Utilization of PBBM/PBPK Models for Building a Safe Space and Regulatory Applications in Support of Drug Product Quality

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GastroPlus® User Group Webinar Series

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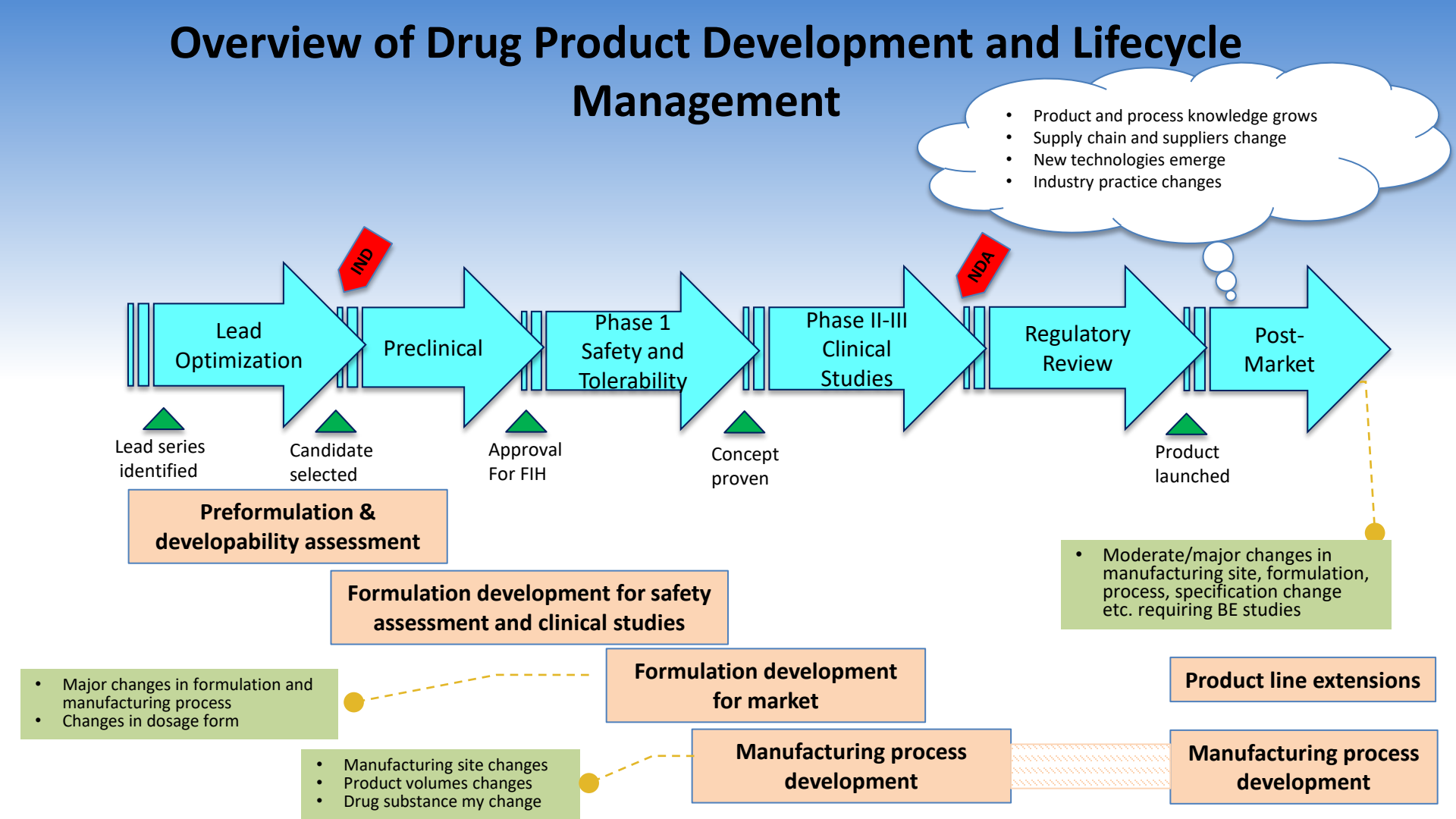
Outline

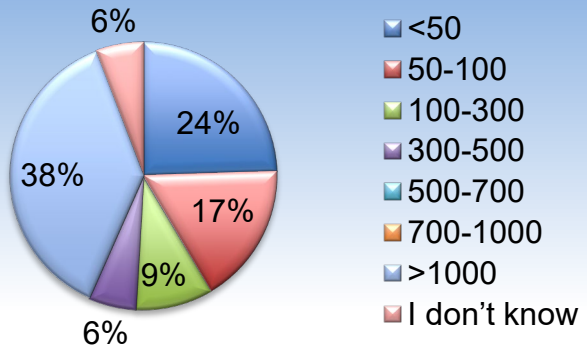
- Overview of Drug Product Development and Lifecycle Management
  - Current Regulatory Framework for Biowaiver Approaches
- The Concept of Safe Space
  - Big Picture: Data Needed to Establish Safe Space
- Approaches to Build Safe Space
  - Conventional IVIVR/IVIVC
  - Exposure-Response Analysis
  - PBBM-based (Mechanistic) IVIVC/IVIVR
- Proposed Workflow for Building a PBBM
  - Building a Safe Space Via Mechanistic IVIVR and IVIVC
- The Role of PBBM-Safe Space in Support of Drug Product Quality
- Case Studies
- Take Home Message

Overview of Drug Product Development and Lifecycle Management

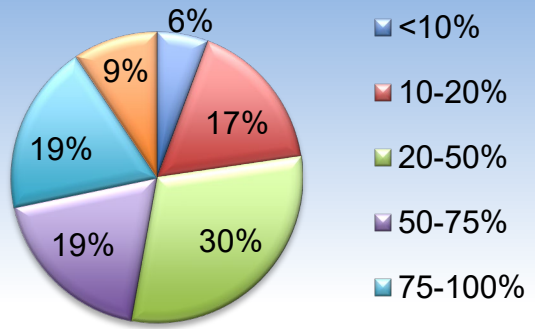


Post-approval Change (PAC) Activities

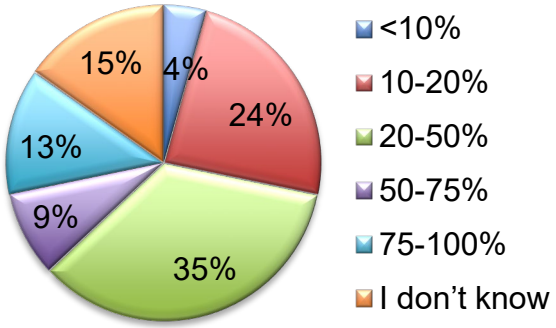
How many PACs, not including submissions, does your company typically process in a given year?



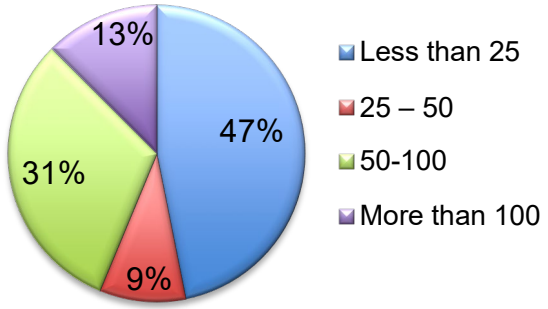
How many PACs require submission to a health authority?



Of those regulatory relevant changes, how many changes were considered moderate to major (i.e. Type 2, PAS, CBE-30)?



