur Mindset

Talia Flanagan

- Using the BioRAM approach, the development plan is driven by the critical knowledge needed and focuses on areas of potential risk identified in the scoring tool.
  - focusses the group on what they need to learn from a particular study or set of experiments, rather than mapping the project to a standard development plan or collecting data without fully assessing its relevance.
- ➢ Encourages the use of novel tools and approaches, rather than relying upon typical or historical approaches to address the problem/question.

Element 12 IVIVR – the model building: fundamental to driving systems thinking / integration of data

Box 1: IVIVR - the model building	Are there suitable techniques/methodologies for developing an IVIVR for the candidate drug product taking into account the intended drug delivery characteristics (release rate and pattern)
Box 2: IVIVR - the model building	In vitro method (or identified predictive method) and in vivo data can be utilized to project in vivo performance (PK) (and/or effect) to support formulation development including target "release" parameters for prototypes to achieve intended in vivo drug delivery profile (scenario)
Box 3: IVIVR - the model building	"A working IVIVR" is achieved/feasible using the knowledge gained *Note: At the BioRAM initiation, the group should outline their expectations for a "working IVIVR" considering what's known about the system and the methodology. If a working IVIVR is not achieved, study designs should be such that the knowledge gained can lead to specific learning studies (Feasibility Assessment Box 2).*
Box 4: IVIVR - the model building	A working IVIVR is confirmed (e.g. Target PK profile or response) is achieved from the expected release rate and delivery pattern). *Note:* ***Score 2 points for yes, otherwise=0*** *Note: At this stage, candidate drug product performance criteria are re-evaluated and may be revised (please see the Third Feasibility Box)*
Box 5: IVIVR - the model building	If changes are made to drug product, process ,or new information emerges that may necessitate additional IVIVR study, the repeated IVIVR study identifies specifications and conditions that are needed to achieve the intended in vivo drug delivery profile (scenario-specific)*Note:* ***Score 2 points for yes, otherwise=0***
Box 6: IVIVR - the model building	The developed IVIVR supports the relationship between **drug product characteristics (designed and developed with the patient in mind)** and it's **in vitro and in vivo performance**. The structural model (available knowledge + modeling tools) can help to interpret observations, and also, predict the impact of changes on the drug product. **Parameters that qualify the drug product as clinically relevant are used for setting drug product specification influencing drug release/delivery pattern and/or rat** ***Note: Score 3 points for yes, otherwise=0*** *Note: Conduct of integrated studies (clinical trials collecting critical drug product information) may further strengthen the link between the intended clinical performance and the drug delivery information (as identified for the QTPP).* ***Structural model refers to the comprehensive combination of knowledge with preclinical/clinical information and modeling tools to link product to clinical performance - does not translate necessarily to an IVIVC following the current IVIVC definition. The structural model incorporates knowledge from multiple sources.***

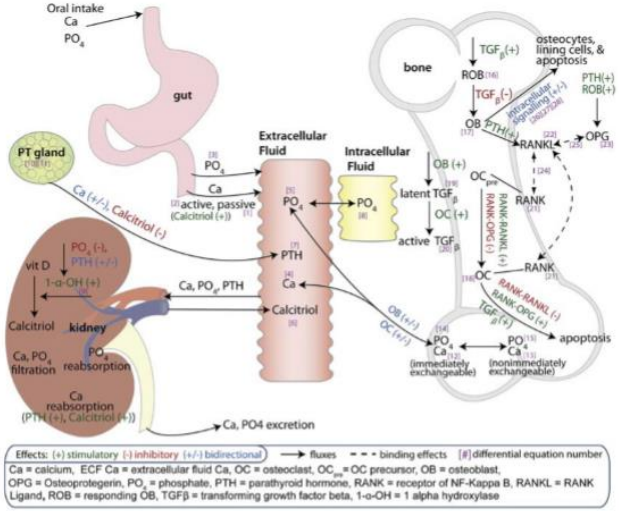
3/12: 25% of the score

Element 12 IVIVR – the model building – the future is near

- Natpura™
- parathyroid hormone
- BLA 125511
- Investigating the ‘optimal’ dose and PK profile using a systems pharmacology approach
- Allows several different conditions an treatment regimens to be investigated quickly

Systems Pharmacology Model:

There are a number of calcium homeostasis models available in the literature including a comprehensive minimal mathematical model of calcium homeostasis by Raposo et al[14]. We adapted a subsequent comprehensive model published by Peterson and Riggs (Implement in R and code available in public domain) for our purpose.



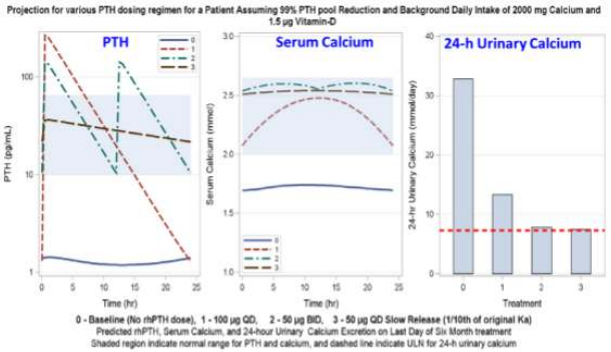


Figure 20 **Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 2000 mg oral Calcium and 1.5 µg Vitamin in a patient representing 99% PTH pool reduction**

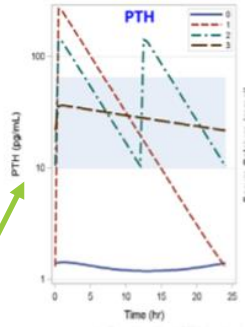
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM413617.pdf

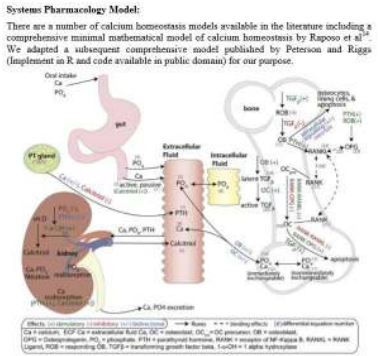
Element 12 IVIVR – the model building –the future is near

Models linking CPP, IPA and CQA to Dissolution

‘IVIVC’ links disso to PK

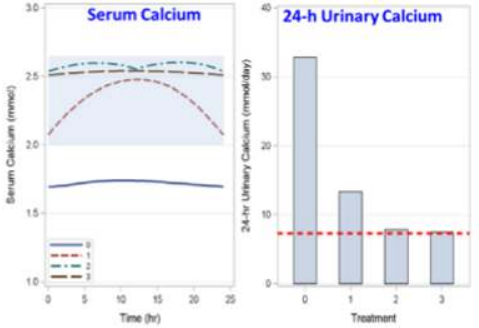
PK in Patient





Could be simpler PK-PD Model

Outcome in Patient



Nothing in BioRAM defines the formulation or route of admin

- This is where BioRAM is different from the other checklists
- BioRAM asks for critical questions / data and outcomes to be defined by the team
- And requires team to decide if they can define the answers to critical questions (decide what is zero or a score)
- If not they need to define experiments to get to the critical answers
- If they can answer the critical questions the team then need to choose the ‘best’ way to meet the QTPP or if the project should close / change direction

Conclusions

- Clear evidence that integrated approaches to development lead to better outcomes for the patient
- Structured approaches exist that support integrated approaches
  - BioRAM
  - Learn and confirm cycles
- Scoring grid supports the identification of the critical information required
- Developing a IVIVR is a key element as this forces us to make the links between product and outcome for the patient

Pharmaceutical Development Services