# Introduction to the Biopharmaceutics Risk Assessment Roadmap (BioRAM), Drug Delivery Scenarios and Scoring Grid

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# Aims and Disclaimer

- Introduce and align you to the roadmap, therapy driven drug delivery scenarios and partially walk though a semi-hypothetical example and the ‘new scoring grid’
- Emphasis: the roadmap as a tool to identify critical data and integrate discovery, development, biopharmaceutics, clinical pharmacology and clinical data while being flexible to patient’s and project needs

- 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

# Acknowledgements


- 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.
- Others :
  - Our organizations
  - Authors and contributors of the referenced publications
  - Participants of the 2009 QbD and Biopharmaceutics workshop and the 2013 and 2015 BioRAM workshops
  - AAPS QbD and Product Performance Focus Group and AAPS
  - University of Wisconsin-Madison School of Pharmacy, Division of Pharmacy Professional Development
  - Individuals continuing to work on BioRAM are gratefully acknowledged

# Bibliography

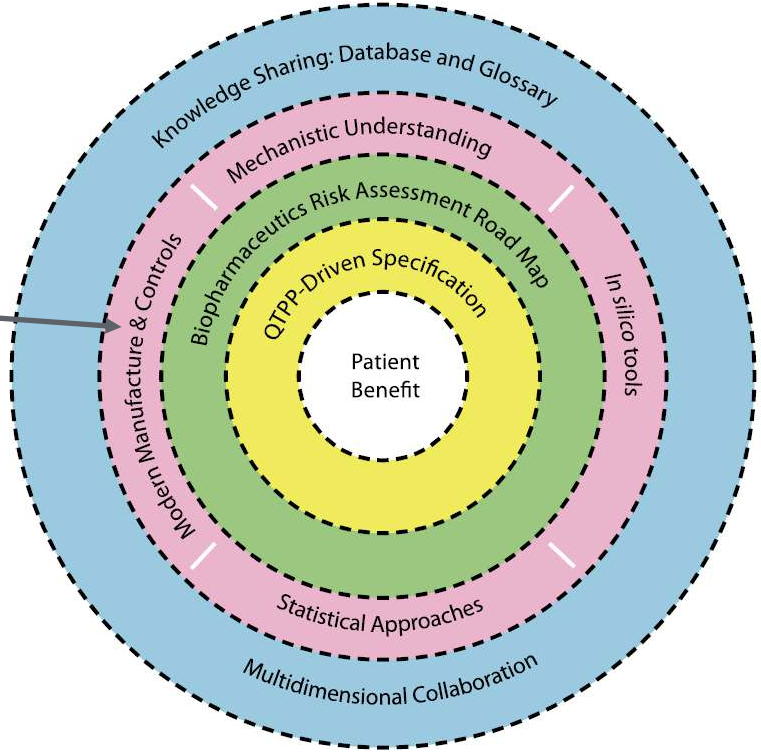

- A. Selen; M.T. Cruañes, A. Müllertz; P.A. Dickinson, J.A. Cook, J.E. Polli, F. Kesisoglou, J. Crison, K.C. Johnson, G.T. Muirhead, T. Schofield and Y. Tsong (2010) Conference Report: Applied Biopharmaceutics and Quality by Design for Dissolution/Release Specification Setting: Product Quality for Patient Benefit. AAPS J. 12 (3): 465-472, http://dx.doi.org/10.1208/s12248-010-9206-0.
- 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. in press
- 3 AAPS Webinars:
  - https://www.pathlms.com/aaps/events/479

# How did the journey start?

- Integration of QbD and Biopharmaceutics

Critical Factors for Product Performance

Dickinson, 2015




Selen et al. Meeting report: applied biopharmaceutics and quality by design for dissolution/release specification setting: product quality for patient benefit. AAPS J. 2010;12:465–72

# ICHQ8 R2: Quality Target Product Profile (QTPP)

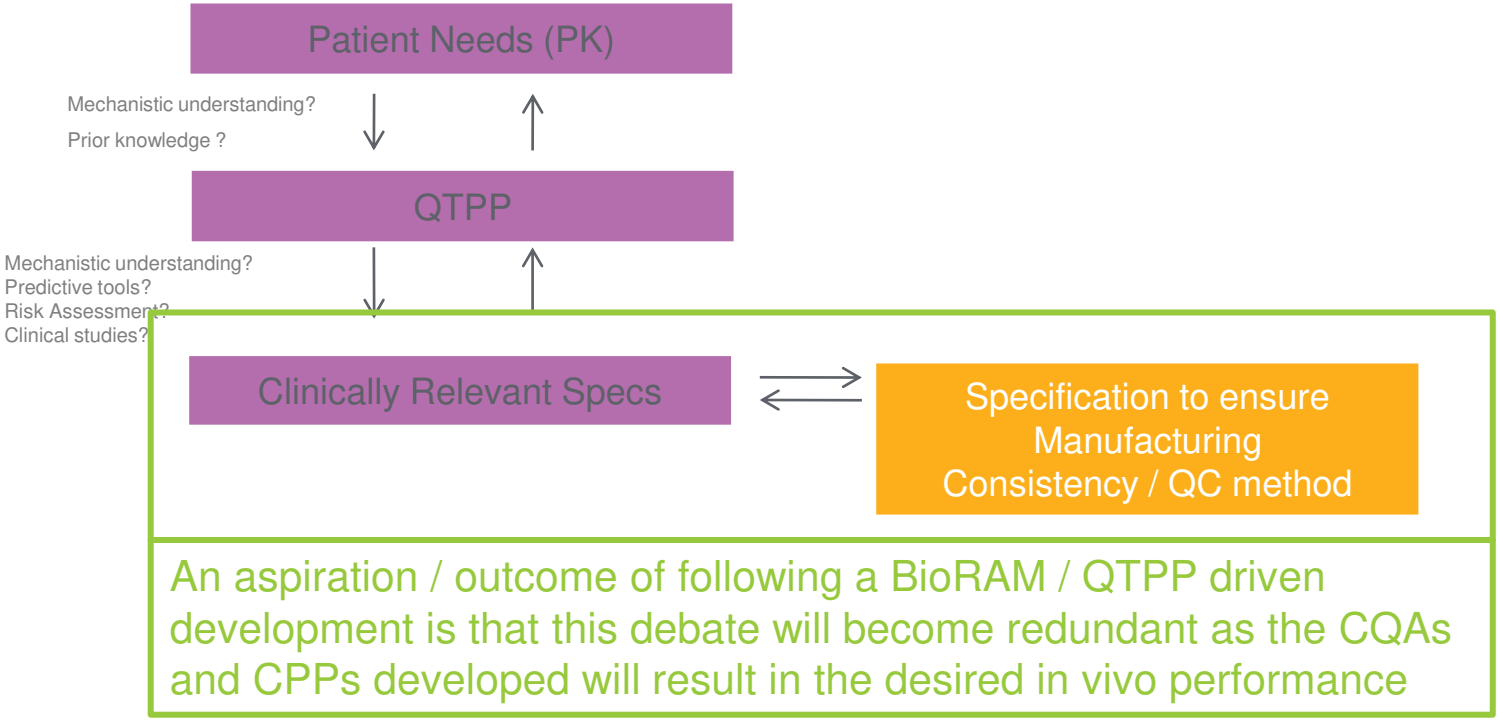
"A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."

