Scoresheet Box 1: Early basic knowledge, starting point

From Blueprint to action: Getting to critical questions and knowledge

Paul A Dickinson

Seda Pharmaceutical Development Services
The Biohub at Alderley Park
Alderley Edge
Cheshire SK10 4TQ
paul.dickinson@sedapds.com
www.sedapds.com

Aim

- Discuss/illustrate what we mean by thinking differently as a system
- Describe BioRAM, the BioRAM Scoring Grid and integration of drug development
- Illustrate importance of the blueprint meeting and efforts leading to and Box 1
  - general and specific for the oncology case study

Acknowledgements and Disclaimer

- The BioRAM Leads/Contributors/Architects (alphabetical):
  - Jack Cook, John Crison, Maria T. Cruañes, Paul Dickinson, Jennifer B. Dressman , Talia Flanagan, Filippos Kesisoglou, Hans Lennernäs, Marilyn Martinez, Hitesh Mistry, Anette Müllertz, James Polli, Leanne Cusumano Roque, Arzu Selen, Abu TM Serajuddin, David Swinney, Tim Wigal, Helen Winkle, and many other colleagues

- The views expressed in this presentation reflect my personal interpretation and the experience of individuals I have collaborated with

- 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:

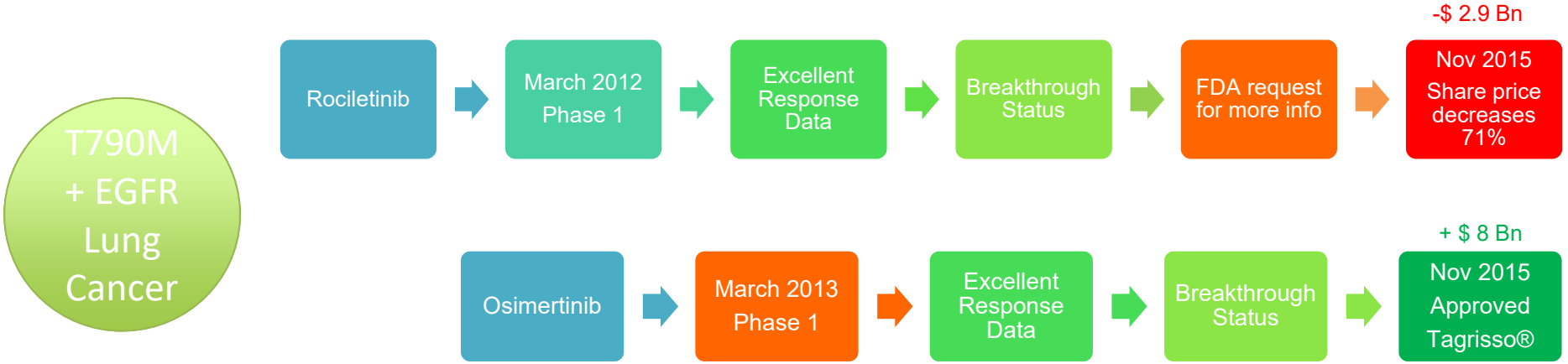
The Annals of Oncology 'Industry Corner' papers review both compounds and cite several key success factors for drug development

