Framework for setting Clinically relevant Dissolution Specification (CRS)

Approach, Information needed and criteria- suggested by the members of the IQ dissolution WG

Andreas Abend
Merck Research Labs

Contributors

- Andre Hermans, Filippos Kesisoglou, Y. Mao: Merck
- Talia Flanagan: Astra Zeneca
- Michael J. Cohen, Dorys A. Diaz: Pfizer
- Limin Zhang: Bristol Myers Squibb
- Gregory K. Webster: AbbVie
- Yiqing Lin: Biogen
- David A. Hahn: Genentech/Roche
- Carrie A. Coutant: Eli Lilly
- Haiyan Grady: Takeda

MERCK
Be well

Outline

- Case for a CRS framework
  - Benefits
  - Concerns
- Key in-put to the CRS framework
  - Risk management
- CRS Roadmap
  - Approach 1/2
- Timing
- Future opportunities
- Conclusions

MERCK
Be well

Case for a CRS framework-antecedents

- In the past, there was reluctance in performing dedicated in-vivo studies to set specifications
- Historically, dissolution specifications were set based on experience from a small number of pivotal clinical batches and registration stability batches
  - This usually led to rather rigid process controls and little flexibility in supply environment
  - Approval of tight dissolution specification always been a concern for industry
    - Batch discards and the extensive root cause investigation

MERCK
Be well

Case for a CRS framework- recent changes

- Advancements in dissolution method approaches and PBPK modeling significantly contribute to enhance product understanding
  - These tools have been mainly used for development internally
- Recent regulatory stimulus to advance the concept of CRS has been met with both excitement and concern
  - Excitement over potential benefits
  - Concern over highly “prescriptive” requirements/inflexibility, global acceptability and method performance/ execution risks

MERCK
Be well

Anticipated Benefits of a framework:

- Elimination of the ambiguity of the Dissolution specifications
  - This benefits everyone:
    - Confidence in the method from a regulatory perspective (ensuring product release to the patient always meets Quality)
    - Confidence from an industry perspective that the specification will not lead to unnecessarily tight process controls, significantly de-risk potential of OOS results, investigations, and batch discards
- Clarity of the use of CRS across product life-cycle
  - Post-approval changes support by a meaningful test

MERCK
Be well

Perceived concerns over a framework

- Pre-investment/cost
- Regulatory Inflexibility
  - Prescriptive in what methodology to use
    - Biorelevant dissolution in physiologically relevant media (FASSIF/FESSIF) may not be robust in a QC environment due to inconsistent reagent quality
    - Biorelevant or Clinically Relevant dissolution methods using new instruments may not be available globally and method robustness concerns
  - Not aligned with development timelines
  - Misalignment with current guidance
- World-wide regulatory acceptability/different expectations