"The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed;
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

# Patient Needs: QTPP: Specifications Based on Desired product Performance

Cruañes and Dickinson



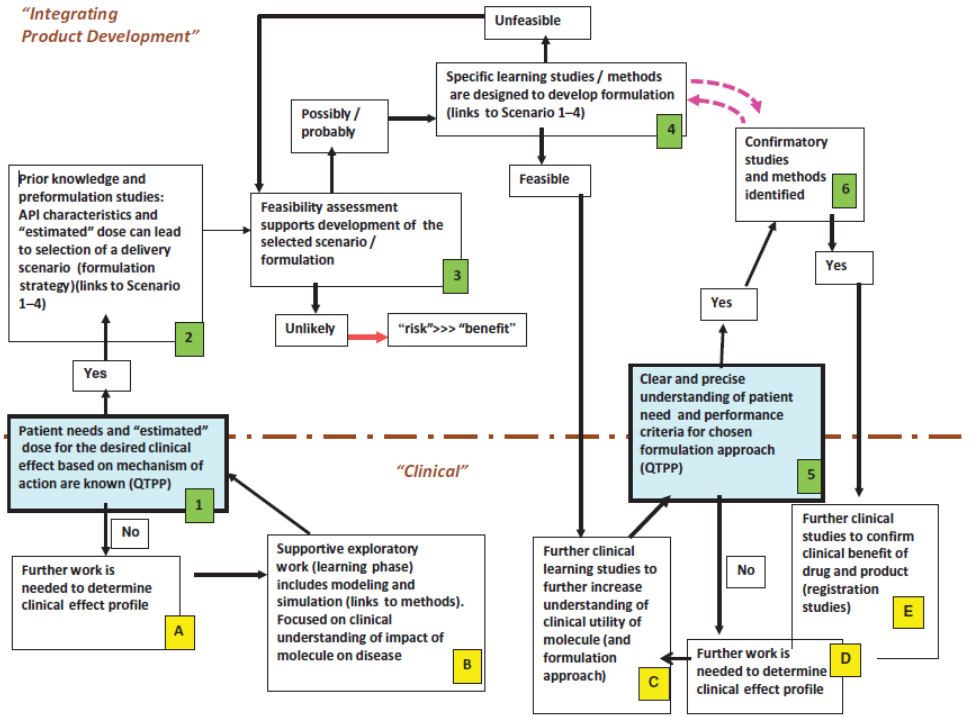
# BioRAM: Biopharmaceutics Risk Assessment Roadmap

- 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.

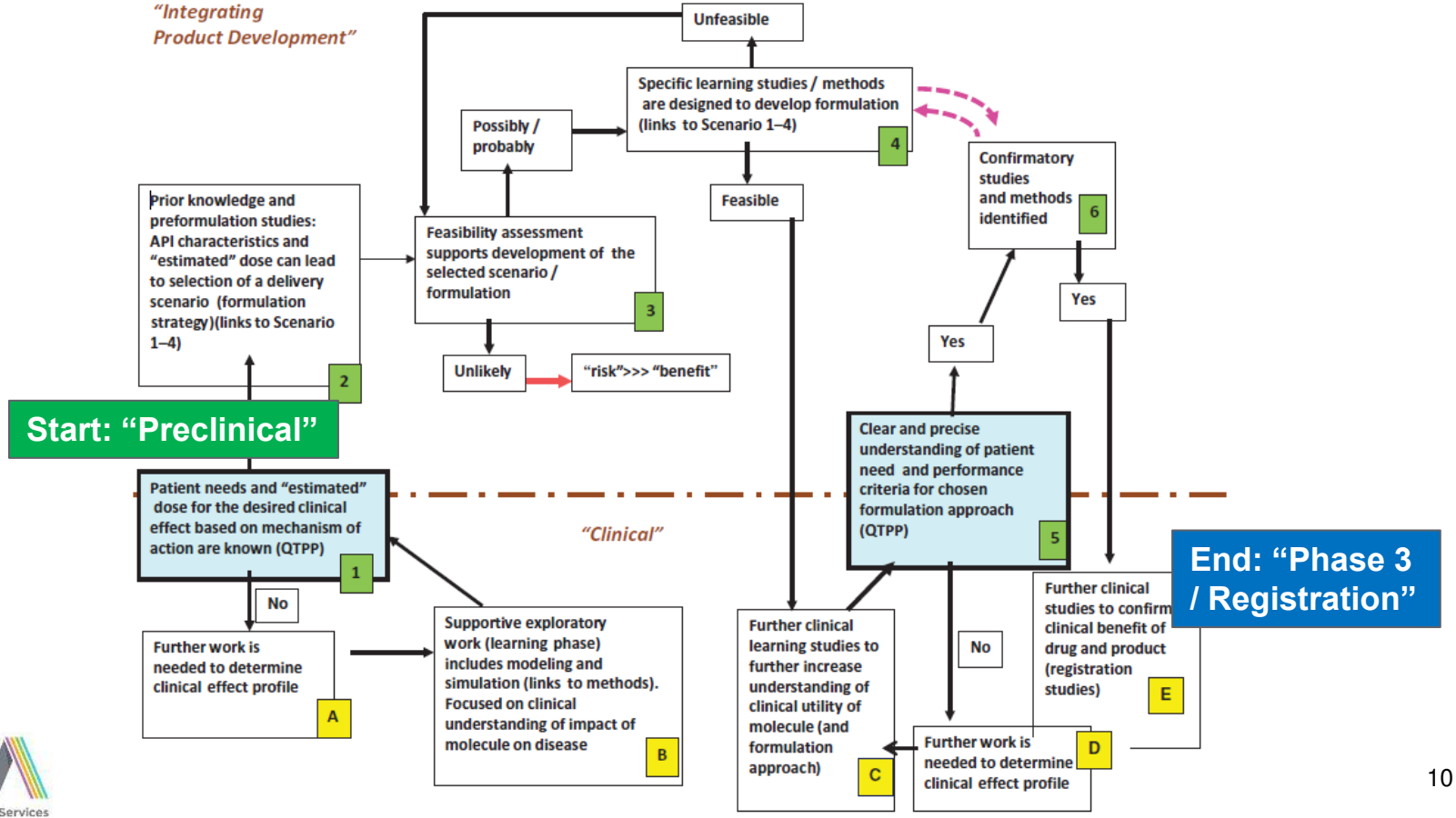
A. Selen, J. Cook, M.T. Cruañes, P.A. Dickinson, T. Flanagan, F. Kesisoglou, M.N. Martinez, A. Müllertz

# The Biopharmaceutics Risk Assessment Roadmap

- 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, Abu T.M. Serajuddin, J.A. Cook, J.B. Dressman. The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance. J Pharm Sci, 103: 3377-3397, 2014