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



Arzu Selen

The ingredients of a successful "Blueprint" Meeting

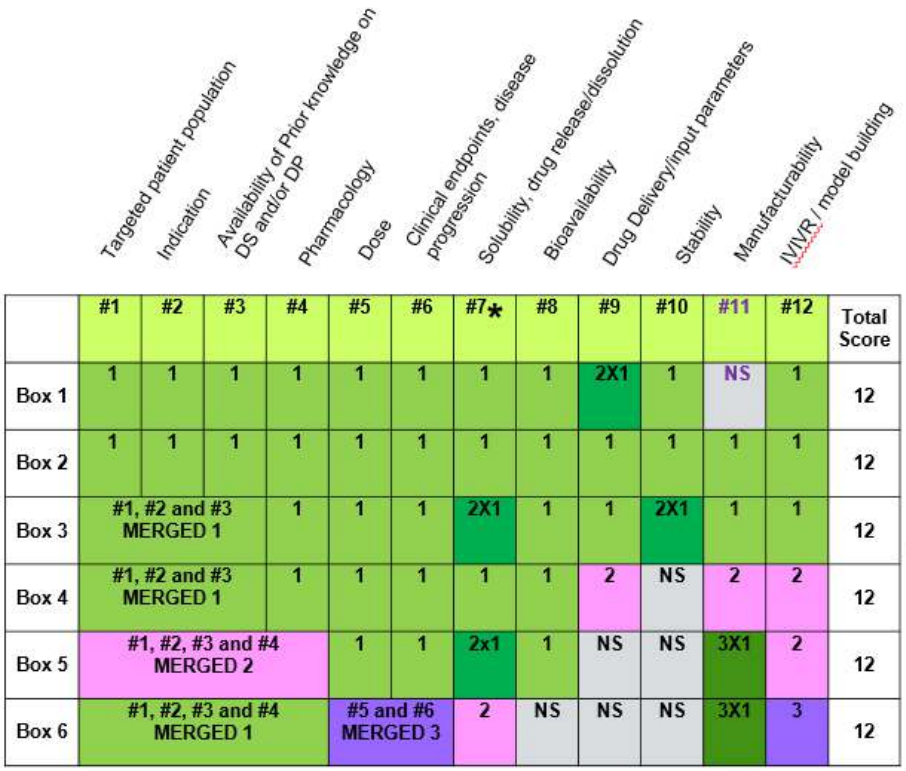
Approach:

1. Reviewing/projecting the likely journey and identifying areas that may prove challenging (or exceed challenging)
2. Creative problem solving for the system (i.e., developing what-if scenarios)
3. Non-judgmental and looking/seeing possibilities

Deliverable:

Preparation for implementing the BioRAM strategy (what knowledge may be critical to move forward, types of expertise and methods that may be needed for the "Box 1" meeting)

Arzu Selen



	#1 Targeted patient population	#2 Indication	#3 Availability of Prior knowledge on DS and/or DP	#4 Pharmacology	#5 Dose	#6 Clinical endpoints, disease progression	#7* Solubility, drug release/dissolution	#8 Bioavailability	#9 Drug Delivery/input parameters	#10 Stability	#11 Manufacturability	#12 IVIVR / model building	Total Score
Box 1	1	1	1	1	1	1	1	1	2X1	1	NS	1	12
Box 2	1	1	1	1	1	1	1	1	1	1	1	1	12
Box 3	#1, #2 and #3 MERGED 1			1	1	1	2X1	1	1	2X1	1	1	12
Box 4	#1, #2 and #3 MERGED 1			1	1	1	1	1	2	NS	2	2	12
Box 5	#1, #2, #3 and #4 MERGED 2				1	1	2x1	1	NS	NS	3X1	2	12
Box 6	#1, #2, #3 and #4 MERGED 1				#5 and #6 MERGED 3		2	NS	NS	NS	3X1	3	12

*: Scoring for Element #7 Relates to solubility in Box 1 and in subsequent Boxes, it relates to drug release/dissolution

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."