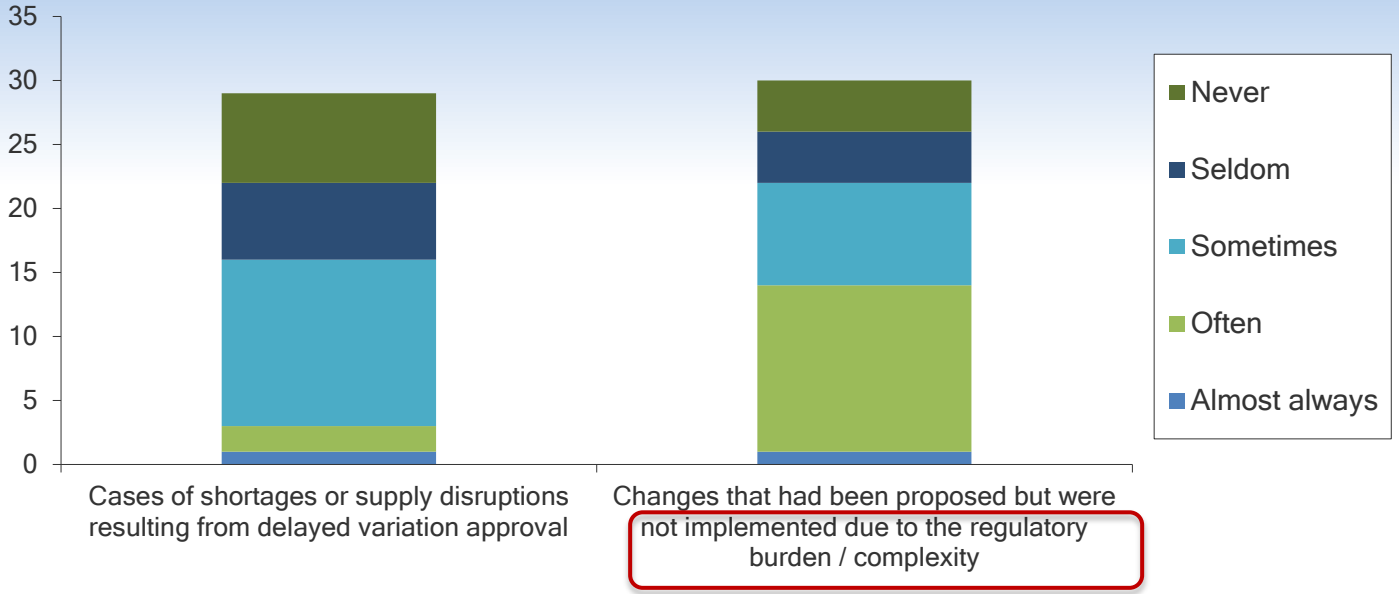
In how many different countries do you typically file changes?



Ref: E. Ramnarine, Post-approval Change and Knowledge Management – Where are We? 2017 PDA Annual Meeting, Anaheim, CA

Post-Approval Change (PAC) Activities – 2017 PDA Survey

How frequently did you experience each of the following situations in the last 5 years:



Ref: E. Ramnarine, Post-approval Change and Knowledge Management – Where are We? 2017 PDA Annual Meeting, Anaheim, CA

Classification of CMC Changes Implemented and Current Regulatory Framework

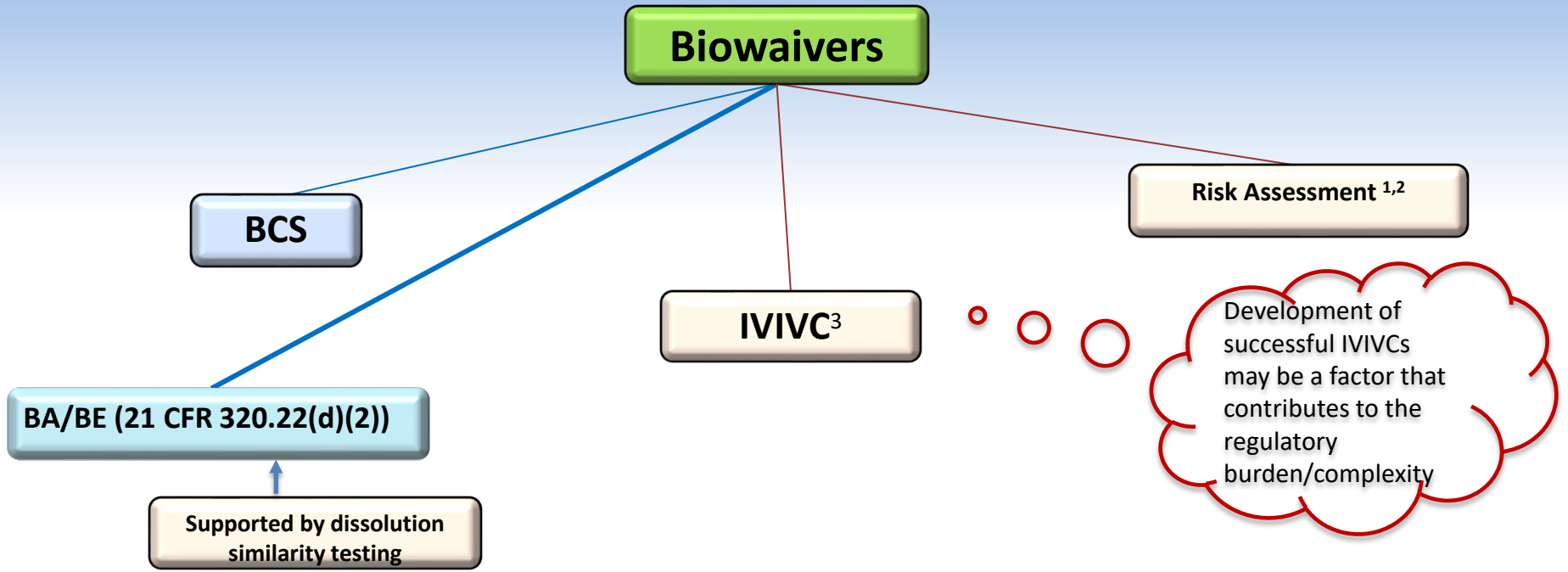
Depends on the ***level of risk*** that the implemented CMC changes could pose to the quality of the product and thus, the patient

During development and post-approval changes

Type of CMC Change[1,2]	Level of Risk	Biopharmaceutics Data Needed to Support the Change	Is Biowaiver Applicable?
Minor	Minimal potential to have an adverse effect	Dissolution data (meets application/ compendial requirements)	No
Moderate	Could have a significant impact	Dissolution Similarity Testing[3] BA/BE data	Biowaiver is applicable
Major	Likely to have a significant impact	Dissolution Similarity Testing BA/BE data	Biowaiver is applicable

1. Guidance for industry: changes to an approved NDA or ANDA; CDER, 2004
2. ICH Q12: Technical and regulatory considerations for pharmaceutical product lifecycle management
3. It is assumed that the dissolution specifications (method and acceptance criterion) have been shown to be discriminating

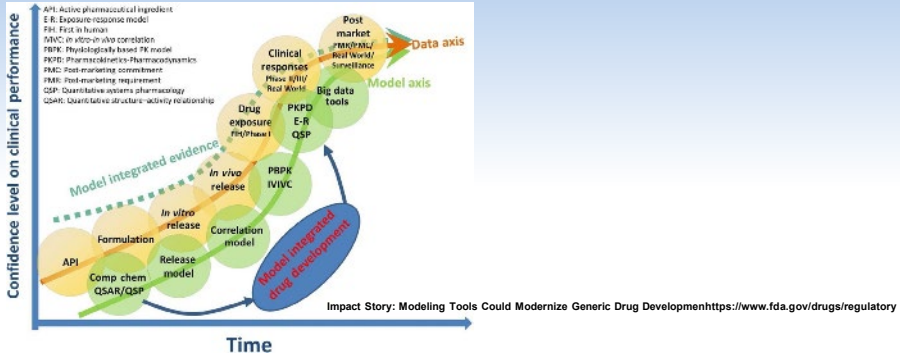
Current Regulatory Framework for Biowaiver Approaches: Solid Oral Dosage Forms



1. P. Delvadia, S. Suarez-Sharp, J. Duan, and P. Seo. Risk Based Approach for Biowaiver Application to Immediate Release (IR) Solid Oral Dosage Forms. 2016 AAPS meeting, poster number 37W0300
2. S Suarez-Sharp, A. Abend, et al. In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality: What, How, When—Workshop Summary Report. AAPS J 22, 74 (2020)
3. S Suarez-Sharp, M. Li, et. Al. Regulatory Experience in IVIVC in New Drug Applications.. *AAPS J.* 2016;18(6):1379-1390.

How can this Regulatory Burden/Complexity be Diminished?