# BioRAM Timeline

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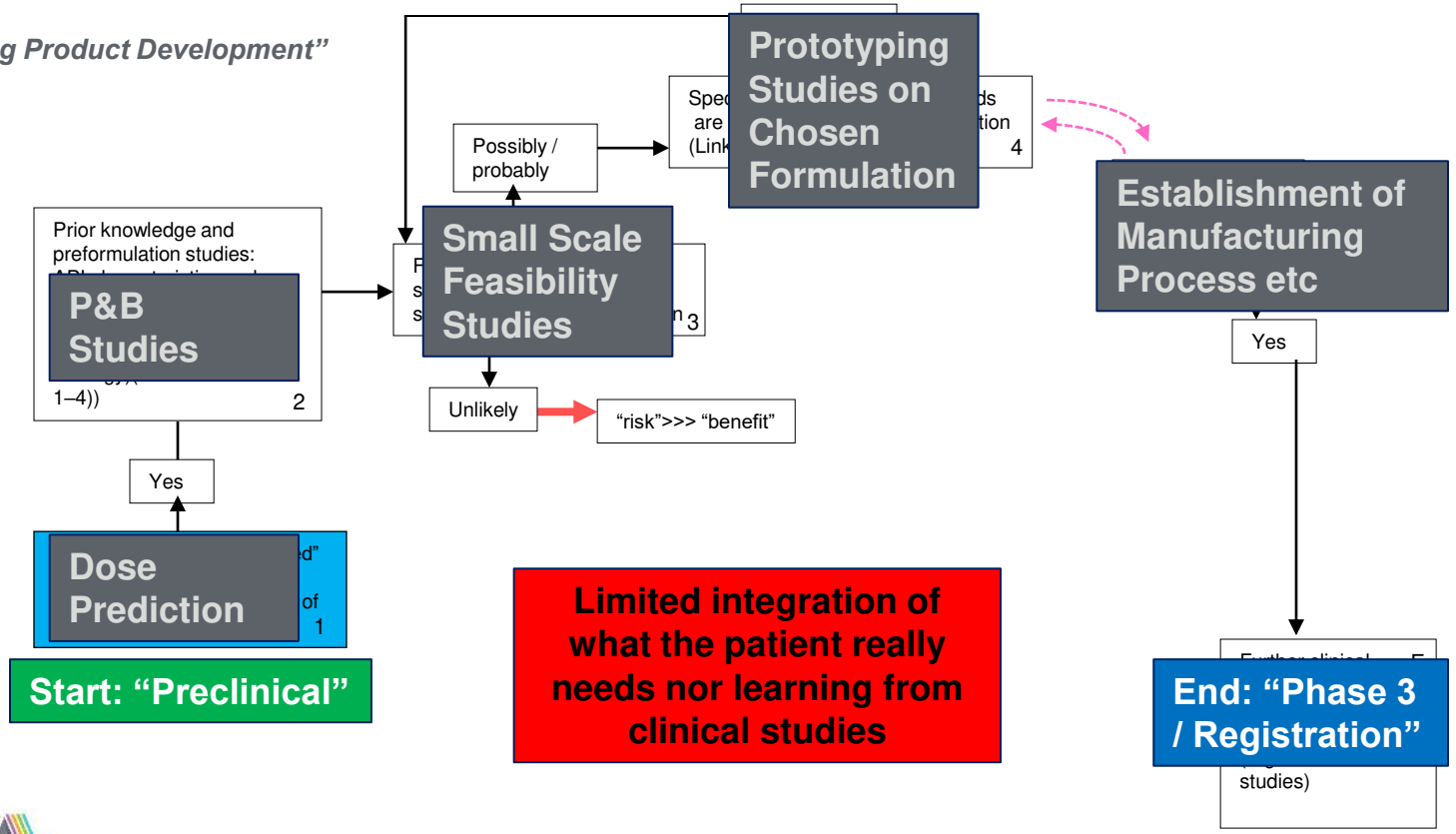
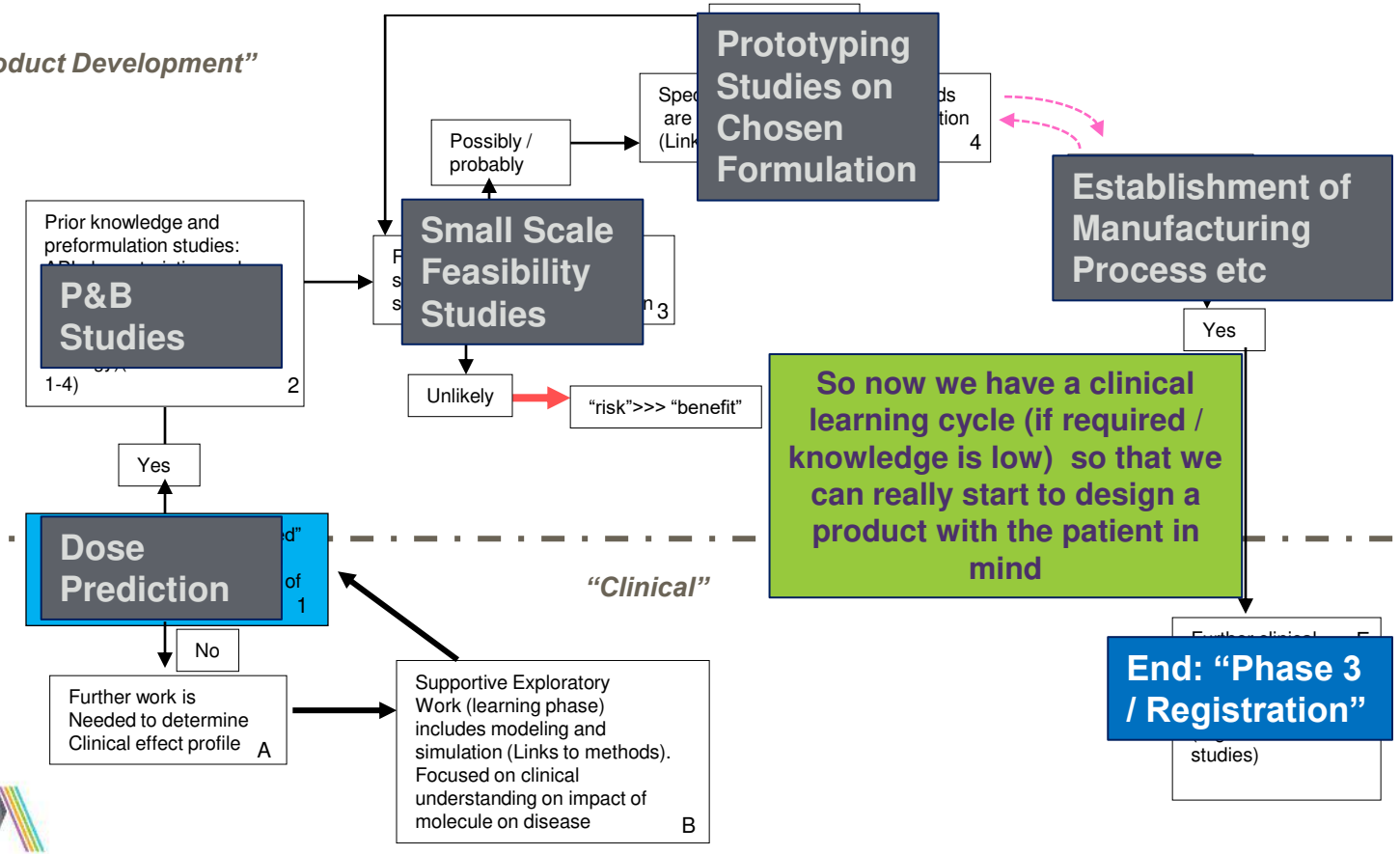
# What linear product development might have looked like / looks like:

*"Integrating Product Development"*



# BioRAM: Making this patient centric

*"Integrating Product Development"*

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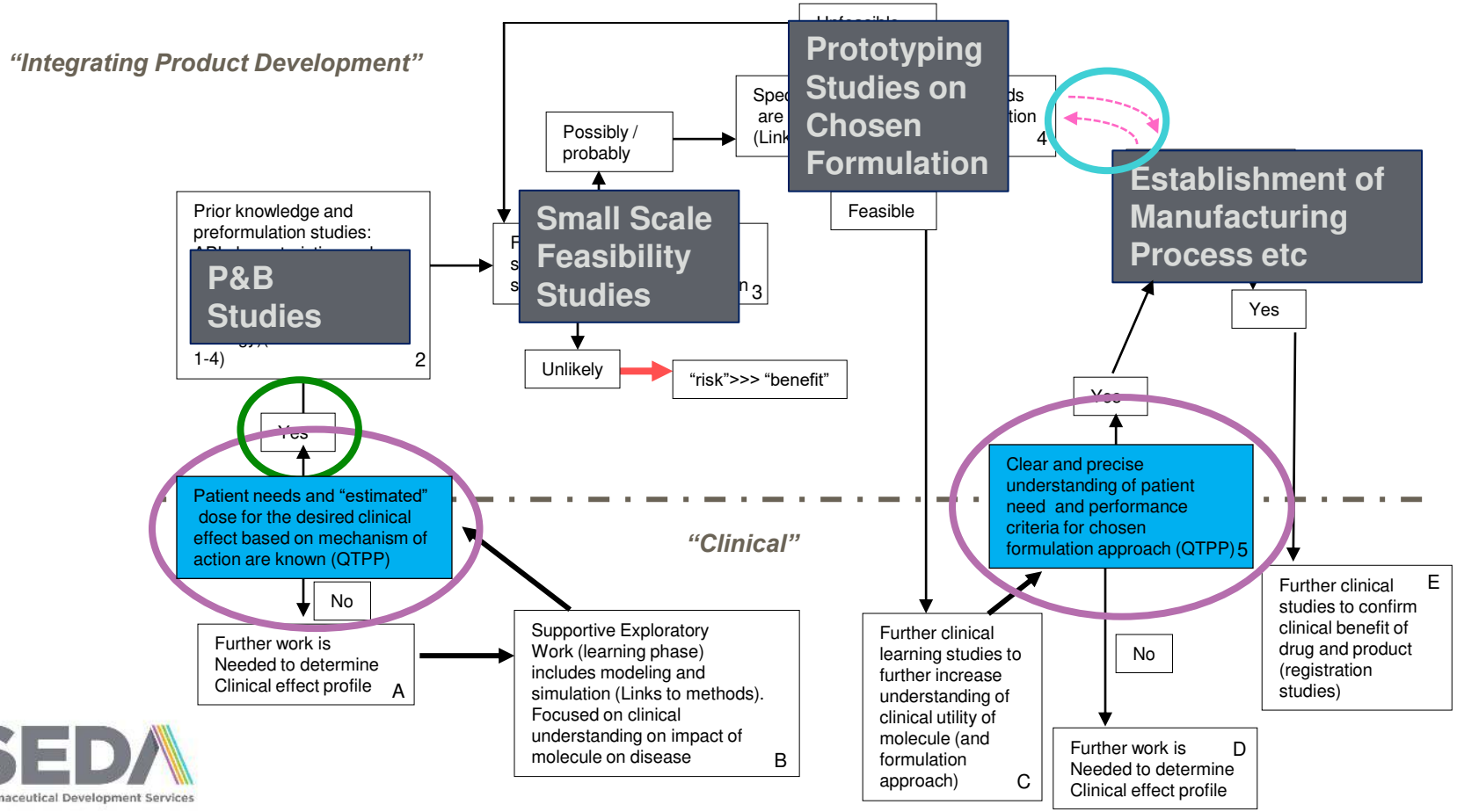
# BioRAM: Integrating clinical learning and an iterative approach to QTPP