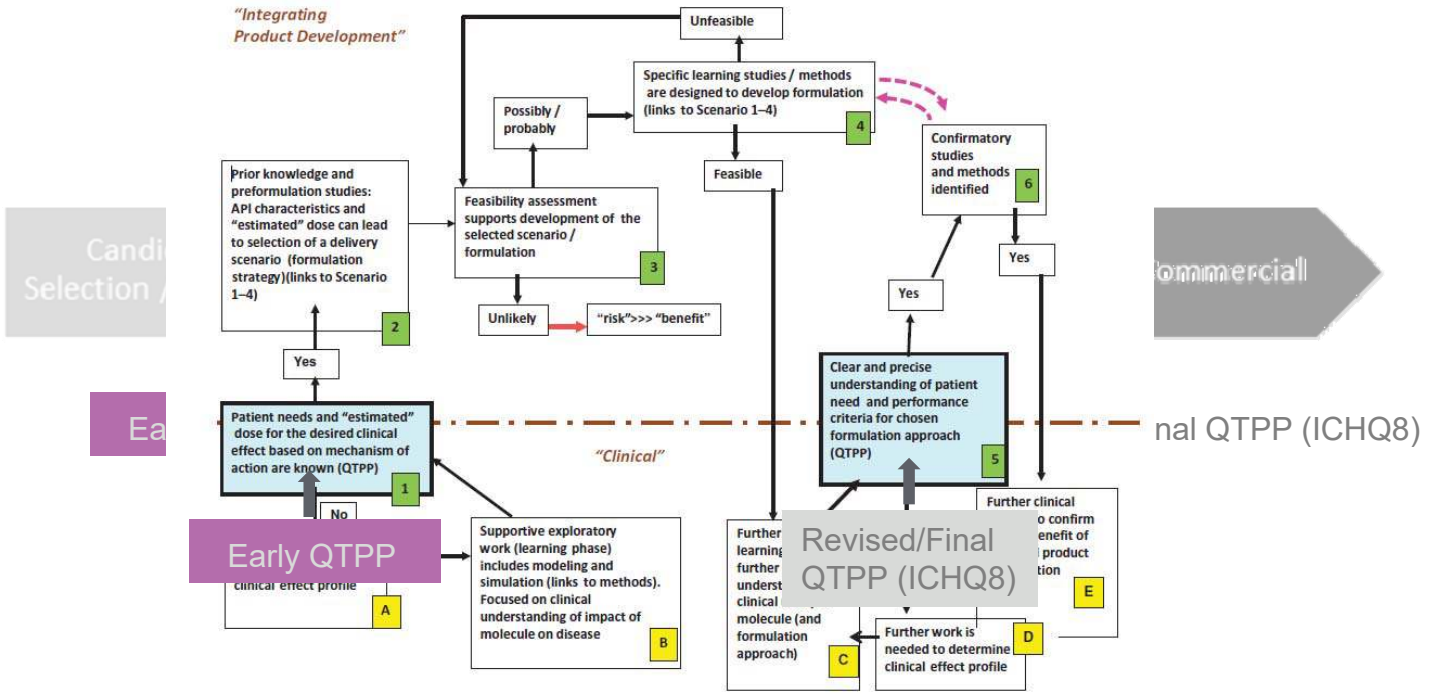
Systems Approach

- 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



Physiological basis of drug absorption in product design

- Efficacy and Safety
  - Concentration at the target site

Depends on

- Bioavailability / Exposure
  - Fraction absorbed
  - Absorption rate
  - First pass metabolism / distribution / elimination

Depends on

- Absorption
  - Dosage form / formulations
  - Solubility / dissolution
  - Permeability

Biopharmaceutics
Interaction between the drug, dosage form and patient

Efficacy and safety: Classical Pharmacology Binding Models and Free Drug Hypothesis

- What (**free**) concentration gives what level of inhibition / activation
  - Isolated system
  - Cell system
  - In vivo
- How does inhibition / activation relate to relate to the outcome?
- Free Drug Hypothesis in vivo:
  - at **steady-state**, the free drug concentration is the same on both sides of any biomembrane
  - the **free drug concentration at the site of action**, the therapeutic target biophase, is the species that exerts pharmacological activity

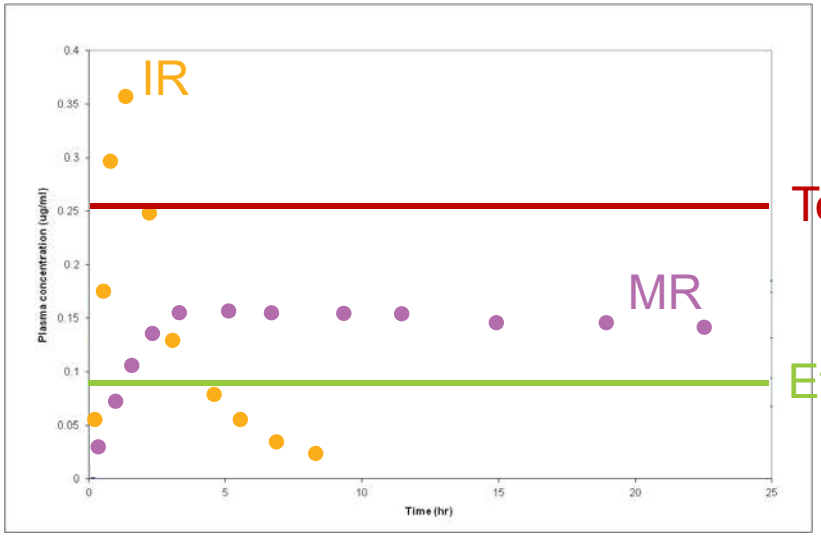
- *Exceptions*
- When a drug has low passive permeability (not if drug at true steady-state)
- When efflux of the drug occurs from the tissue of the therapeutic target by P-glycoprotein and other efflux transporters
- When influx of the drug occurs into the tissue of the therapeutic target, mediated by active transporters
- When the drug encounters tissues with low discontinuous blood flow