- By implementation of QbD (ICH *Q8 R2)*
- By implementing tools that facilitate the establishment of an in vitro in vivo link[1]
- By expanding the regulatory framework beyond IVIVC leveraging prior knowledge and data generated during drug product development



Impact Story: Modeling Tools Could Modernize Generic Drug Developmenthttps://www.fda.gov/drugs/regulatory

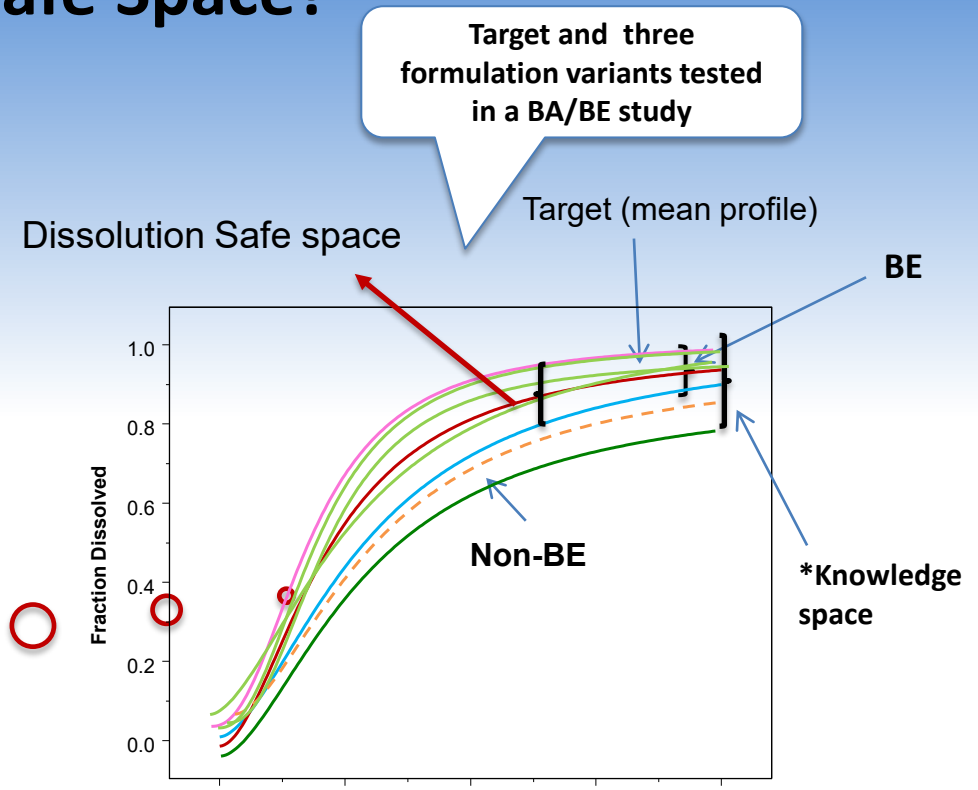
The concept of safe space/PBBM[2]

1. Heimbach, T., Suarez-Sharp, S., Kakhi, M. *et al.* Dissolution and Translational Modeling Strategies Toward Establishing an *In Vitro-In Vivo* Link—a Workshop Summary Report. *AAPS J* **21,** 29 (2019).
2. Pepin XJH, Parrott N, Dressman J, Delvadia P, et al. Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls: A Workshop Summary Report. J Pharm Sci. (2020).

What is Safe Space?

- Boundaries defined by dissolution profiles within which drug product variants **(around the target)** are anticipated to be bioequivalent to one another[1,2]

How can one expand this safe space within an area of confidence without additional BE studies?



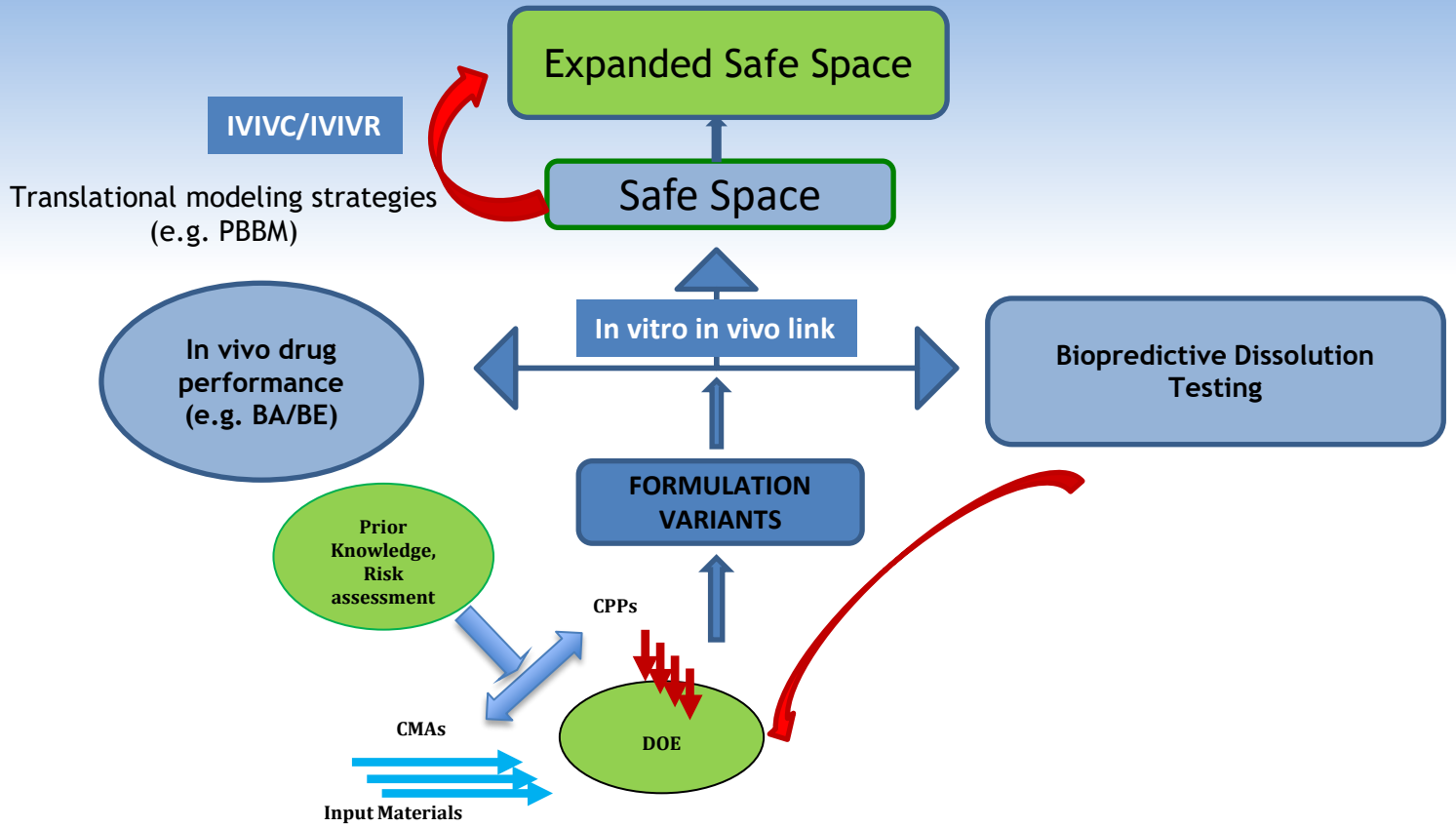
*Knowledge space (KS)= Constitutes the range/set of ***observed*** in vitro and corresponding in vivo data used in building the space

1. Andreas Abend, T. Heimbach, et al. Dissolution and Translational Modeling Strategies Enabling Patient-Centric Drug Product Development: the M- CERSI Workshop Summary Report. AAPS Journal (2018) 20:60.
2. Y. Zhao. FDA expectations in building a safe space to gain regulatory flexibility based on PBBM. 2019 REdI/M-CERSI Workshop. College Park, MD https://cersi.umd.edu/sites/cersi.umd.edu/files/Day%203-1%20Zhao%20Suarez%20LM.pdf