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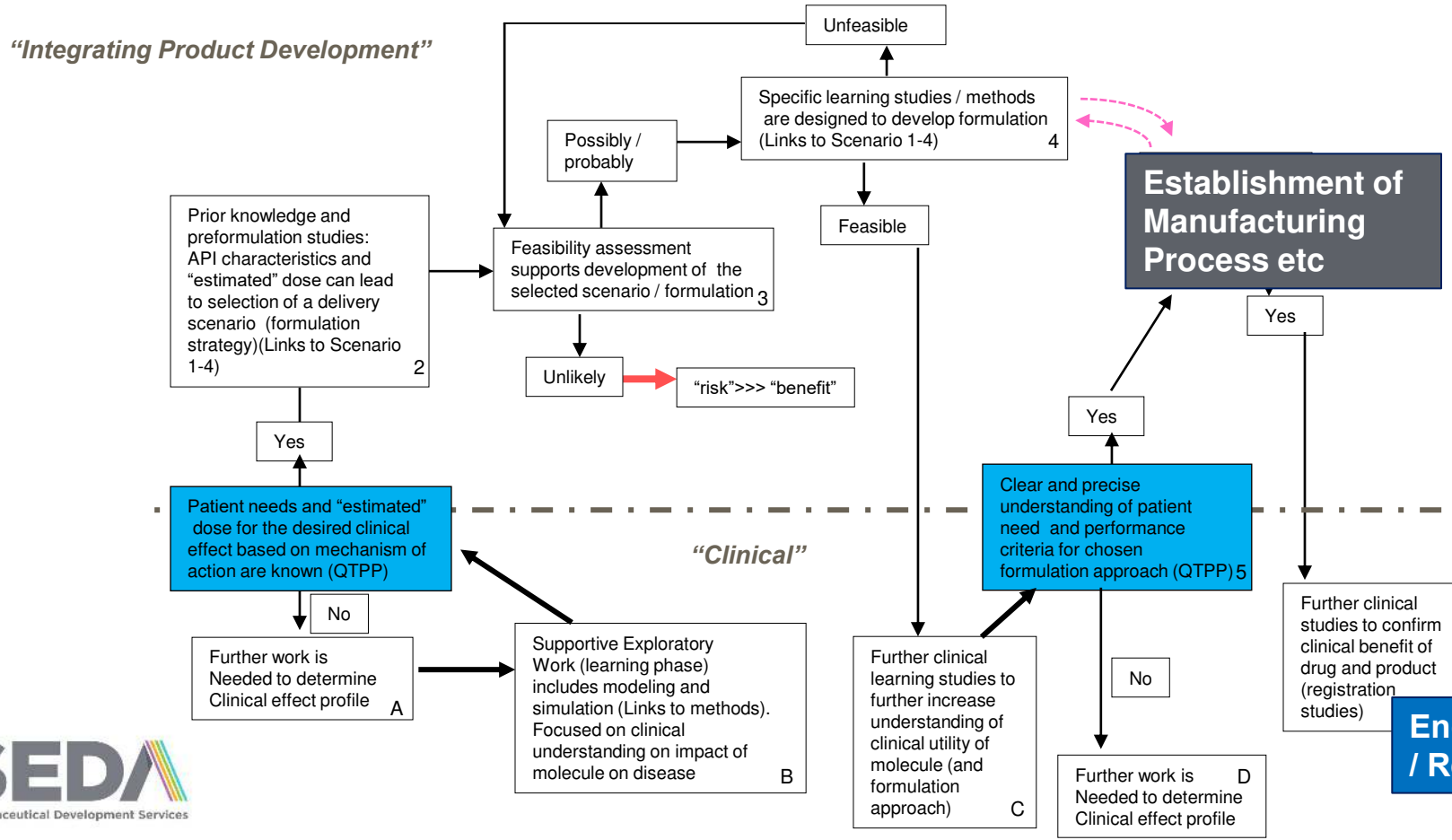
# BioRAM: Integrating clinical learning and an iterative approach to QTPP

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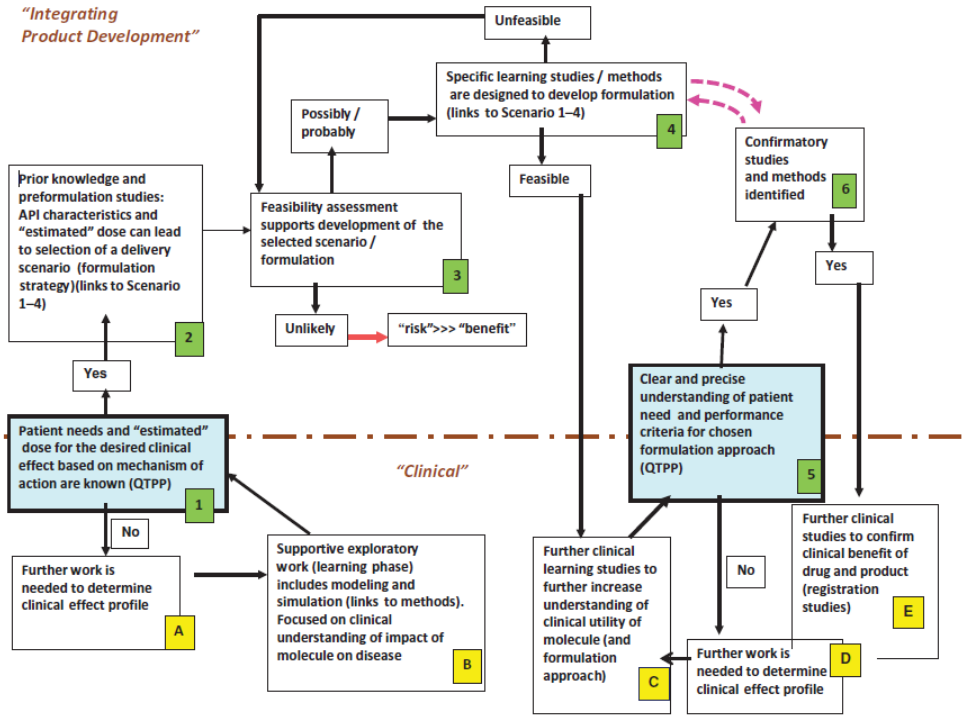
# The Biopharmaceutics Risk Assessment Roadmap

- 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, Abu T.M. Serajuddin, J.A. Cook, J.B. Dressman. The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance. J Pharm Sci, 103: 3377-3397, 2014



# Can BioRAM lead to more successful development?

Images: Shutterstock

- 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 BioRAM 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**