- *Exceptions*
- When the action of the drug results in irreversible inactivation of the target, for example, with covalent binding
- When the action of the drug involves multiple mechanisms and the activation of target-mediated events

Smith et al, Nature Reviews Drug Discovery 2010

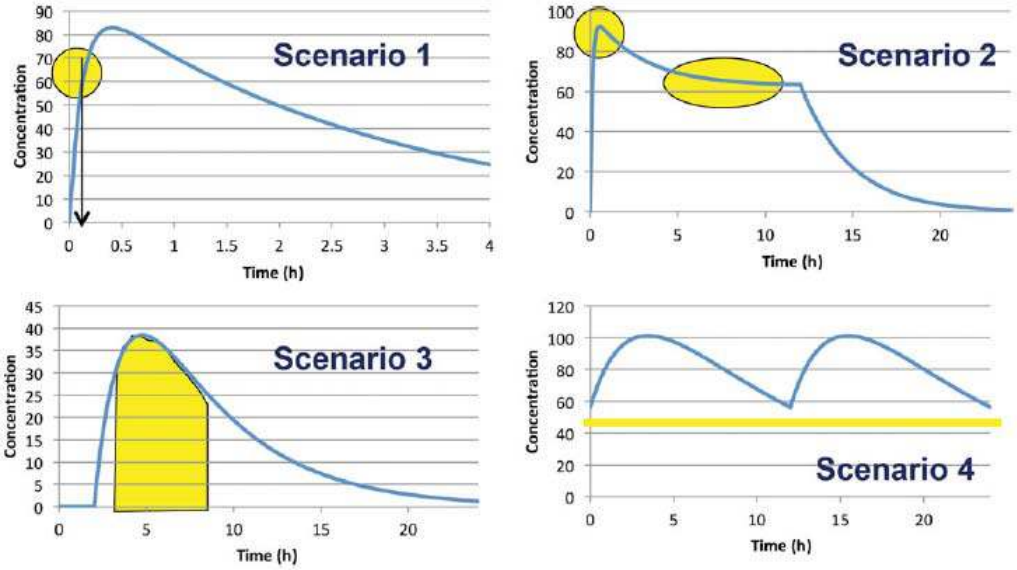
Concentration at the target site is dependent on the rate of input and elimination

- Rate of elimination constant for a particular drug so consistency in the shape of the plasma concentration time profile is dependent on the input rate
  - As the absorption rate slows the PK profile changes
- E..g modified release formulations the rate of elimination is very/too fast
- So if a slow release rate is used it becomes the major determinant of the PK profile (as the slowest process)



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

BioRAM: Biopharmaceutics Risk Assessment Roadmap

- The starting point for BioRAM approach is the clinical indication which drives the drug delivery scenarios that are specific and consistent with the patients' needs. BioRAM benefits are
  - **Access to critical knowledge**: Recognition of the system and its components will drive targeted studies to generate and/or leverage critical knowledge
  - **Ability to optimize the drug product**: Understanding the patients' needs, therapeutic target and drug substance characteristics can lead to optimization of a drug product formulation and manufacturing process prior to major clinical trials.
  - **Enhanced patient benefit**: Early understanding and integration of patient therapeutic needs and drug product characteristics and timely decisions can streamline drug development, make it more efficient and enhance patient benefit.
- BioRAM is multidisciplinary and enables knowledge sharing and leveraging in a fluid manner through stages of drug development. The scientific principles used in BioRAM and the current drug development processes are same.