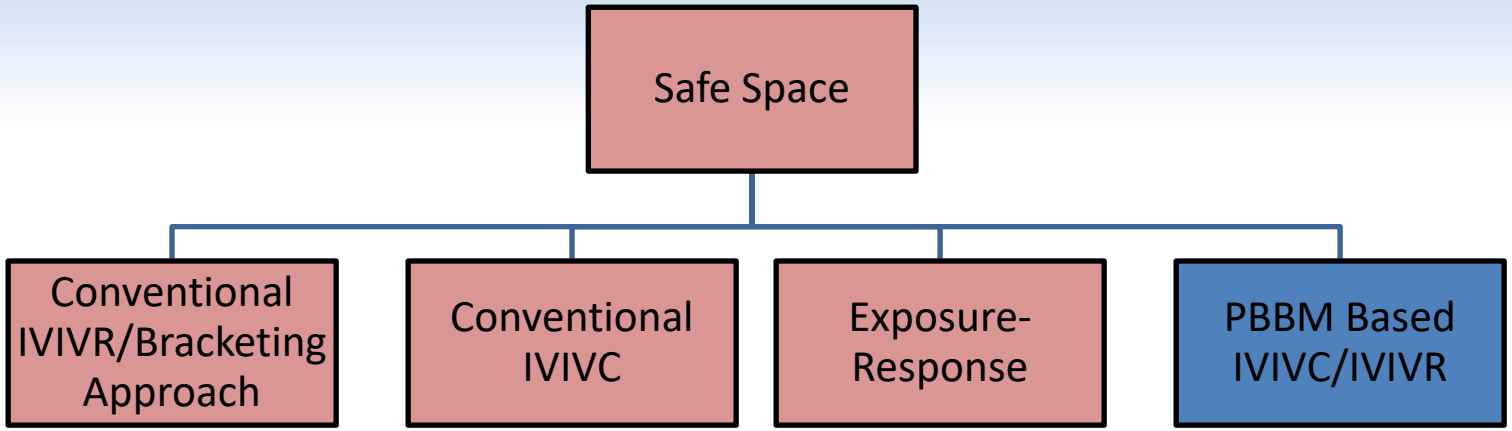
Benefits of Establishing a Safe Space

- Achieve patient centric drug product development
- Achieve enhanced control strategy
- Gain regulatory flexibility

What Data are Needed to Establish a Dissolution Safe Space?

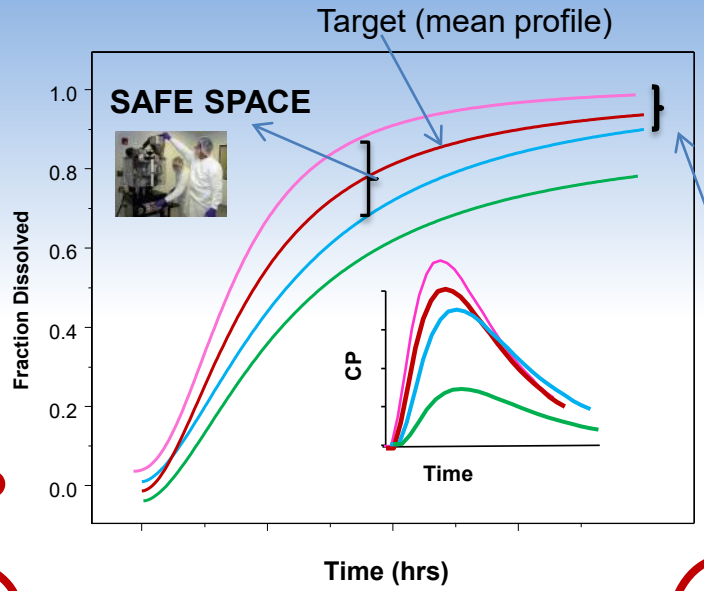


Approaches to Establish Dissolution Safe Space



Safe Space via Conventional IVIVR/Bracketing Approach

- **IVIVR:** Process for determining the link between CMAs/CPPs/CFVs and a response derived from an in vitro dissolution and its in vivo impact (e.g. PK profile)



Bracketing approach

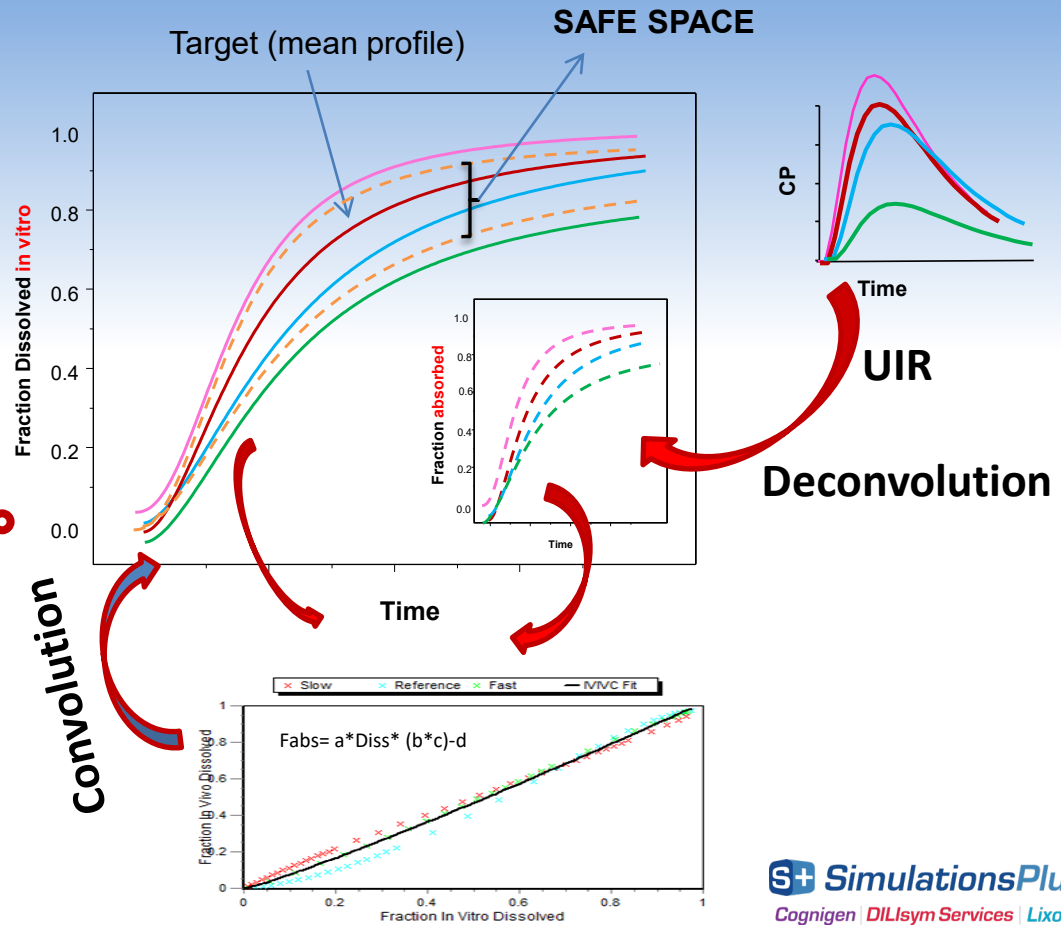
Evaluation of several formulation variants is critical to determine the sensitivity of the dissolution method **within this range**

Bracketing approach empowers IVIVR to have regulatory application

Safe Space via Conventional IVIVC

- **IVIVC:** Process for determining a correlation (i.e., mathematical equation) between a response derived from an in vitro dissolution and its in vivo impact (e.g. absorption rate) ***using conventional modeling approaches (e.g. numeric deconvolution)***

SAFE SPACE: For non-NTI drugs, the difference in predicted means of Cmax and AUC from the upper and lower release limits should be no more than 20%



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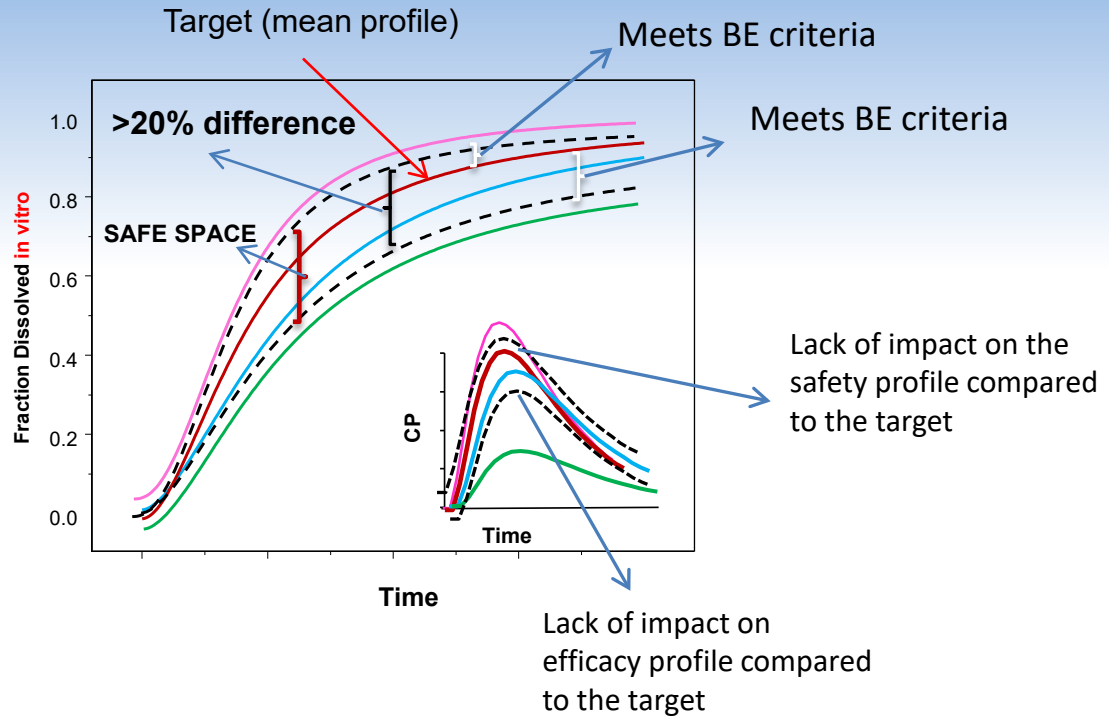
Safe Space via Exposure-Response (ER) Analysis

- **Safe Space/ER Analysis:** Process of relying on ER data to perform risk analysis on extrapolating outside the dissolution safe space



What is PBBM?