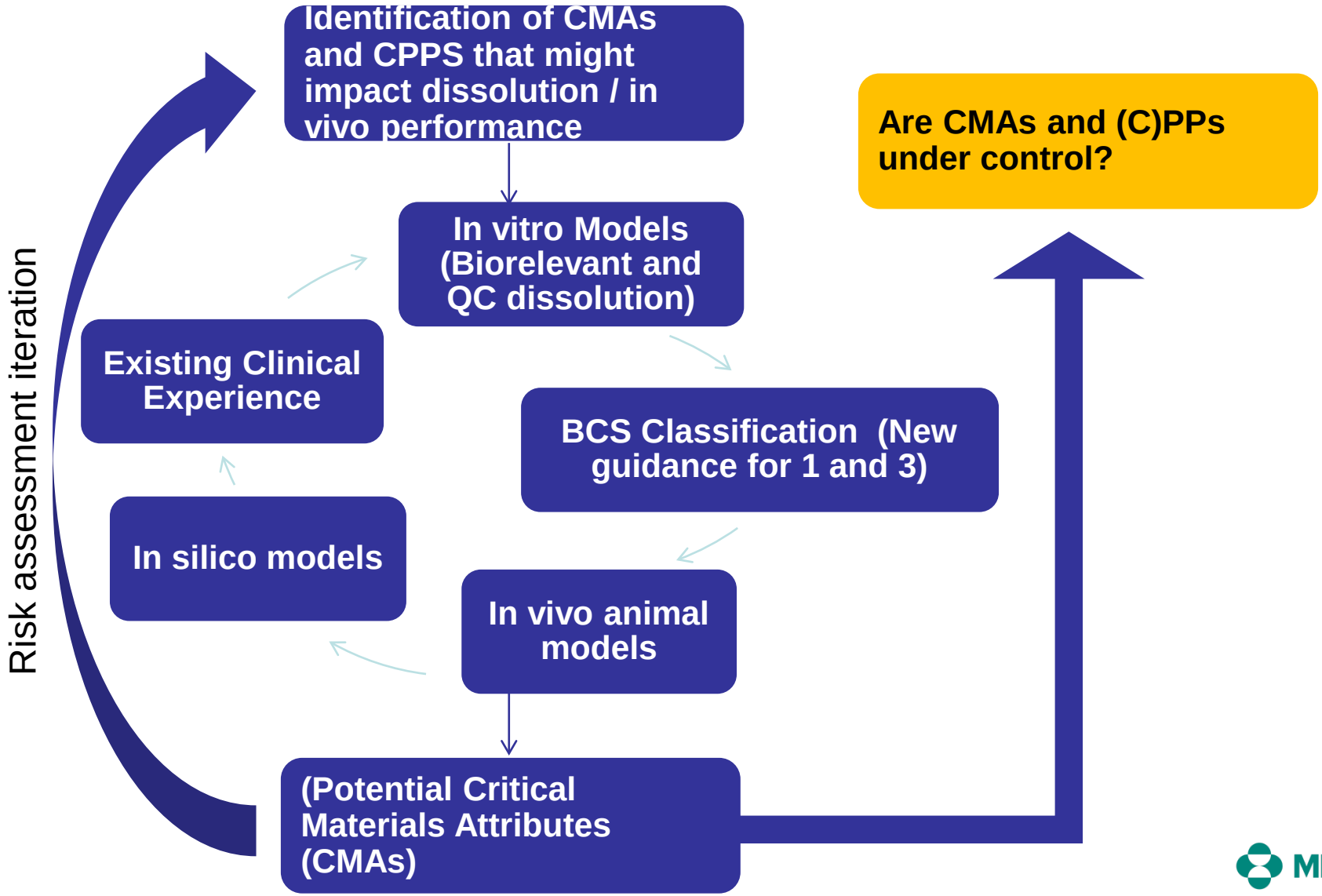
MERCK
Be well

Key in-put: Risk management Strategy

- Despite industry's desire to standardize and develop Drug Products as rational as possible, most Drug Products have different clinical development challenges and CMC risks
- Best practices can be applied to formulation and process development which usually provide input into early product risk assessment
  - Variety of analytical tools to inform and mitigate CMC risks are deployed including various dissolution methodologies even before drug candidates are evaluated in the clinic
- Early/Late stage drug product development follows principles outlined in ICH and equivalent guidances