A. Selen, J. Cook, M.T. Cruañes, P.A. Dickinson, T. Flanagan, F. Kesisoglou, M.N. Martinez, A. Müllertz

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

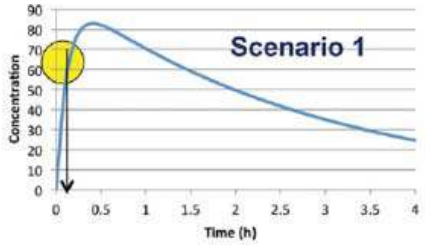
Talia Flanagan

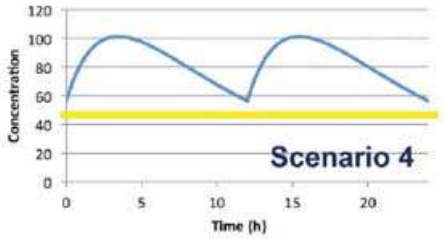
- The questions are not generalised numerical criteria (e.g. is solubility greater than *x* mg/mL?)
  - Constructionist rather than reductionist
- Rather, the scoring criteria center around how well understood the indication, the patient population and the desired drug delivery profile are, and whether 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: Phase Appropriate

Talia Flanagan

- For example, consider scenarios 1 and 4
- Both can potentially be achieved with a ‘simple’ immediate release tablet.





- But are the required API attributes the same (PK and Phys Chem)?
- And are the clinical learn-and-confirm studies you would design the same?

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: Zero Score

Talia Flanagan

What is the concept of zero score:

- the inability to score ‘yes’ due to missing information,

Drives development plans, focusses the team on generating this missing critical knowledge

or

- if data exists which indicate that the answer to the question is ‘no

Current scenario may not be/is not achievable on the current path:
- change development path, or
- terminate the project

BioRAM Scoring Grid: Dealing with Uncertainty

Talia Flanagan

- Particularly in the early stages of development, uncertainty can potentially be perceived as a barrier to patient-centric product design
  - Can be a tendency to put off considerations
    - e.g impact of delivery profile on therapeutic outcomes until later in the development program
  - By which point, there can be a reluctance to move away from the current development path…
- The BioRAM Scoring Grid provides groups with a structure to identify the **critical knowledge that is missing**, and to proceed with an integrated pharmaceutical and clinical development plan
- Ensures that the critical knowledge connecting formulation to the patient is generated in a timely manner

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****.*

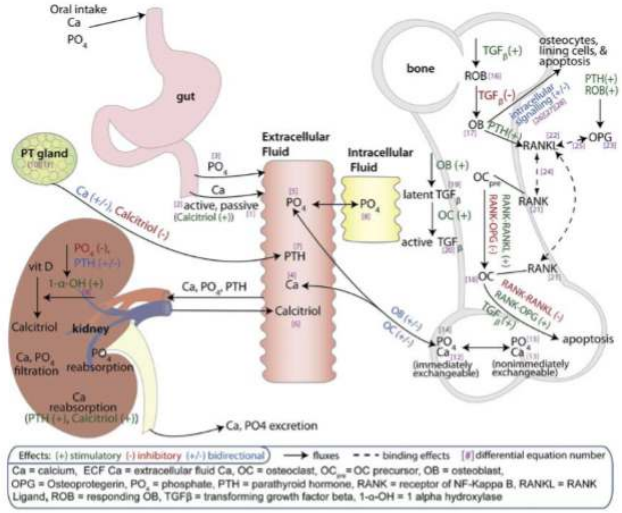
3/12: 25% of the score

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.