- PBBM[1,2] has been created to emphasize the role of biopharmaceutics modeling combined with PBPK modeling to facilitate the establishment of the essential in vitro in vivo link needed to:
  - Enhance drug product understanding
  - Ensure patient centric drug product quality
  - Gain regulatory flexibility (e.g. waive major CMC changes)

- PBBM vs. PBPK commonalities such as:
  - Steps/data in building the disposition and absorption models and its verification using the appropriate data

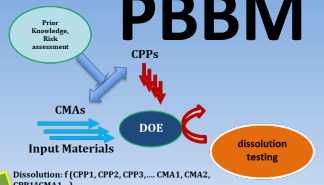
- PBBM vs. PBPK differences:
  - PBBM provides a mechanistic understating of in vivo drug release with emphasis on the effect of formulation, manufacturing changes
    - In PBPK modeling drug absorption rate constant is sometimes fixed or characterized based on some general factors
  - In PBBM (for regulatory decision making), IVIVR or IVIVC needs to be developed /validated
    - Dissolution data from formulation variants around the target must be an input into the model

1. Heimbach, T., Suarez-Sharp, S., Kakhi, M. *et al.* Dissolution and Translational Modeling Strategies Toward Establishing an *In Vitro-In Vivo* Link—a Workshop Summary Report. *AAPS J* **21,** 29 (2019).
2. Pepin XJH, Parrott N, Dressman J, Delvadia P, et al. Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls: A Workshop Summary Report. J Pharm Sci. (2020).

Proposed General Workflow for Building a PBBM

At least three formulation variants with different release rate to ensure a robust model and expanded regulatory application

In the absence of demonstrated biopredictive method, it is important to generate dissolution data using different dissolution methods that are discriminating



Verified PBPK baseline model

PBBM

Data Collection

In vitro data:
- Dissolution data from formulation variants (at least two, one of which includes target)
- Other (biopredictive dissolution testing)

In vivo data:
Cp-time profiles of the corresponding formulation variants (rank order relationship)

Data Integration

Baseline PBBM Development
Using target profile

Development of IVIVC/IVIVR

Model validation

Safe space establishment

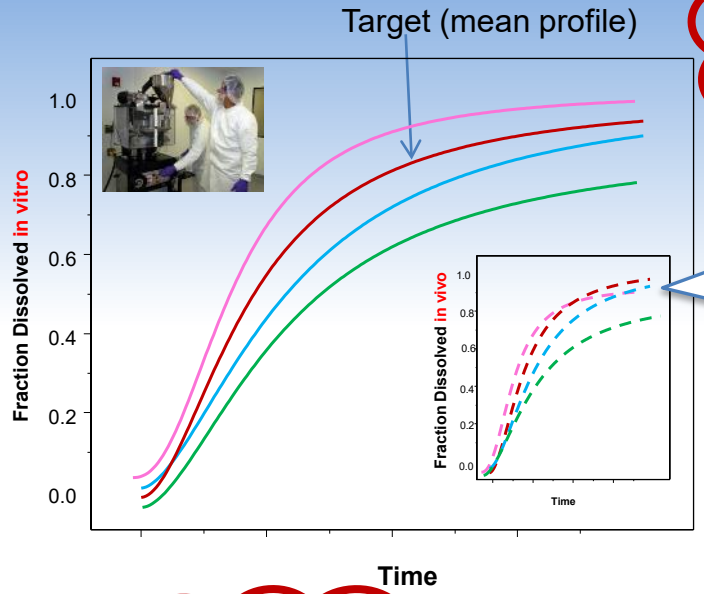
Approaches to input CQA (e.g., dissolution)*

1. Direct input
2. Empirical functions to fit dissolution data
3. API PSD with single correction scalar to fit dissolution data
4. Composite parameter (e.g. Z-factor) to fit dissolution data
5. Fit dissolution data to "effective" PSD
6. Other

*Filippos Kesisoglou (2019). Approaches for entering dissolution data into an absorption model. M-CERSI/REDi workshop https://cersi.umd.edu/sites/cersi.umd.edu/files/Day%202-6%20Filippos%20Kesisoglou.pdf

What is PBBM (Mechanistic) IVIVR?

- **PBBM/IVIVR:** Process for determining the link between CMAs/CPPs/CFVs and a response derived from an in vitro dissolution and its in vivo impact (e.g. ***in vivo dissolution/release profile***) using PBBM
  - To have regulatory application, this response should be a surface response derived from evaluating several formulation variants around the target profile



IVIVR is not defined by a mathematical equation relating in vitro/in vivo

As part of drug product development, relying on this initial in vitro in vivo link is warranted given the relatively smaller amount data available

Critical to determine the ***predictive*** ability of the dissolution method ***within this range***

Proposed Workflow for Building a Safe Space Via Mechanistic IVIVR

Verified PBPK baseline model

PBBM

Data Collection

In vitro data:
- Dissolution data from formulation variants (at least two, one of which includes target)

In vivo data:
Cp-time profiles of the corresponding formulation variants (rank order relationship)

Data Integration

Baseline PBBM Development
Using target profile

Examples of approaches to input CQA (e.g., dissolution)*

1. Direct input
2. Empirical functions to fit dissolution data
3. API PSD with single correction scalar to fit dissolution data
4. Composite parameter (e.g. Z-factor) to fit dissolution data
5. Fit dissolution data to "effective" PSD

Input dissolution from each formulation variant

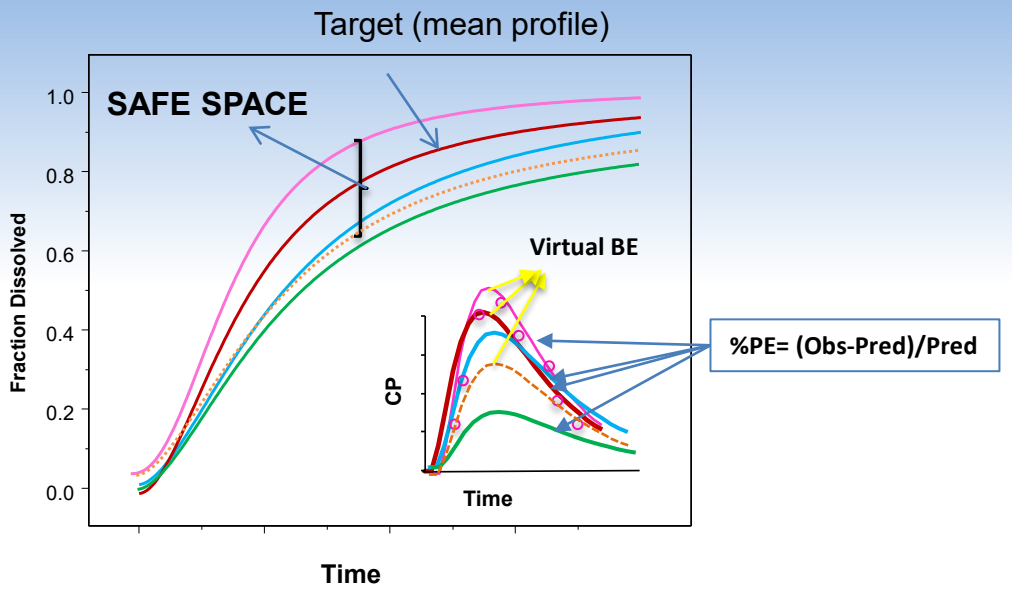
Predict Cp time profile for each formulation variant