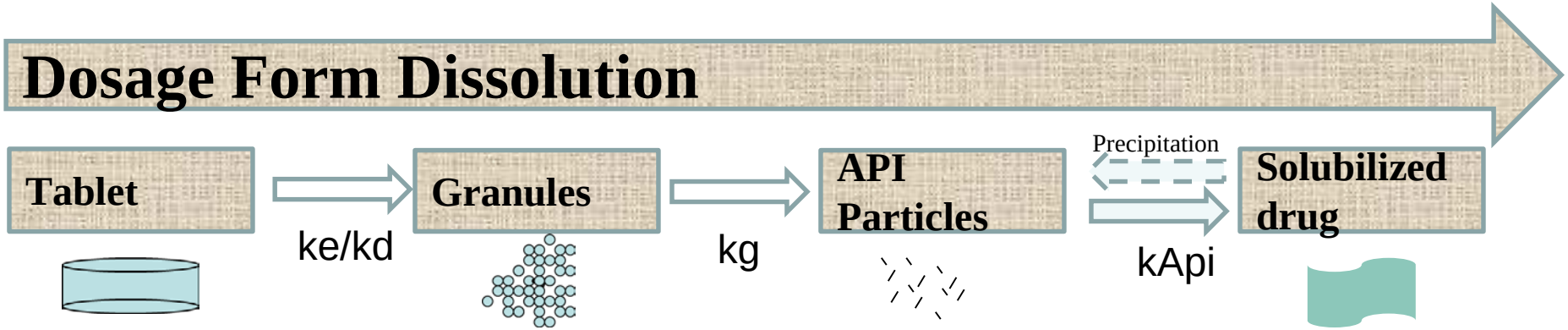
MERCK
Be well

Early Development risk assessment as essential piece for clinically relevant specifications strategy