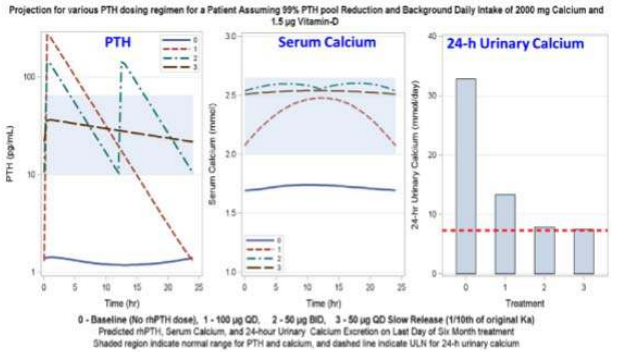


Figure 20 **Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 2000 mg oral Calcium and 1.5 µg Vitamin in a patient representing 99% PTH pool reduction**

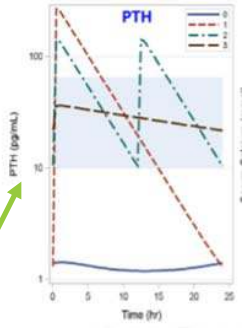
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM413617.pdf

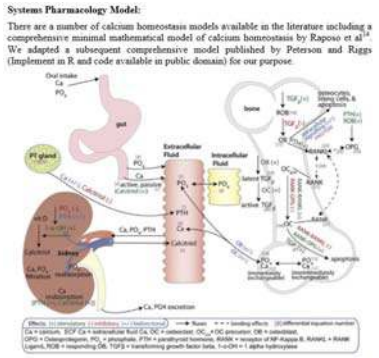
Element 12 IVIVR – the model building –the future is near

Models linking CPP, IPA and CQA to Dissolution

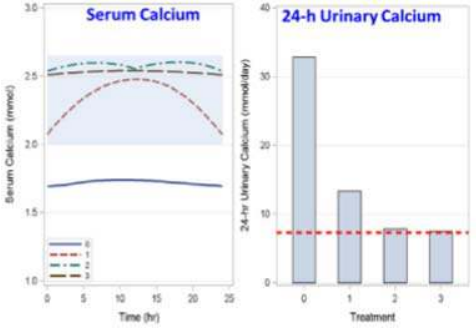
‘IVIVC’ links disso to PK

PK in Patient





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

Introduction to the case study

‘4th Generation’ EGFR TKI for Non-Small Cell Lung Cancer (NSCLC)

Disclaimer:

This case study is loosely based on scientific data and based on some experiences of the organising committee however ‘data’ has been invented and the conclusions drawn should not be considered as reality.

We have not tested / confirmed the critical information

4th Generation EGFR TKI: Lung Cancer

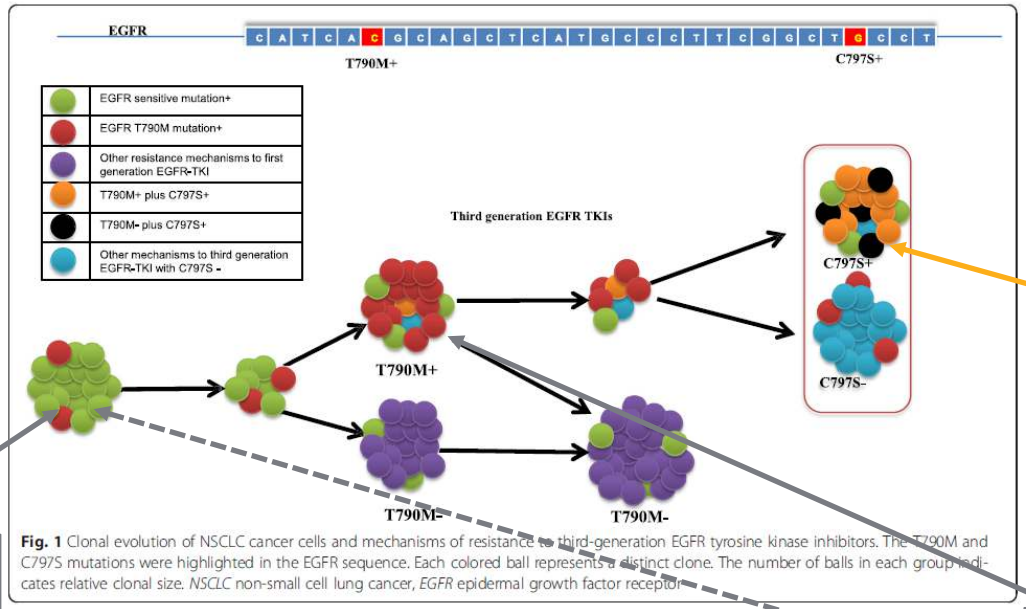


Fig. 1 Clonal evolution of NSCLC cancer cells and mechanisms of resistance to third-generation EGFR tyrosine kinase inhibitors. The T790M and *C797S* mutations were highlighted in the EGFR sequence. Each colored ball represents a distinct clone. The number of balls in each group indicates relative clonal size. *NSCLC* non-small cell lung cancer, *EGFR* epidermal growth factor receptor