Determine %PE for each formulation variant

Select those profiles that meet the %PE criterion

IVIVR validation

Using Virtual BE, establish a safe space within the knowledge space (extrapolation not appropriate)



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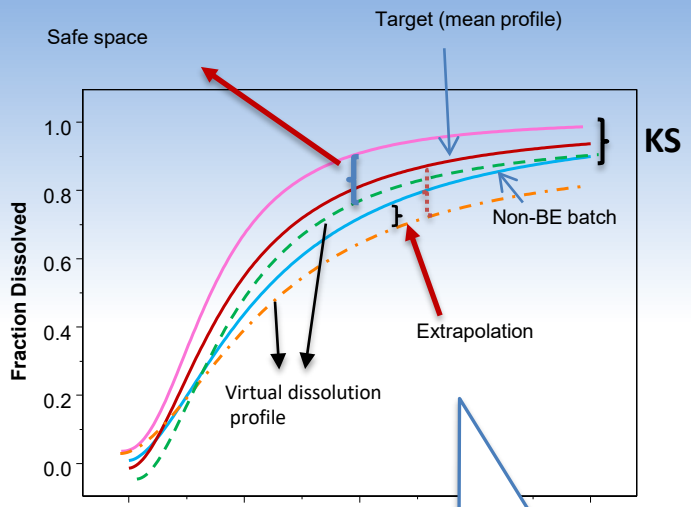
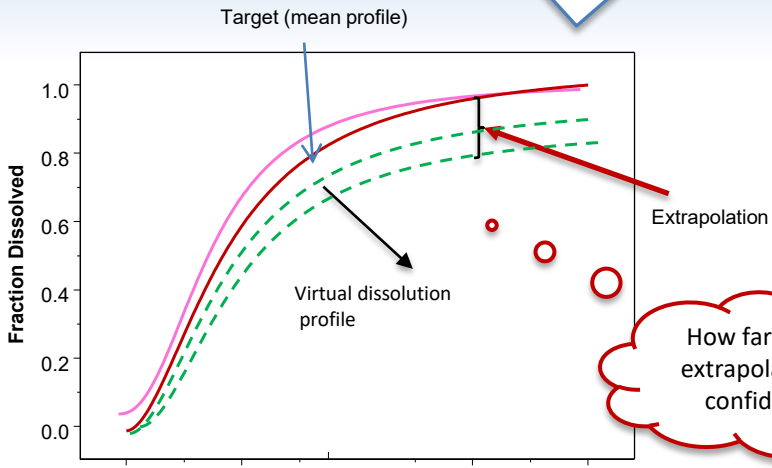
Extrapolation Outside Knowledge Space



Target and two formulation variants tested in a BA/BE study

For regulatory decision making, extrapolation outside KS is not encouraged specially for extended release dosage forms

Extrapolation outside the KS may be justified for very low risk products e.g., justification of lack of clinical impact of BCS class I drug product which failed the dissolution criterion requirements/same excipients.



How far can we extrapolate with confidence?

*Knowledge space (KS)= Constitutes the range/set of ***observed*** in vitro and corresponding in vivo data used in building the space

Proposed Workflow for Building a Safe Space Via PBBM-IVIVC

Verified PBPK baseline model

PBBM

Data Collection

In vitro data:
- Dissolution data from formulation variants (at least three, one of which includes target)

In vivo data:
Cp-time profiles of the corresponding formulation variants (rank order relationship)

Data Integration

Fit a Weibull function to the *in vitro* dissolution

Obtain in vivo release profiles using mechanistic absorption model

Fit the *in vivo* release profile (using the Weibull function) for each formulation

Obtain correlation between in vitro and in vivo release profiles

IVIVC validation

Perform internal predictability

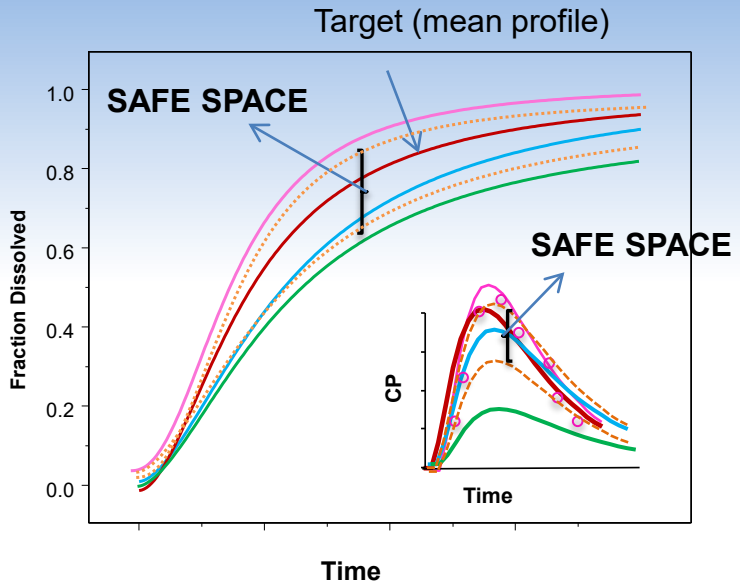
Perform external predictability

Input dissolution profiles of the desired space range

Using correlation, predict Cp time profiles

VBE (population simulator)

Establish a safe space within the knowledge space



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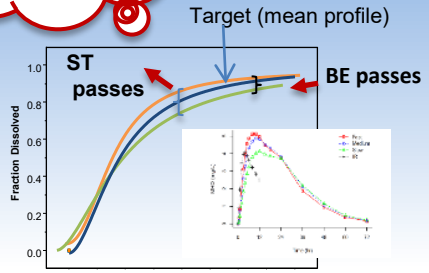
Likelihood for Building a Robust Dissolution Safe Space via PBBM

PBBM is likely to define a very narrow safe space and unlikely to expand the ranges of safe space



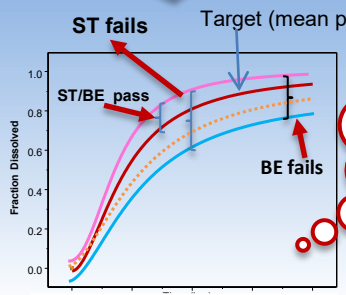
ST passes/BE passes

Dissolution method not sensitive to changes in CMAs/CPPs within tested ranges

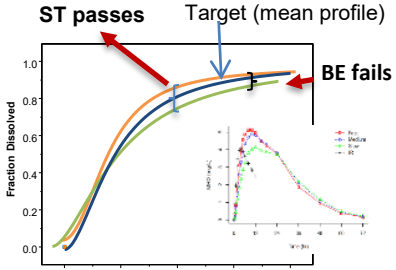
ST passes/BE passes and ST fails/BE fails

(rank order relationship)

Target and two formulation variants tested in a BA/BE study



PBBM is likely to define/expand the ranges of safe space

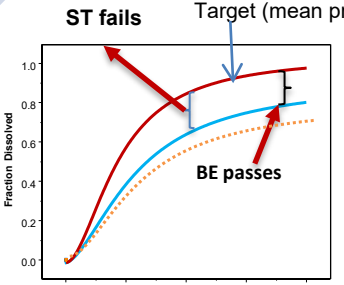


ST passes/BE fails

Dissolution method is under discriminating Within evaluated ranges

ST fails/BE passes

Dissolution method is over discriminating within evaluated ranges



PBBM is likely to define but may not expand the ranges of safe space

Target and formulation variant tested in a BA/BE study

Target and two formulation variants tested in a BA/BE study

It is unlikely to build a safe space ***with in vitro dissolution as an input***

Lack of similarity in in vitro dissolution does not indicate lack of BE within given ranges

