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):

• 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


• 3 AAPS Webinars:
  – https://www.pathlms.com/aaps/events/479
How did the journey start?

- Integration of QbD and Biopharmaceutics

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.
An aspiration / outcome of following a BioRAM / QTPP driven development is that this debate will become redundant as the CQAs and CPPs developed will result in the desired in vivo performance.
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.
The Biopharmaceutics Risk Assessment Roadmap

BioRAM Timeline

Start: “Preclinical”

1. Patient needs and “estimated” dose for the desired clinical effect based on mechanism of action are known (QTPP)
   - Further work is needed to determine clinical effect profile

2. Prior knowledge and preformulation studies: API characteristics and “estimated” dose can lead to selection of a delivery scenario (formulation strategy) (links to Scenario 1–4)
   - Feasibility assessment supports development of the selected scenario / formulation
     - Unlikely “risk” >>> “benefit”

3. Possibly / probably
   - Specific learning studies / methods are designed to develop formulation (links to Scenario 1–4)
     - Unfeasible

4. Feasible
   - Confirmatory studies and methods identified
     - Yes

5. Clear and precise understanding of patient need and performance criteria for chosen formulation approach (QTPP)
   - Further work is needed to determine clinical effect profile

6. Further clinical studies to confirm clinical benefit of drug and product (registration studies)
   - No

End: “Phase 3 / Registration”
What linear product development might have looked like / looks like:

“Integrating Product Development”

Start: “Preclinical”

1. P&B Studies (1-4)
2. Dose Prediction
3. Limited integration of what the patient really needs nor learning from clinical studies
4. End: “Phase 3 / Registration”

Prototyping Studies on Chosen Formulation

Prior knowledge and preformulation studies:

API characteristics and “estimated” dose can lead to selection of a delivery scenario (formulation strategy) (links to Scenario 1-4)

Small Scale Feasibility Studies

Possibly / probably

Unlikely

Yes

“risk”>> “benefit”

Establishment of Manufacturing Process etc

Yes

Further clinical studies
**BioRAM: Making this patient centric**

**“Integrating Product Development”**

1. Prior knowledge and preformulation studies: Yes
   - P&B Studies (1-4)
   - Yes

2. Small Scale Feasibility Studies
   - Possibly / probably
   - Unlikely
   - “risk” >>> “benefit”

3. Prototyping Studies on Chosen Formulation
   - Specific learning studies / methods are designed to develop formulation (Links to Scenario 1-4)

4. Establishment of Manufacturing Process etc
   - Yes

5. So now we have a clinical learning cycle (if required / knowledge is low) so that we can really start to design a product with the patient in mind

6. Further work is Needed to determine Clinical effect profile A

7. Dose Prediction of 1
   - Yes
   - No

8. Supportive Exploratory Work (learning phase) includes modeling and simulation (Links to methods). Focused on clinical understanding on impact of molecule on disease B

9. End: “Phase 3 / Registration” studies

**“Clinical”**
BioRAM: Integrating clinical learning and an iterative approach to QTPP

"Integrating Product Development"

Prior knowledge and preformulation studies: API characteristics and "estimated" dose can lead to selection of a delivery scenario (formulation strategy)(Links to Scenario 1-4)

Possibly / probably Feasibility assessment supports development of the selected scenario / formulation "risk">> "benefit"

Specific learning studies / methods are designed to develop formulation (Links to Scenario 1-4)

Confirmatory Studies and methods identified

Establishment of Manufacturing Process etc

"Clinical"

Further work is Needed to determine Clinical effect profile

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

Supportive Exploratory Work (learning phase) includes modeling and simulation (Links to methods). Focused on clinical understanding on impact of molecule on disease

Further clinical learning studies to further increase understanding of clinical utility of molecule (and formulation approach)

Further work is Needed to determine Clinical effect profile

Clear and precise understanding of patient need and performance criteria for chosen formulation approach (QTPP)

Further clinical studies to confirm clinical benefit of drug and product (registration studies)

Scenarios to provide guidance on selection of patient group for further clinical learning and studies to provide data to support QTPP

Unlikely

Unfeasible

Feasible

Yes

"Integrating Product Development"
BioRAM: Integrating clinical learning and an iterative approach to QTPP

“Integrating Product Development”

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“risk”>> “benefit”

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Possibly / probably

Establishment of Manufacturing Process etc

End: “Phase 3 / Registration”

Clear and precise understanding of patient need and performance criteria for chosen formulation approach (QTPP)

Further clinical learning studies to further increase understanding of clinical utility of molecule (and formulation approach)

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Further clinical studies to confirm clinical benefit of drug and product (registration studies)

Yes

No

Feasible

Unfeasible

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Further work is Needed to determine Clinical effect profile

Further clinical studies to confirm clinical benefit of drug and product (registration studies)

Yes

No
The Biopharmaceutics Risk Assessment Roadmap

Can BioRAM lead to more successful development?