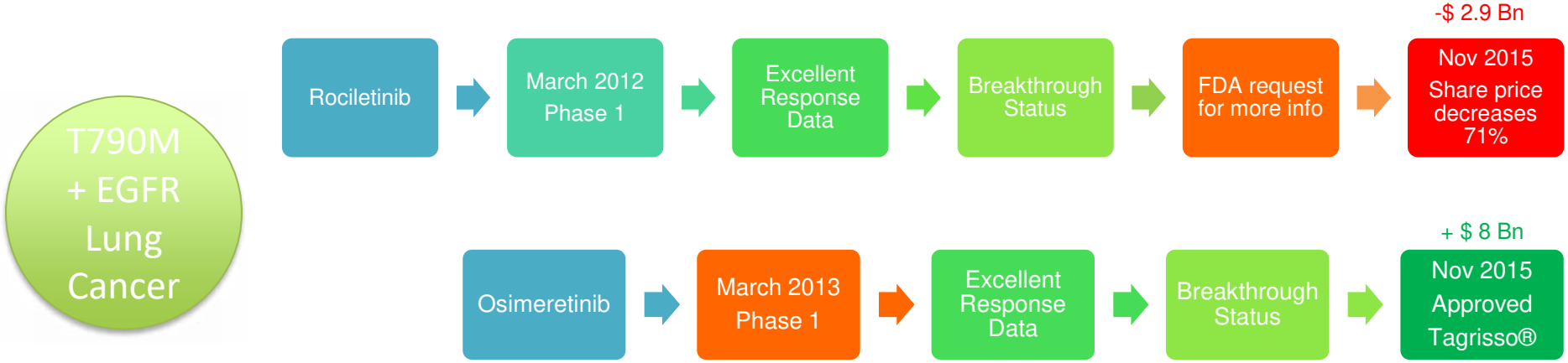
  The Annals of Oncology 'Industry Corner' papers review both compounds and cite several key success factors for drug development
  - key success factors include:
    - formulation
    - bridging
    - dose selection
    - patient selection

**Aka: BioRAM and the scoring grid**

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

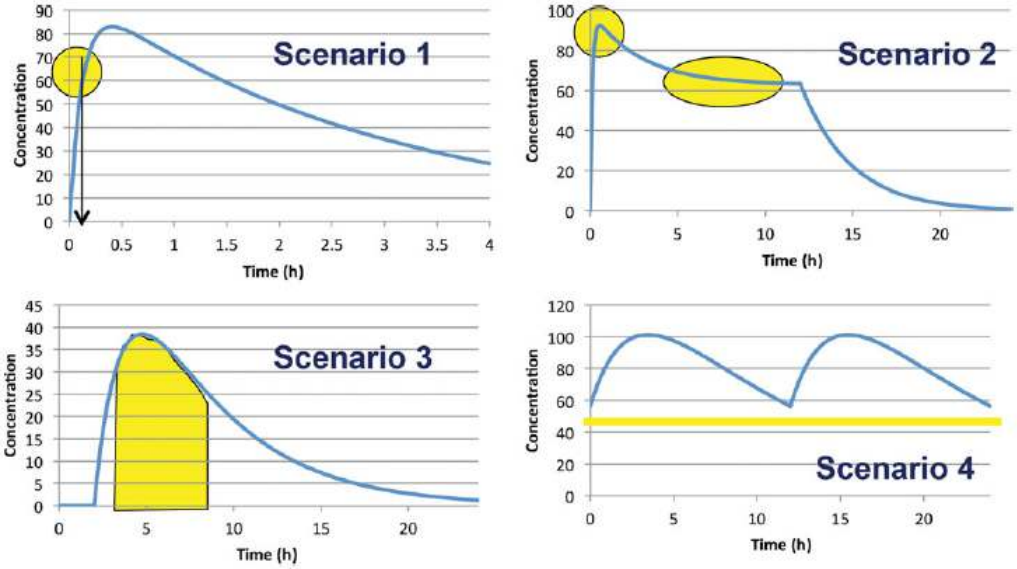
Subsequent ODAC 12 April 2016 meeting: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm486395.htm

# Recent case studies imply that BioRAM thinking wins



# BioRAM: Four drug delivery scenarios / drug concentration-time profiles

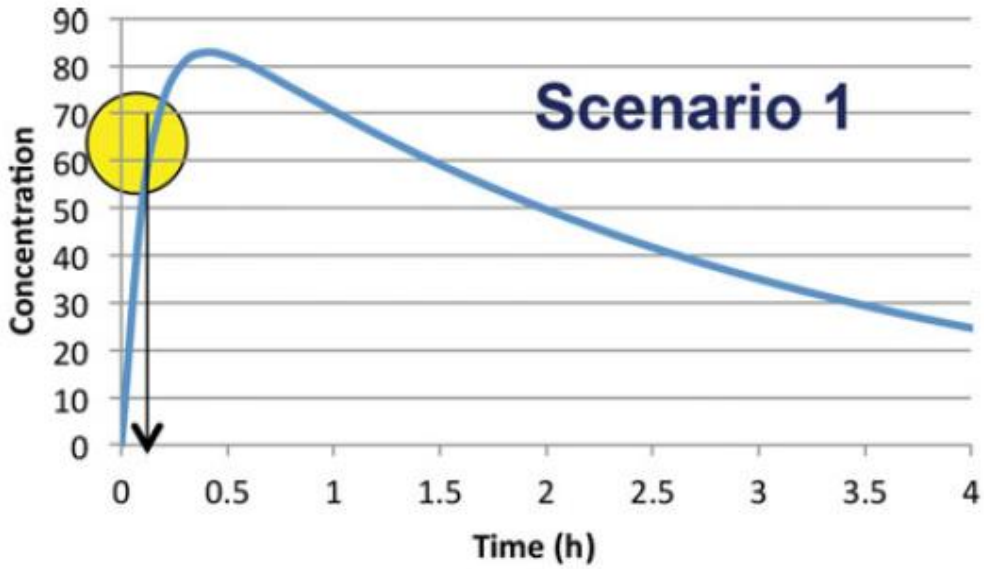
- The BioRAM discusses four drug delivery scenarios / PK profiles that cover many of the potential PK considerations for therapy driven product performance
- These are not intended to be exhaustive or for classification of the drug
- Instead they serve as analogues which can act as learning tools for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

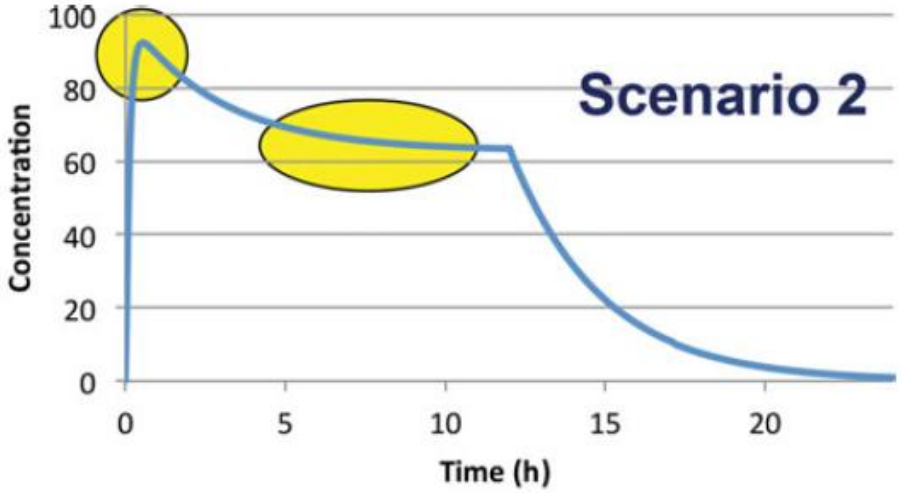
# Scenario 1: Rapid therapeutic onset


Dinendra Haria / Shutterstock.com



# Scenario 2: Multi-phasic delivery

- Methylphenidate tablets, oral (ADHD)
- Zolpidem CR (Insomina)
- Insulin Pumps



# Scenario 3: Delayed therapeutic onset (e.g. Chronotherapy)

Concept that partial AUCs are important

- Fluoroucil (5-FU) infusion
- Verapamil
- Prednisolone
- Hydrocortisone for adrenal insufficiency:

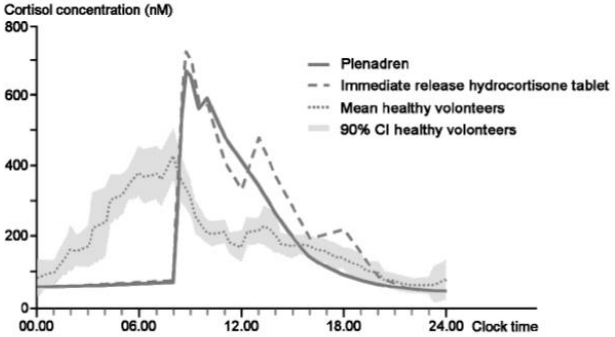
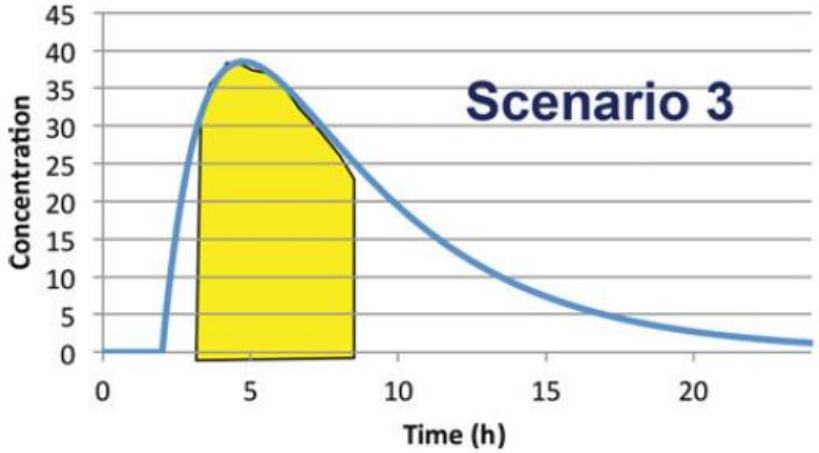


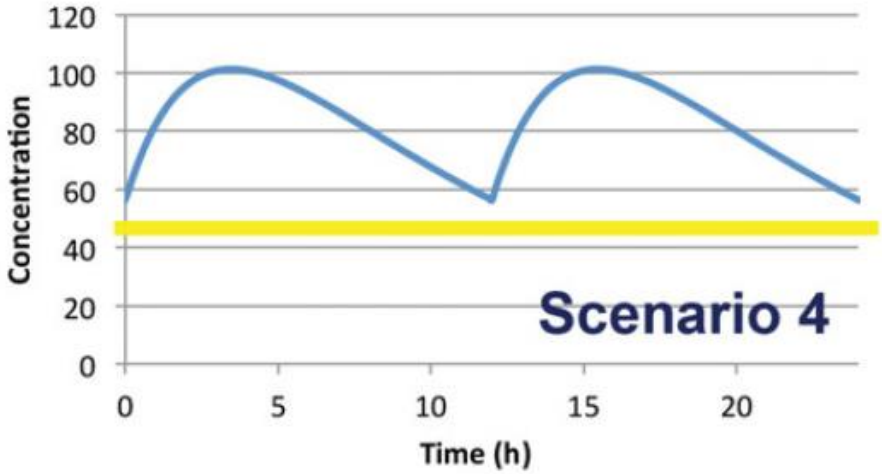

**Figure 7. Observed mean serum cortisol concentration versus clock time in primary adrenal insufficiency patients (n=62) after oral administration of Plenadren once daily, hydrocortisone tablets thrice daily and healthy volunteers (HV; n=13). CI=confidence interval.**



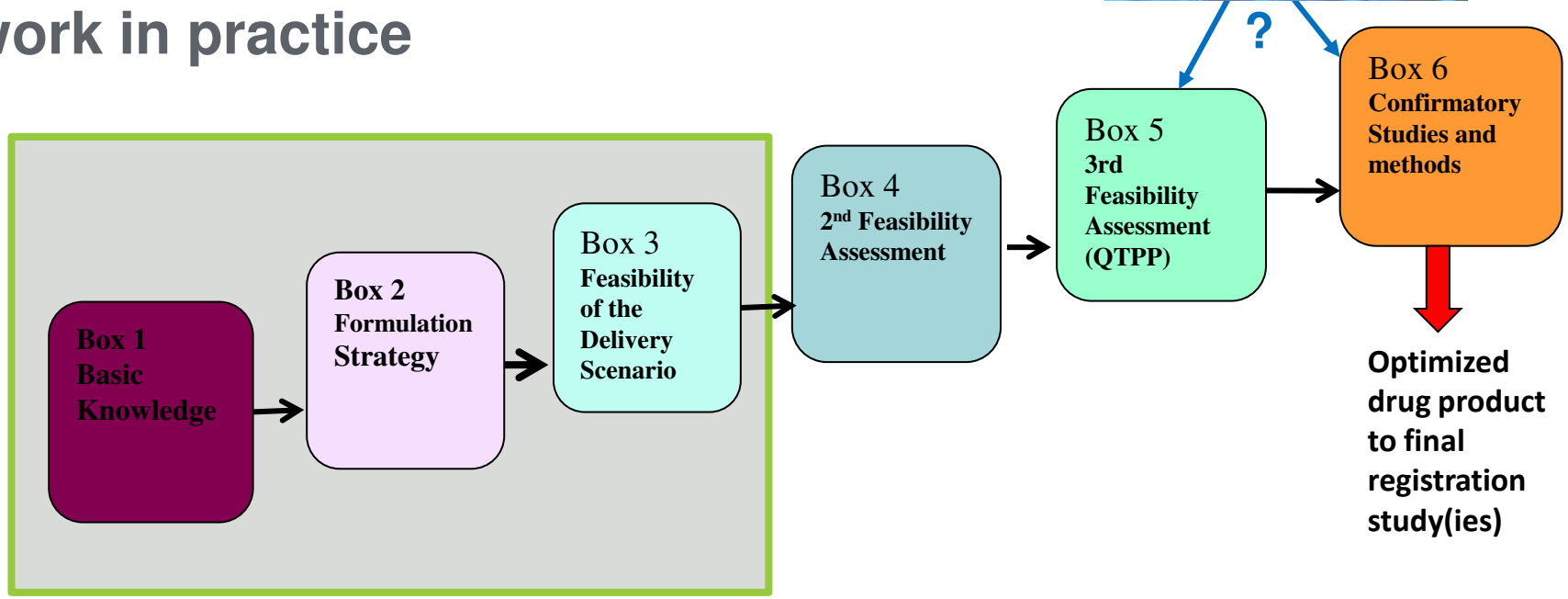

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002185/WC500117639.pdf

# Scenario 4: Maintenance of target exposure

- Numerous drugs
- In numerous presentations:
  - Immediate release, oral
  - Modified release, oral
  - Long acting depot injections
  - Transdermal patches
  - etc



# Partially working through an example in the 2014 paper to show how this can work in practice


**Note: Depending on the project & what's known– efforts can start at any one of the boxes (life-cycle management)**

# Scenario 4: Targeted steady-state and/or trough concentration is critical

- Example therapeutic situations that would classically have this need are:
  - Atypical antipsychotic
  - Antibiotic
  - Oncology product
- Generally these broad therapeutics areas would lead to a different unique (product specific) roadmap
  - For example,
    - Atypical antipsychotic may be amenable to formulation as modified/extended release depot injections
    - many antibiotics are not BCS Class 1 and require high doses
      - that makes MR challenging
      - short duration treatment so multiple daily dosing may be okay.
    - Oncology may tolerate more frequent dosing, food effect (?) and bigger dosage forms etc
- Additionally:
  - Anti bacterial has nice translation from preclinical data
  - Oncology – poorer translation and likelihood being dosed at maximum tolerated dose / smaller therapeutic index