"4th generation"

"1st and 2nd generation"

"3rd generation"

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

1: Targeted Patient Population	Well characterized and "reasonably" homogeneous or if heterogeneous, distinct groups are well characterized

- Yes (‘1’)
- E.g. EGFR TKI
  - EGFRm Lung Cancer
  - Largely Female, Elderly, Asian
- Impact on Drug Product:
  - Small/dispersible dosage form
  - Or none oral route of admin
  - pH independent dissolution (if oral)
  - Ideally no food effect (if oral)
- Other critical questions arising
  - Titration for body weight (West vs Asia) – is global fixed dosing approach suitable?
  - ? combi with immuno-oncology, does this affect formulation design?

- We really don’t know
- ‘Zero’
- Impact on QTPP:
  - ????

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

2: Indication	Indication and registrational endpoints are precedented (vs. novel), and duration of treatment known (acute or chronic)

- Yes ('1')
- Well precedented pathway which requires continual inhibition (scenario 4)
- Likely new indication (NSCLC with 'new mutation' detected with approved test)?
- Validated clinical endpoints (ORR, PFS, OS)
- Chronic therapy
- Other critical questions arising
  - Are RECIST criteria really sensitive enough to fully inform drug development
    - Other biomarkers. Dosing to toxicity approach (The Oncologist 2011;16:1729–1740)
  - Can anything smart be done with circulating tumour DNA to understand and control the expected development of resistance ?
  - Is there a threshold for when the marker for resistance becomes important? ctDNA.
  - How to develop the 'approved test'?
  - What is the test (biopsy, blood, something else)?
  - What is the cut-off in the test for drug response?

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

3: Availability of prior knowledge on Drug Substance and / or Drug Product	There is prior knowledge about the DS (and DP, if applicable)

- Yes ('1')
- Some evidence of reasonable crystalline form, buffer and biorelevant solubility available.
- Free base. No knowledge of polymorphs/solid state.
- Good permeability, reasonable F in rat, mouse, dog,
- Anomalous/unscaleable clearance across species
- Other critical questions arising
  - Question mark re. human half-life and dose (poor scaling of clearance)

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

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

- Yes ('1')
- Limited API quantities at present so limited in vitro testing conducted.
- Pathway is well precedented in this disease area. PK-PD models for earlier gen (e.g. Yates et al 2016, Mol Cancer Ther; 15: 2378).
- Potent **irreversible** inhibitor of new resistance mutation. Which other mutants does it also inhibit?
- Suboptimal margin to WT EGFR
- Other critical questions arising
  - 1/3 patient progress with Brain metastasis – same for 4th gen? (e.g. Ballard et al. 2016 doi: 10.1158/1078-0432.CCR-16-0399)
  - Risks for:
    - idiosyncratic liver tox (e.g. Harandi et al. 2009 doi:10.1155/2009/567486) ,
    - local effect in gut leading to WT toxicity (e.g. Harandi et al. 2009 doi:10.1155/2009/567486)
    - TKI tend to have QTc liability (http://oncologypro.esmo.org/Guidelines-Practice/Drug-Drug-Interactions-with-Kinase-Inhibitors/Types-of-Drug-Drug-Interactions/QT-Prolongation)
  - ? would non-oral route reduce tox and improve outcomes and increase no of treatable patients?
  - Prior knowledge (rociletinib) - potential question mark of metabolite with off target tox

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

5: Dose	Dose range can be estimated

- Otherwise (0)
- Prior knowledge suggests continual inhibition of target required (C_{min} / Scenario 4), supported by preclinical models.
- Allometric scaling suggests low dose (<10mg) but uncertainty with regard to half-life: difficulty in determining protein binding and metabolism in vitro due to covalent binding and clearance scaling poorly
- Difficult to predict human dose and PK profile
- Other critical questions / knowledge arising
  - What is human PK profile
  - Low C_{max}/C_{min} ratio desirable to control tox (rash and QTc etc) and avoid drug waste
  - Will dose reduction schedule may be required
  - Fixed dose or body weight adjusted doses required?