- Two camps

“A good drug declares itself big, early”

“Drug development is an iterative process following learn and confirm cycles”

Images: Shutterstock
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](http://annonc.oxfordjournals.org/content/27/6/1165)
Dhingra, 2016: [http://annonc.oxfordjournals.org/content/27/6/1161](http://annonc.oxfordjournals.org/content/27/6/1161)

Subsequent ODAC 12 April 2016 meeting: [http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm486395.htm](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm486395.htm)
Recent case studies imply that BioRAM thinking wins

**Rociletinib**
- March 2012 Phase 1
- Excellent Response Data
- Breakthrough Status
- FDA request for more info
- Nov 2015 Share price decreases 71%

**Osimeretinib**
- March 2013 Phase 1
- Excellent Response Data
- Breakthrough Status
- Nov 2015 Approved Tagrisso®

T790M + EGFR Lung Cancer

- $2.9 Bn
- + $8 Bn
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
Scenario 2: Multi-phasic delivery

- Methylphenidate tablets, oral (ADHD)
- Zolpidem CR (Insomnia)
- Insulin Pumps
Scenario 3: Delayed therapeutic onset (e.g. Chronotherapy)

Concept that partial AUCs are important

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

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

Box 1: Basic Knowledge
Box 2: Formulation Strategy
Box 3: Feasibility of the Delivery Scenario
Box 4: 2nd Feasibility Assessment
Box 5: 3rd Feasibility Assessment (QTPP)
Box 6: Confirmatory Studies and methods

Optimized drug product to final registration study(ies)

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

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 \( C_{\text{min}} \) the majority of developed antibiotics have a target AUC in fact \( \text{AUC}_{0-24h} : \text{MIC} \) ratio to achieve therapeutic outcome.
    - Where the MIC is minimum inhibitory concentration for the target bacteria strain.
  - Very good translation of target \( \text{AUC}/C_{\text{min}} \) 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
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 preclinical DMPK department (10 mg o.d. to 500 mg t.d.s)
Scenario 4: walking through the roadmap

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

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

Prior knowledge and preformulation studies: API characteristics and “estimated” dose can lead to selection of a delivery scenario (formulation strategy) (Links to Scenario 1-4)

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

Further work is needed to determine clinical effect profile A

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

Scenario 4: walking through the roadmap

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

Further work is needed to determine clinical effect profile

Supportive Exploratory Work (learning phase) includes modeling and simulation (Links to methods). Focused on clinical understanding on impact of molecule on disease

- 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 500mg t.d.s.
- The increased dosing frequency also means that the product will ideally not be subject to a fed/fasted difference
Scenario 4: walking through the roadmap

Prior knowledge and preformulation studies: API characteristics and "estimated" dose can lead to selection of a delivery scenario (formulation strategy)(Links to Scenario 1-4)

Yes

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

Yes

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

Scenario 4: walking through the roadmap

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.
  1. standard approach based on micronized drug
  2. enhanced approach based on amorphous drug
     - low solubility in lipidic excipients
Scenario 4: walking through the roadmap

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
Scenario 4: walking through the roadmap

Fast forward to the end of box 3>>

Enhanced formulation:

- Possibly / probably
- 3 Feasibility assessment supports development of the selected scenario / formulation
- Unlikely "risk">>> "benefit"

Standard Tablet:

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

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

- The latest BioRAM paper formerly describes a scoring grid intended to drive systems thinking and integrate multi-disciplinary views.
- It contains 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.
  - Focuses 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
<table>
<thead>
<tr>
<th>Box 1 (starting point)</th>
<th>QTPP</th>
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<tbody>
<tr>
<td><strong>Patient needs and “estimated” dose for the desired clinical effect based on mechanism of action are known (QTPP)</strong> Unless otherwise noted, score each response as: yes=1, otherwise=0</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1: Targeted Patient Population</th>
<th>Well characterized and “reasonably” homogeneous or if heterogeneous, distinct groups are well characterized</th>
</tr>
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<tbody>
<tr>
<td>2: Indication</td>
<td>Indication and registrational endpoints are precedented (vs. novel), and duration of treatment known (acute or chronic)</td>
</tr>
<tr>
<td>3: Availability of prior knowledge on Drug Substance and / or Drug Product</td>
<td>There is prior knowledge about the DS (and DP, if applicable)</td>
</tr>
<tr>
<td>4: Pharmacology of DS</td>
<td>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</td>
</tr>
<tr>
<td>5: Dose</td>
<td>Dose range can be estimated</td>
</tr>
<tr>
<td>6: Understanding clinical endpoints, disease progression and effect on clinical endpoints</td>
<td>Effect of disease progression on clinical endpoints can be identified</td>
</tr>
<tr>
<td>7: Bioavailability (BA)</td>
<td>Is BA estimable and if it is, estimated BA &gt;5%</td>
</tr>
<tr>
<td>8: Solubility</td>
<td>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</td>
</tr>
<tr>
<td>Note: In subsequent boxes solubility becomes release / dissolution</td>
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</tbody>
</table>
| 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) |
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
- if data exists which indicate that the answer to the question is ‘no’

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

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

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