MERCK
Be well

Key in-put: Mechanistic understanding of DP dissolution

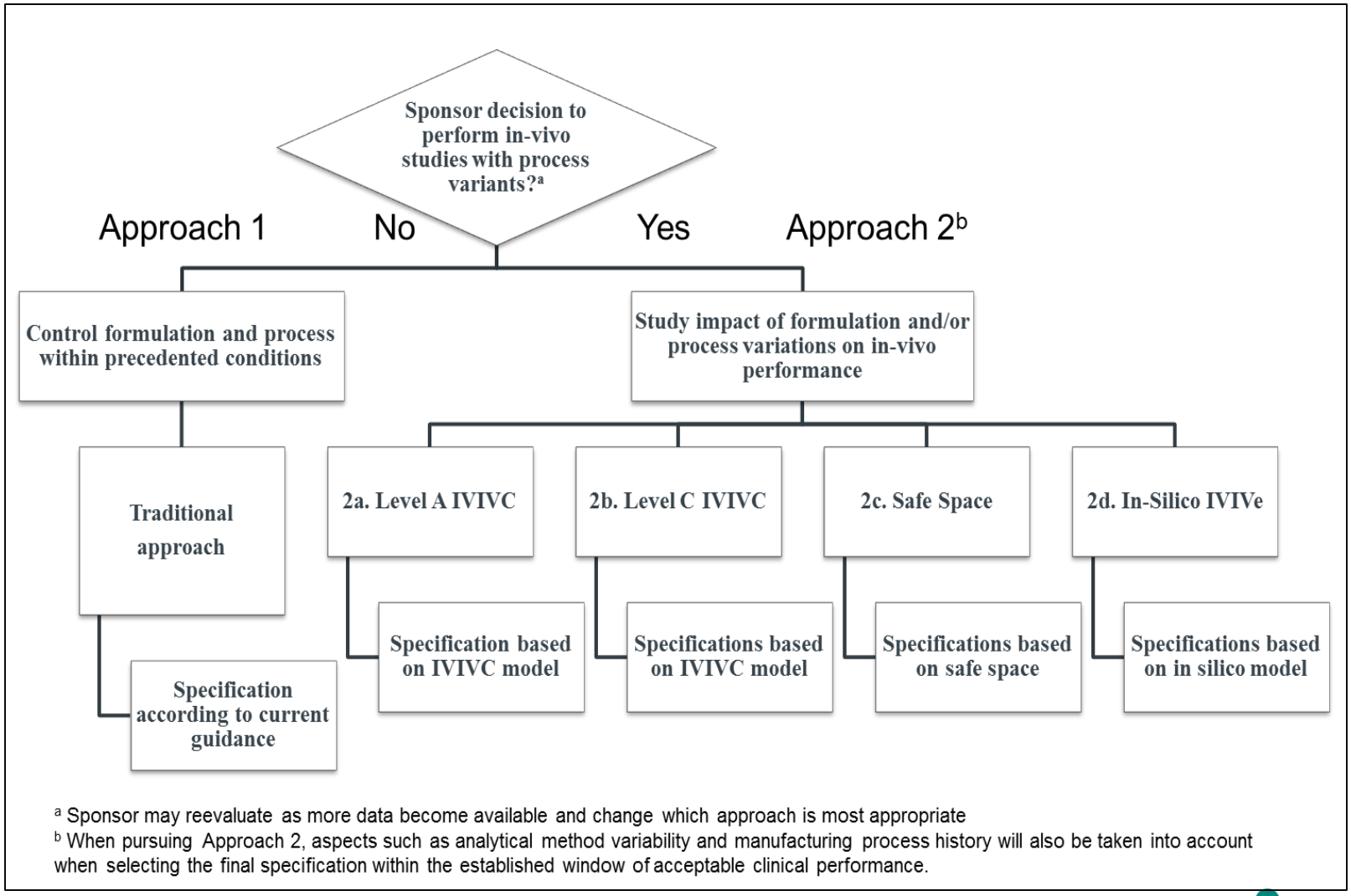


$$k_{dissolution} = k_{erosion\ (disintegration)} + k_{granule\ diss} + k_{APIdiss}$$

- Interrogate the contribution of each step to the overall dissolution rate
- Each rate constant is often impacted by different formulation and process parameters
- Focus on the formulation and process parameters that have the most significant impact on *in-vitro* dissolution rate
- Identify Critical Materials Attributes and (Critical) Process Parameters and develop a sensitive dissolution method (based on prior knowledge, deliberate changes/variations)

MERCK
Be well

CRS Road-Map ties it all Together!



[a] Sponsor may reevaluate as more data become available and change which approach is most appropriate

[b] When pursuing Approach 2, aspects such as analytical method variability and manufacturing process history will also be taken into account when selecting the final specification within the established window of acceptable clinical performance.

MERCK
Be well

Approach 1 (“Historical” approach)

- The biopharmaceutical risks are understood and under control:
  - A discriminating QC method indicative of unacceptable process and formulation variability has been developed
  - This may be achieved by either
    - Using animal PK studies
    - Applying biorelevant dissolution under various conditions
    - Modeling and Simulation including PBPK modeling using animal PK data
- Examples:
  - Drug Products for which *in-vivo* studies to establish wider dissolution specifications is ethically irresponsible
    - Highly potent oncology or CNS drugs
  - Products with very limited demand and tight process controls are acceptable
- BCS 1 and 3 IR products that meet the rapid and very rapidly dissolving criteria respectively across the physiological pH range

MERCK
Be well

Approach 1 - examples

- Januvia™ – BCS 1
  - Direct compression formulation process resulting in fast dissolving tablets
  - Tablet hardness controls disintegration rate
  - PSD impacts API dissolution rate
    - Controlled up-stream and hence disso not performed at product release

- Propriety BCS 4 compound
  - In-licensed and very tight development timelines, impact of API particle size not known
  - Carefully interrogated the dissolution mechanism:
    - Dissolution mainly impacted by granulation process
    - API is friable and the granulation process and granule properties control the tablet dissolution rate and not API PSD

- In both cases dissolution method specifications were justified based on clinical and registration stability data and process controls
  - The method conditions were justified based on mechanistic dissolution understanding

MERCK
Be well

Advantages and Disadvantages of Approach 1

Advantage

- Speed of development
- Avoidance of unnecessary PK studies

Disadvantage

- Residual concern that the method doesn't have adequate sensitivity
- Risk of setting dissolution specification too tight leading to unnecessary tight process controls and potential products discards
- Risk of releasing drug product that is not meeting product quality

Approach 2

- If the Biopharmaceutical and regulatory risks associated with a tight dissolution specification lead to significant number of batch failures, then Approach 2 is highly recommended
  - A tight disso acceptance criteria may be acceptable if the process is not changing, but understanding the risk of failing disso similarity in multi-pH media to justify a moderate formulation or manufacturing change would be a significant incentive for additional PK studies
- By studying formulation and process variants *in-vivo*, a correlation of the disso profiles and PK performance can be achieved
- The most likely outcome for IR products studying reasonable formulation and process variants is a PK safe space (IVIVR)
- Another potential outcome is that only one average PK parameter (AUC) is not impacted, but C_{max} could be leading to an IVIVC level C
- Recent advances in dissolution modeling and PBPK modeling provide additional opportunities to understand the impact of varying dissolution profiles on PK