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

5: Dose	Dose range can be estimated

- Otherwise (0)
- Impact on QTPP:
  - EGFR TKI > Cmin driven (scenario 4)
    - IR (dose frequency) vs MR vs Depot
  - Target dose range
- Can start to think about dosage forms that will deliver
- Will have framework to assess the next round of data against

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

6: Understanding clinical endpoints, disease progression and effect on clinical endpoints	Effect of disease progression on clinical endpoints can be identified

- Yes (1)
- See element 1
- but unclear what the resistance progression will be.
- Learn from first and third generation compounds

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

7: Bioavailability (BA)	Is BA estimable and if it is, estimated BA >5%

- Yes (1)
- Yes via oral route.
- Low solubility, good permeability,
- BCS2.
- BA >5%, good bioavailability in animals and predicted from in silico PBPK abs modelling,
- >50%, but evidence of potential gastric pH dependence
- Other critical questions / knowledge arising
  - What about other routes of delivery?

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

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

- Yes ('1')
- For oral: based on preclinical data and in silico modeling
- Potential issue at high gastric pH
- Other critical questions arising
  - Impact of gastric pH?
  - Impact of food?
  - What about none oral routes?

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

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)

- Yes ('1')
- Subject to critical info on half-life and solubility/PPIs ie. what is dose and dosing interval
- Oral route once daily may be feasible (or twice daily)
- Modified release might be possible
- Depot intra-muscular / sub-cutaneous may also be feasible
- Yes ('1')
- For oral standard dissolution tests / biorelevant dissolution should be sufficiently informative
- Less confidence for parenteral depot formulations
  - Technology dependent

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

10: Stability	DS is stable in physiologic pH range (slow or no degradation)

- Yes (‘1’)
- No physiologically / clinically relevant instability

11: Manufacturability	Not scored, Note: Manufacturability is scored in subsequent development stages boxes

- Not scored in box 1

Simplified example of how Box 1 question allow QTPP to be developed (critical question and knowledge)

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)

- Yes ('1')

1. For oral route, standard in vitro tests can be applied to relate drug realise to PK profile
   - For parenteral route, test likely to be technology specific and quantitative and qualitative link to clinic less clear
2. For earlier generation EGFR TKI: PK-PD-System-Biology-Efficacy models exist suggesting these can be developed for this molecule (e.g. Ballard et al. 2016 doi: 10.1158/1078-0432.CCR-16-0399 and Yates et al 2016, Mol Cancer Ther; 15: 2378)

- **These models two systems can be joined to create the IVIVR**
- Other critical questions arising
  - What preclinical and clinical data needs to be collected to allow the IVIVR to be developed

Overall summary

	Targeted patient population	Indication	Availability of Prior knowledge on DS and/or DP	Pharmacology	Dose	Clinical endpoints, disease progression	Bioavailability	Solubility, drug release/dissolution	Drug Delivery/input parameters	Stability	Manufacturability	IVIVR / model building	**Total score**	
Box 1													**11**	At Box 1 looking OK for this stage of development. Oral route and parenteral depot both under consideration and appear feasible (although predictive ability of in vitro tests less certain for the parenteral route), Several critical questions are identified which guide next steps: • Difficulty in predicting human t1/2 predictions leads to uncertainty around dose additionally dose reduction schedule may be required • Potential to combine with immuno-oncology agents, what does this mean for dose? • Is there a threshold for when the marker for resistance becomes important? • Risks for idiosyncratic liver tox, local binding in gut leading to WT reducing compliance and outcome • query would non-oral route reduce tox and improve outcomes and increase no of treatable patients? • Prior knowledge (roclitinib) - potential question mark of metabolite with off target tox • Predictive ability of simple solution stability and in vitro release tests for parenteral depot

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


SEDA
Pharmaceutical Development Services