ST= Dissolution similarity testing

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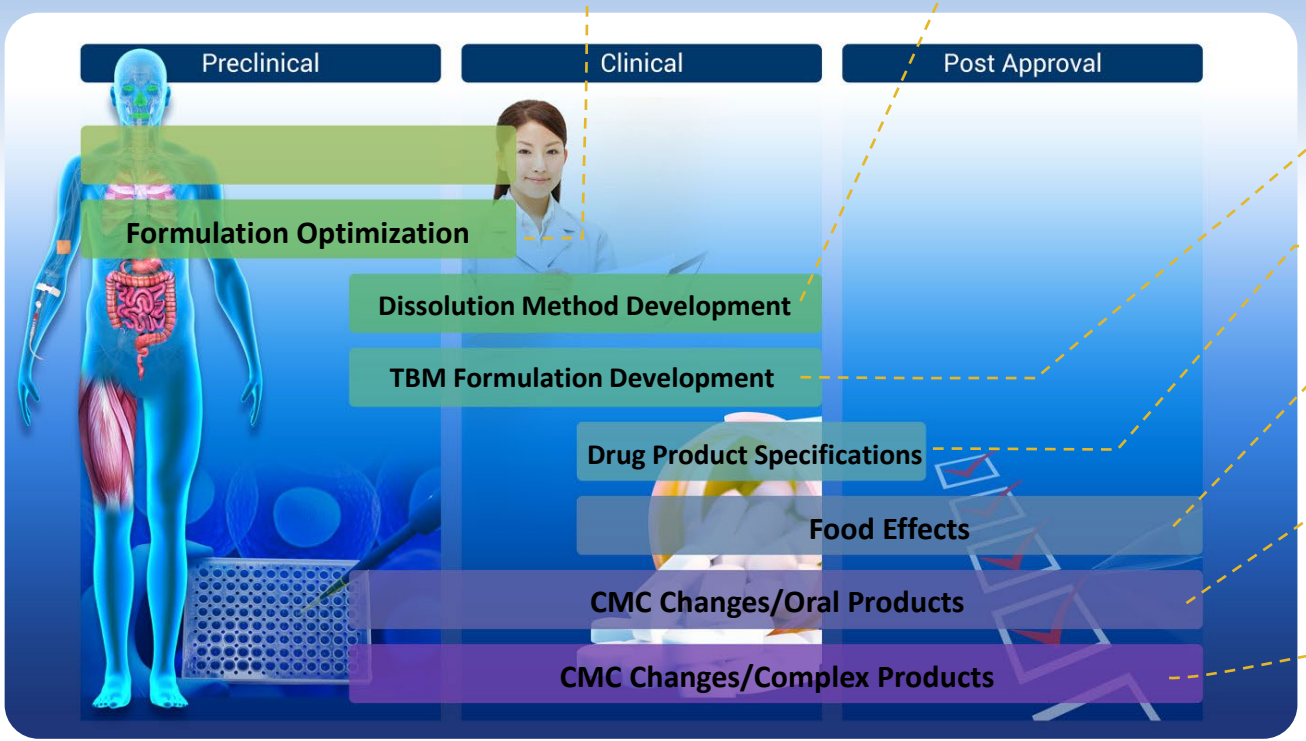
Role of PBBM/Safe Space in Support of Drug Product Quality



Support of optimal formulation selection based on pre-clinical/clinical and biorelevant dissolution data (PBBM-extrapolation beyond KS)

Guide the development of biopredictive dissolution methods (PBBM-IVIVR)

Guide study designs and biowaiver plans (PBBM-IVIVR/C)

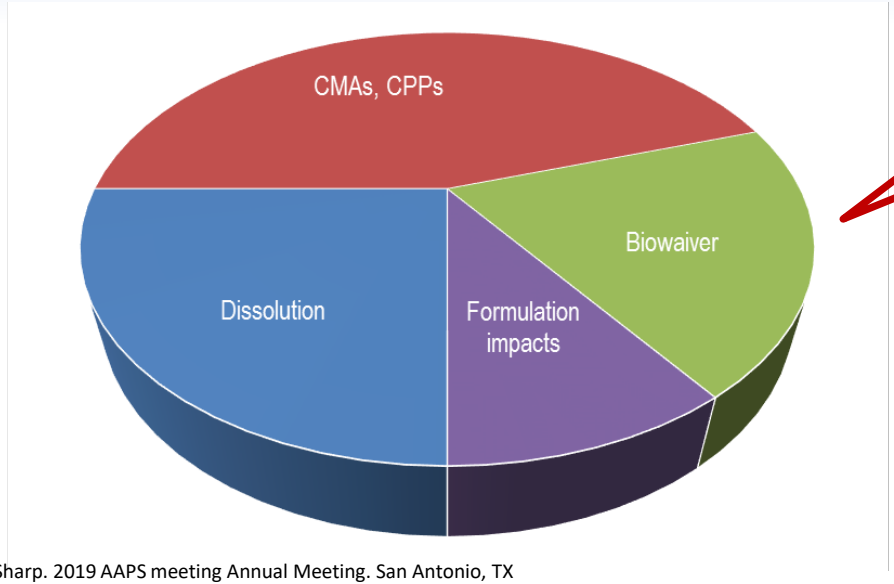
Establishment of clinically relevant drug product specifications (safe space)

Guide study designs and biowaiver plans (PBBM)

Guide the design of BE studies and biowaiver plans for oral route of administration (safe space)

Guide the design of BE studies and biowaiver plan for non-oral route of administration (safe space)

FDA Experience in PBBM in Support of Drug Product Quality (2008-2018)

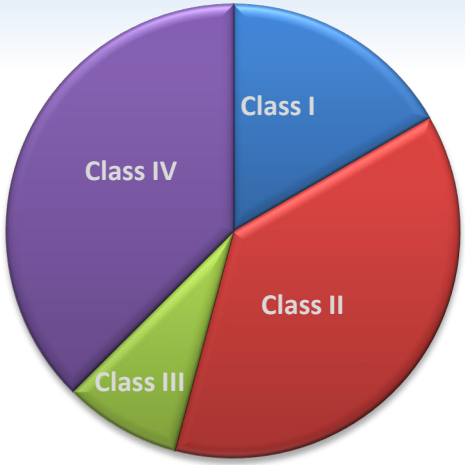


A total of 29 submissions included in INDs and NDAs from 2008-2018 (about 22 submitted from 2015- 2018) (three of which attempted IVIVC)

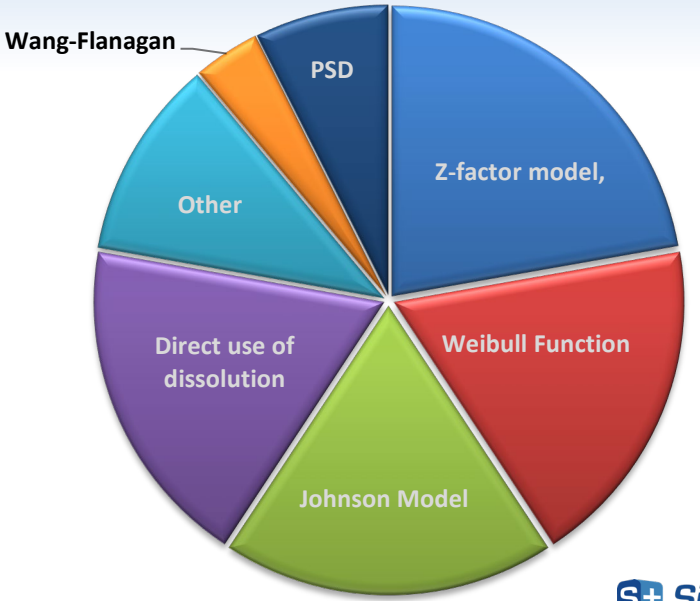
S. Suarez-Sharp. 2019 AAPS meeting Annual Meeting. San Antonio, TX

FDA Experience in PBBM in Support of Drug Product Quality, Cont.

By BCS Class Type



By Dissolution Model



S. Suarez-Sharp. 2019 AAPS meeting Annual Meeting. San Antonio, TX

CASE STUDY 1

Establishment of a Safe Space via PBBM-IVIVR to Justify Wider Dissolution Acceptance Criterion and PSD ranges of Drug Product Y

(IR formulation, BCS Class II)

Summary of Model Development and Validation

MODEL DEVELOPMENT

- Physicochemical properties of drug product Y
- Information on Metabolic pathways and rate
- IV PK Data : Used to build PBPK disposition model
- Oral PK Data from several doses: Used to develop PBPK absorption model
- PBBM model: Composite parameter (e.g. Z-factor) to fit dissolution data of target profile, and four formulation variants one of which was non-BE to the target

IVIVR VALIDATION

Individual % PE values were less than 15% in all cases

MODEL APPLICATION

1. **Dissolution safe space:** Virtual BE of proposed lower bound vs. target
2. **PSD safe space:** predictions performed using dissolution profiles representing the proposed particle size distribution limits. Virtual BE for lower/upper bounds of D50 vs. target.