MERCK
Be well

Approach 2 practical considerations

- Several examples are in the open literature and they follow more or less the proposed CRS road map including:

- Dickinson PA, Lee WW, Stott PW, Townsend AI, Smart JP, Ghahramani P, et al. Clinical relevance of dissolution testing in quality by design. Aaps J. 2008 Jun;10(2):380-90
- Kesisoglou F, Hermans A, Neu C, Yee KL, Palcza J, Miller J. Development of In Vitro-In Vivo Correlation for Amorphous Solid Dispersion Immediate-Release Suvorexant Tablets and Application to Clinically Relevant Dissolution Specifications and In-Process Controls. Journal of pharmaceutical sciences. 2015 Sep;104(9):2913-22.

- These approaches differ when CRS is established
  - AZ: as part of formulation and process understanding/development
  - Merck: as part of process understanding
  - Both strategies lead to CRS!

MERCK
Be well

Advantages and Disadvantages of Approach 2

Advantage

- Dissolution specifications are being set on a variety of formulation/process variants
- Avoidance of unnecessary PK studies in the future
- Depending on level of IVIVC, regulatory flexibility

Disadvantage

- Additional cost/pre-investment
- Potential failure to meet BE bounds may be perceived as unacceptable risk
- Uncertain global regulatory acceptance

MERCK
Be well

When is the “right” time to perform additional PK studies?

Clinical Development Phase	Goal	Common Drug Product Development Challenges	CRS –Opportunity	Potential Return on Investment
Phase 2	Safety, POC- and dose ranging	Selecting the API, formulation and process that have the highest chance to be successfully developed into a product that meets the TPP.	Establishing CRS based on Risk assessment	High: Increased likelihood of success of the product coupled with the flexibility to explore wider ranges of formulation compositions and process variants
Phase 3	Pivotal Clinical and Safety Studies	Finalizing the to be commercialized formulation and process	Studying CRS based final API, formulation and process conditions / controls.	High: high degree of success of the product and advanced understanding of biopharmaceutical risks based on late development risk assessment
Post-product approval	Post market surveillance	Post approval changes	PK studies in support of formulation and process changes.	High: Although the product is already approved, establishing CRS at this stage could provide additional flexibility with post-approval changes.

MERCK
Be well

What are potential future opportunities?

- Up-dates to the 1997 IR disso development guidance and documents like it?
  - Include 2 method option?
  - Eliminate some of the constraints of 80% released in 60 min for BCS 1 and 3 and similar requirements for BCS 2&4 if specifications are set based on Approach 2
- Clarify BCS based Biowaiver and SUPAC (a CRS method developed/approved following Approach 2 should at minimum supersede multimedia disso for certain changes
  - (for safe space)
- A validated Multiple level C IVIVC for IR DPs could be considered equivalent the same value as an IVIVC Level A?

MERCK
Be well

What are additional future opportunities?

- More frequent dialogue? When?
  - The dissolution method development report may be a key document to allow agencies better understand a companies CRS approach and to ensure meaningful specifications that can be applied globally can be achieved

- *With products developed using QbD principles and when a Clinically Relevant In-Process control strategy that links process parameters and in-process controls to PK performance, Real-Time Release for IR products independent of BCS should be acceptable*

MERCK
Be well

Conclusion

- Each DP development situation is unique!
  - The decision what CRS approach (Approach 1 or 2) to pursue should be determined during the biopharm risk assessment and build into QRM
  - Formulation and Process parameters and their variability on the *in-vitro* rate and extend of DP release should be understood
  - This knowledge is instrumental when developing a discriminating dissolution method for Quality Control
    - A method developed under Approach 1 will likely be overly sensitive to process variability – is this risk acceptable?
    - For most BCS 2 and 4 compounds (and “slowly” dissolving BCS 1 and 3 drugs) setting dissolution specifications according to Approach 2 is preferred:
      - This eliminates the ambiguity of the dissolution method
- Consistent acceptance/approval of CRS and Global regulatory alignment will be a key factor for companies to successfully integrate principles outlined in the CRS roadmap in DP development and through-out a a products life-cycle

MERCK
Be well