Kapur et al. (2000) Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 157(4):514-20.
Tanaka et al. (2008) Identifying Optimal Biologic Doses of Everolimus (RAD001) in Patients With Cancer Based on the Modeling of Preclinical and Clinical Pharmacokinetic and Pharmacodynamic Data J Clin Oncol 26:1596-1602;
O'Donnell, et al. (2008) Phase I Pharmacokinetic and Pharmacodynamic Study of the Oral Mammalian Target of Rapamycin Inhibitor Everolimus in Patients With Advanced Solid Tumors J Clin Oncol 26:1588-1595
Tabernero, et al. (2008) Dose- and Schedule-Dependent Inhibition of the Mammalian Target of Rapamycin Pathway With Everolimus: A Phase I Tumor Pharmacodynamic Study inPatients With Advanced Solid Tumors. J Clin Oncol 26:1603-1610
Mouton, et al. (2011) Conserving antibiotics for the future: New ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. Drug Resistance Updates 14: 107–117.
Breilh et al. (2013). Carbapenems J Chemother 25:1-17.
R. Kumar, B. Suttle (2011) The Importance of PK/PD Data-Key Biological Answers Needed to Evaluate the Success of Potential Cancer Therapeutics. Molecular Cancer Therapeutics 10: 2028

# Targeted steady-state and/or trough concentration is critical

- So we'll work through an hypothetical example based on an antibiotic (taken from the 2014 paper).

- Which means we have these considerations:
  - Although some antibiotics have a target concentration of $C_{min}$ the majority of developed antibiotics have a target AUC in fact $AUC_{0\text{-}24h}$ : MIC ratio to achieve therapeutic outcome.
    - Where the MIC is minimum inhibitory concentration for the target bacteria strain.
  - Very good translation of target AUC/$C_{min}$ from pre-clinical data (based on MIC) with 'Clinical Breakpoints' to drive treatment choice (i.e. which 'bugs' will be susceptible to the drug)
  - Other aspects of the clinical situation are:
    - To ensure that resistance does not develop and include considerations related to dosing frequency.
    - Managing PK variability so adequate exposure in the whole population treated and is not just a mean exposure value.

  - Treatment for bacterial infection is largely acute
    - multiple dosing throughout the day and large oral formulation size can be tolerated by the patient.
    - This is in contrast to chronic therapies where dosing once daily or a maximum of twice daily and small dosage form size are important considerations

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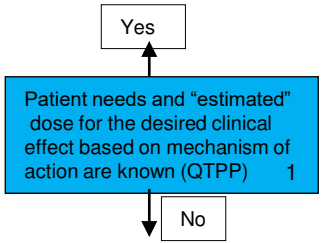
# Scenario 4: walking through the roadmap




Box 1

- There is a high degree of confidence in the clinical target (AUC)
- However there is less confidence in the dose needed to achieve target AUC because of uncertainty in preclinical predictions of human oral clearance.
- This has made estimating human PK difficult and thus there is a large predicted range for estimated dose coming from the pre-clinical DMPK department (**10 mg o.d. to 500 mg t.d.s**)

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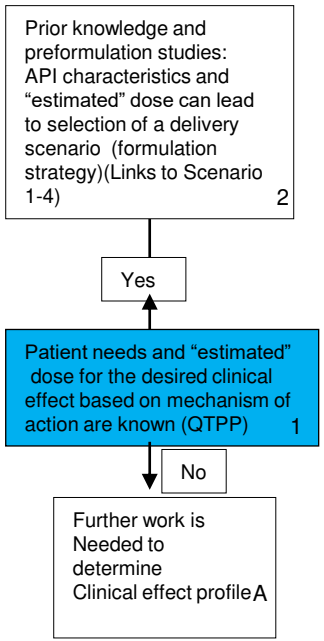
# Scenario 4: walking through the roadmap




Box 2

- Collect data on the compound and identify any rate limiting steps for absorption (dose range)
- Relatively straight forward compound
- High permeability, Log P = 2, absorption throughout the GI tract (no absorption window) and no impact of the drug on GI physiology.
- Risk assessment for formulation strategy focuses on **drug solubility**.
- Neutral, stable polymorph with a solubility of 50 mcg/mL in aqueous buffers across the physiological pH range.
- Make a estimate of the likely formulation technologies needed (dose range).
- Low dose: tentative BCS/DCS Class 1 compound (dose to solubility ratio less than 250/500)
- Higher dose : DCS Class 2a (dissolution rate limited) or DCS Class 2 (solubility limited) (Butler and Dressman, 2010).
- Problem for the formulator (risk/uncertainty) should s/he assume (insufficient evidence):
  - lower dose for which a standard IR product should meet the need
  - higher dose where some sort of enabling technology is likely to be required

This is where semi-parallel activities in Box A/B could be considered.

Butler and Dressman,(2010) The developability classification system: application of biopharmaceutics concepts to formulation development. J Pharm Sci.. 99(4940-54. doi: 10.1002/jps.22217.

Box A

- A preliminary study to learn what the human systemic PK is
  - therefore improve the **human dose prediction**.
- This likely could be part of simple Phase 1 SAD studies in healthy volunteers
  - using a fit for purpose formulation (for instance an extemporaneously prepared suspension with suitable drug particle size).
- This will allow the human PK to be accurately characterized
  - but the use of a none enhanced formulation may mean that if clearance is high and consequently a high dose is required , then clinically relevant exposures will not be achieved
  - and the SAD study may have to start again with a new formulation.
- Nevertheless the project will be able to move forward as the human PK will now be known and therefore the **likely dose** that may provide the necessary exposure

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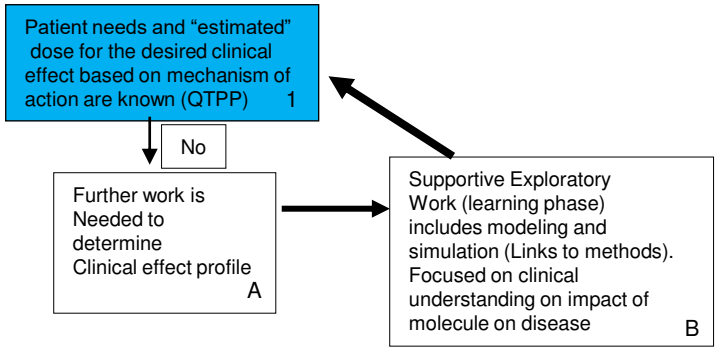
# Scenario 4: walking through the roadmap




- Box 1 Revisited
- Based on the output of Box A and B have better estimation of dose need to be delivered
- Box 1 can be revisited.
  - Reasonable estimate of mean human PK (from Healthy Volunteers)
  - but as yet there will not be the understanding of all sources of variability in PK (population PK)
  - and so exactly what the dose is required to ensure >90% target attainment (i.e. achieved in 90% of patients).
  - Nevertheless **range of doses** can be calculated from the first clinical study making some assumptions about PK variability.
  - Now **250mg b.d. to 500 mg t.d.s.**
  - The increased dosing frequency also means that the product will ideally not be subject to a fed/fasted difference

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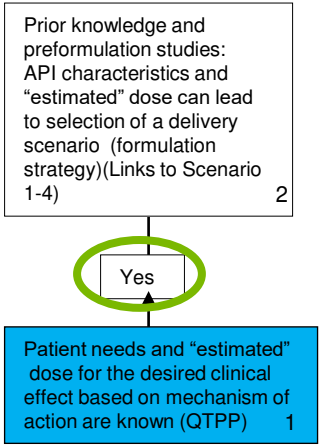
# Scenario 4: walking through the roadmap




Box 2 Revisited, Part 1

- DCS2a or DCS2 compound it is likely **enhanced formulation** will be required to meet the AUC target.
- To confirm :
  - additional biorelevant solubilities need to be generated, foremost will be solubilities in media more representative of the small intestinal (FaSSIF, FeSSIF etc)
  - robust estimates of permeability
    - Deconvolution / convolution / line shape analysis of the FTiM clinical data
    - examination of pre-clinical data
    - additional CaCo-2 permeability (several concs and comparing to a more extensive standard curve)
    - Ussing with human tissue?
    - Conclude that Human intestinal permeability is high and in the region of 3.8 x 10-4 cm/s.
  - This data was built into absorption modelling software to assess:
    - the likely fraction absorbed from a conventional formulation
    - the impact of dose, particle size and variability in patient GI physiology on fraction absorbed from a conventional formulation
    - Additionally when an absorption / **solubility limitation** was found
      - the **solubility enhancement** needed to provide **complete absorption**

Mathias and Crison (2012) The Use of Modeling Tools to Drive Efficient Oral Product Design The AAPS J. 14: 591-600.