CASE STUDY 2

Attempts to building a Safe Space via PBBM-IVIVR to justify dosage form change of Drug Product Z (IR formulation, BCS class IV)

Summary of Safe Space Building Strategy

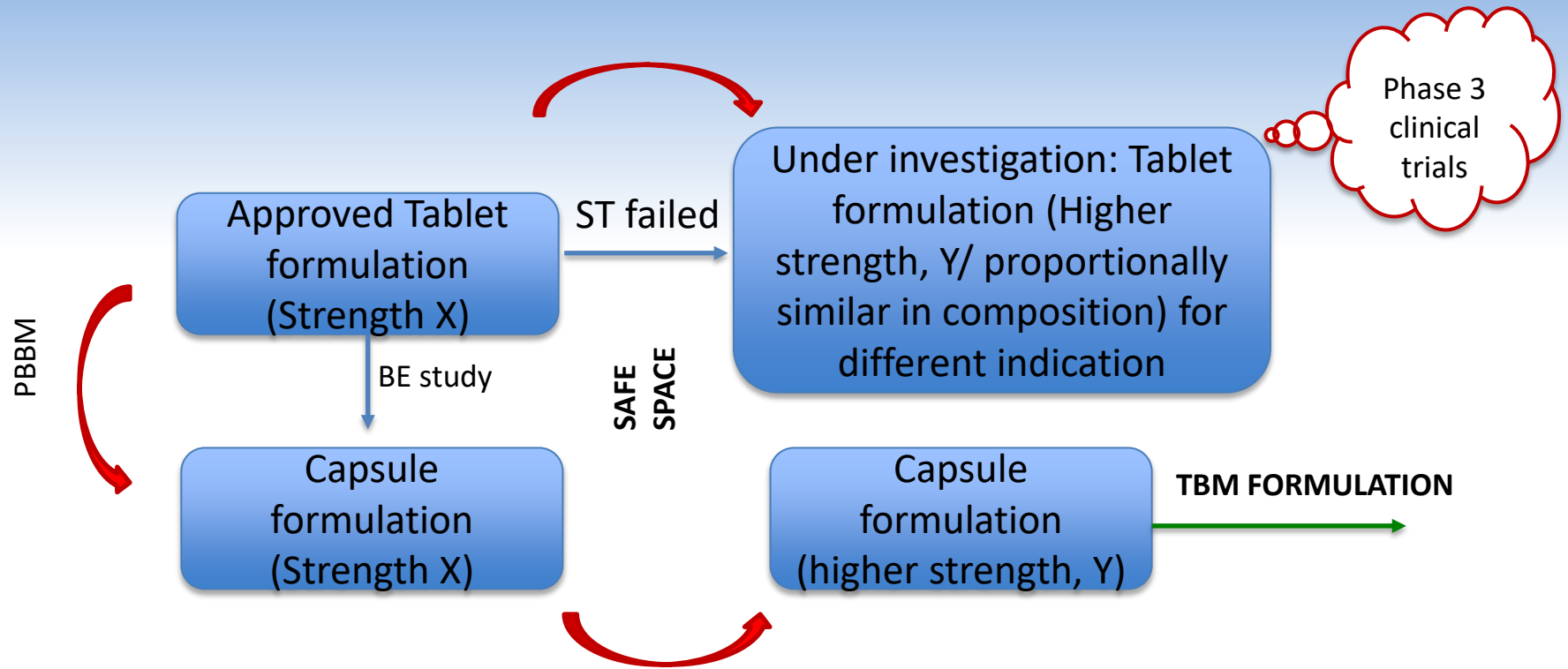
MODEL DEVELOPMENT /VALIDATION

- PBPK model originally approved for the tablet formulation at lower strength

MODEL APPLICATION

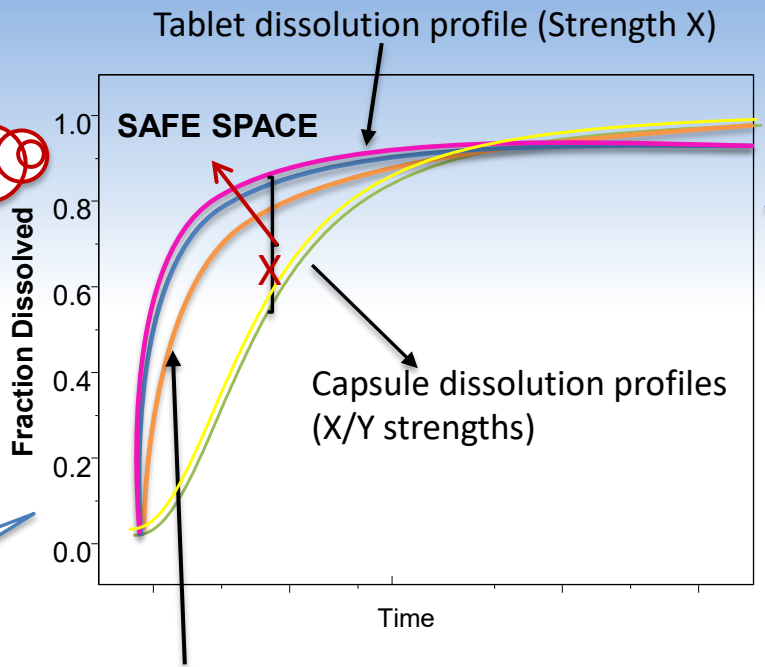
- Applicant proposed to use/expand the approved model to support the approval of a capsule formulation at a higher strength
- The proposal was to establish safe space using dissolution data from the tablet and capsule formulations

Big Picture: Drug Product Z Development Strategy



Attempts to Establish a Safe Space

Is the establishment of a dissolution safe space between dosage forms appropriate?



The target tablet and capsule formulations were shown to be **BE** in a crossover PK study at lower strength

Similarity testing between tablet strengths failed criteria requirements

Common Challenges in Building PBBM/Safe Space

Challenge	Impact	Potential solution
Lack of IV PK data to accurately characterize the systemic disposition	All products, specially drugs with complex metabolic pathways/transport	• Rely of in vitro (e.g. metabolic pathway/transporter information) and preclinical PK across species to characterize critical PK parameters (Vd, Cl) and create an IVIVE*; • Information for different doses (when saturable transport/metabolism present) • Simultaneous oral/IV microdose
Differential characterization of in vivo release/absorption profile along GI tract	Extended release dosage forms	• Rely on preclinical/human colonic infusion data • Detail characterization of metabolic pathways /transporter along of GI tract
Lack of biopredictive dissolution profiles	ER dosage forms; BCS class II/IV IR drug products	• Generate dissolution data in different media/methods (including biorelevant methods) for target and formulation variants
Lack of sufficient formulation variants (with in vitro/in vivo data) around target profile	Robustness of safe space/regulatory application	• At least one formulation variant (preferably non-BE) around the target with dissolution data generated via biopredictive dissolution methods

* Miller, N.A., *et al.* . *Clin Pharmacokinet* **58,** 727–746 (2019). https://doi.org/10.1007/s40262-019-00741-9

Take Home Message

- PBBM expands beyond PBPK modeling and must have dissolution profiles as an input (preferably from biopredictive methods) from several formulation variants to support drug product quality regulatory questions

- To ensure its predictive ability, a PBBM needs to be verified and validated using data fit for purpose

- Safe space via PBBM approach has the potential to expand the regulatory flexibility delineated under several regulatory frameworks such as BCS, IVIVC, similarity testing
  - Through the implementation of VBE, a safe space can be defined to facilitate regulatory decision making

Take Home Message, cont.

- Since Safe Space pillars are IVIVC and IVIVR, it is then "governed' by IVIVC/IVIVR principles
  - For regulatory decision making, at least two release rates with corresponding Cp-time profiles are needed to establish a Safe Space
    - For Safe Space-based IVIVRs, non-BE data is highly desirable
    - To support high risk CMC changes, at least three formulation variants should be used in the construction of the safe space
  - From regulatory perspective, extrapolation outside the knowledge space for high risk dosage forms e.g. ER formulations/BCS class II/IV compounds is not recommended
    - During drug product development, the need for extrapolation is warranted
- Safe space is dosage form specific and should be built using formulation variants around the target test product
- For generic drug products, in addition of building it around the target test formulation, the RLD should also be included
- Safe Space is a steppingstone towards patient centric drug product quality

Future Directions

Further work is needed to answer the following questions:

1. Whether and for which kind of drug products/dosage forms extrapolation outside the knowledge space is appropriate
2. Whether the acceptance criteria for IVIVR/IVIVC validation should be expanded beyond current criteria as per published IVIVC guidance
3. The need to create safe space that is permeability-based to expand the BCS class 3 regulatory framework

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