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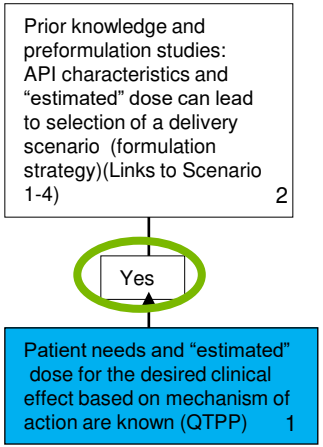


Box 2 Revisited, Part 2

- Additionally need to gather preformulation data to inform the likely enhanced formulation strategy (roadmap) such as:
  - Log P
  - melting point
  - solubility in lipidic excipients
  - Solubility was only moderately increased in biorelevant media and solubility in lipidic excipients was low

**Sufficient evidence to make decision?:**

- A conventional dosage form with micronized drug may provide:
  - the necessary exposure if the dose was around the 250 mg level
  - would not provide complete absorption and therefore necessary exposure if the dose was nearer to 500 mg
- So the project decided to take two formulation approaches forward for feasibility assessment.
  i. standard approach based on micronized drug
  ii. enhanced approach based on amorphous drug
    - low solubility in lipidic excipients

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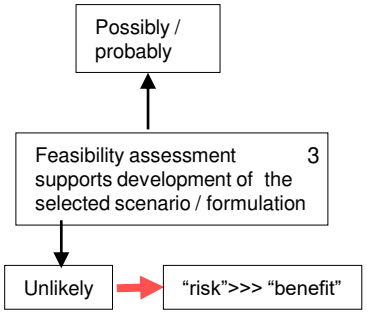


Box 3, Workstream 1

- Standard formulation based on micronized drug:
- To confirm the accuracy of the in silico simulations and understand 'formulatability'

**Biopharmaceutics assessment** (use a suspension as a 'best case' tablet or capsule?)

- Dissolution across the physiological pH range and in biorelevant media
- More advanced dissolution systems (to overcome fixed volume issues)
  → better understanding of the actual release / dissolution profile versus dose.
  → optimize in silico models wrt dissolution and assess the impact of patient GI Physiology variability on exposure.
- Output:
  - **range of potential input profiles for input into the developing population PK model**

**Formulation assessment**

- Microniser performance, how to formulate, compressibility, stability, excipient compatibility and so on

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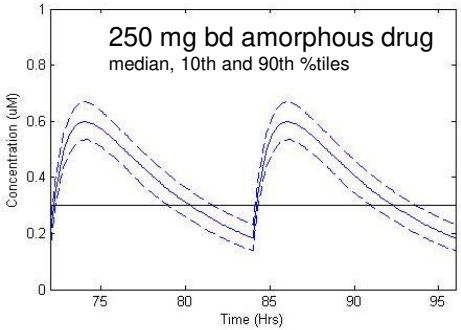
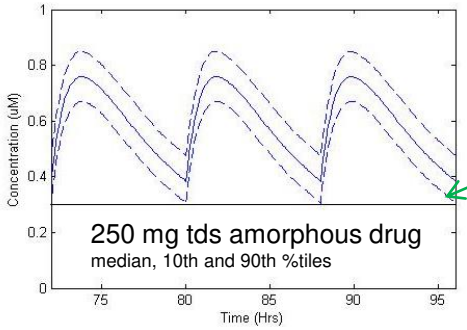
## Fast forward to the end of box 3>>

Enhanced formulation:



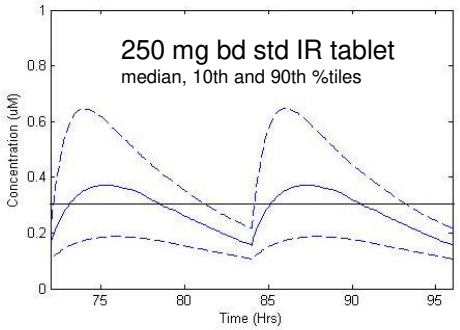

where >90% of the population achieve the target exposure when dosing at 250 mg t.d.s.

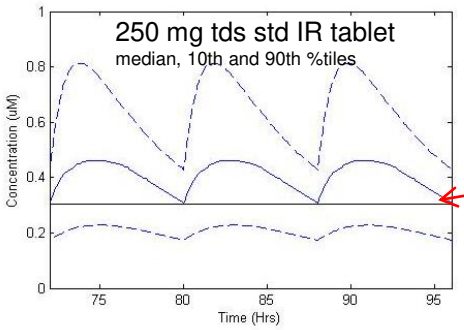
Possibly / probably

Feasibility assessment supports development of the selected scenario / formulation 3

Unlikely → "risk">>> "benefit"

Standard Tablet:




only 50% of the population achieve the target concentration when dosing at 250 mg t.d.s.

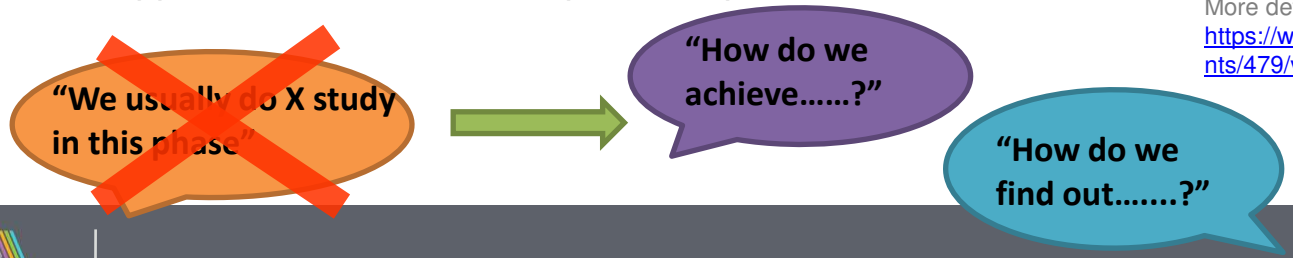
SEDA Pharmaceutical Development Services

# Optimization in BioRAM is Multidisciplinary

- The twelve elements of the BioRAM Scoring Grid are integrated to optimize clinical performance of a drug product
- The elements of the BioRAM Scoring Grid include:
  - knowledge on needs and characteristics of targeted patient population, indication, pharmacology and characteristics of the drug substance, dose, bioavailability, understanding clinical endpoints, and disease progression, drug substance and drug product characteristics and
  - integrated model linking in vitro product performance to clinical performance.

# BioRAM Scoring Grid

- The latest BioRAM paper formerly describes a scoring grid intended to drive systems thinking and integrate multi-disciplinary views.
- It contain important elements that are scored.
- There is a grid for each box
- Using the BioRAM approach and scoring grid, 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.




More detail in this webinar:
https://www.pathlms.com/aaps/events/479/video_presentations/34513

## 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**<br>**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)<br>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) |

# Scoring in the Grid

- For each question, answer either yes or no/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

# Zero Score

Possible scenarios that could lead to a zero score:

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

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

- 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

➢ Drives timely actions and decisions

# Dealing with “I don’t know…”

- 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 of 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

# Summarising BioRAM

| Principle | Illustrated by |
|---|---|
| **Systems approach** | BioRAM strategic Roadmap |
| Providing drug development strategy | Risk-based approach to identify critical knowledge needs for the system |
| **Patient-centric** and **drug product performance** is aligned with the **patient needs** | Therapy-driven drug delivery framework -- facilitates **drug product optimization** and identifies critical quality attributes for **building in clinical relevance** |
| Transparency for decision-making | **The BioRAM Scoring Grid can promote rapid thinking/deciding and acting together (= Success)** |
| Effective knowledge leveraging | **The BioRAM group determines** and decides on the strategy and **what constitutes "zero"** |