



Establishing Clinically Relevant Specifications During Product Life Cycle: Case Studies

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Disclosure

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Outline

Quality vs Clinical Relevance

Examples of Clinically Irrelevant specification

Steps to Minimize Clinically Irrelevant Specifications

Setting Dissolution Specifications for IR class 1 and 3

Setting Dissolution Specifications for IR class 2 and 4

Setting Dissolution Specifications for ER Drug Products

Case Study

Summary and Conclusions

Is Quality Synonymous With Clinically Relevant?

Depends on who you talk to and how the specifications are chosen

If product always passes the specification then it is consistent and of high quality and therefore should be clinically relevant

If specifications are set based on in vitro considerations only clinical relevance is not always assured

Quality should be decided based on clinical considerations where only lots with consistent and reproducible clinical benefit are only released on the market

Clinically relevant specifications should not reject lots with acceptable safety and efficacy profiles

Example of Non Clinically Relevant Specifications

Levothyroxine is considered to be a narrow therapeutic window drug yet the USP monograph dissolution specifications does not ensure consistent release characteristics from lot to lot and from product to product

Method: 500 ml of 0.01 N HCl with 0.2 Na Lauryl Sulfate using USP apparatus 2 at 50 rpm

- Q value of 70 % in 45 minutes
- Q value of 80 % in 15 minutes
- Q value of 80 % in 45 minutes

Method: either 500 ml or 900 ml of 0.01 N HCl using Paddle at 75 rpm

- Q value of 80 % in 45 minutes.

Completely irrelevant clinically and does not assure adequate safety and efficacy profile for the released lots

Could potentially lead to therapeutic failures or incidence of toxicities when substituting from one product to the other

Good Practices to Minimize Clinical Irrelevance of the Dissolution Specification

Assure that you have a sensitive and discriminating dissolution method

Set the Q value to 80 % for completely dissolving drug product

Choose the time value as close as possible to the time where 80 % dissolution occurs even if it is below 30 minutes

Setting Clinically Relevant Specifications

Involvement of many groups

- Pre-formulation group for solubility determination
- DMPK for permeability determination
- Formulations
- Dissolution
- PBPK modeling
- Clinical Pharmacology
- Manufacturing Science
- Regulatory

Interactions of all these various groups at different stages of the project is crucial in achieving clinically relevant specifications

IR Formulation

If Drug product is deemed as class I or class III then follow the recommendation of the FDA draft guidance for setting dissolution specifications

- Relatively straightforward
- Minimal effort to develop the dissolution method and set the specifications
- Early determination of the BCS classification is crucial
- Unfortunately minority of the projects fall in this class

IR Class II or IV Drug Products

Manufacturing product variants with different release characteristics resulting in markedly different plasma concentrations is the most desirable way to establish the discriminating ability of the dissolution method and set clinically relevant specifications

Produce formulation variants with different release characteristics



Select optimal dissolution method with adequate discriminating power



Determine bioavailability for all formulation variants



Establish preferably a level A IVIVC



Use the IVIVC to set the dissolution specifications

IR Class II or IV Drug Products

If no in vivo data available, need to demonstrate the discriminating ability of the dissolution method

- By conducting additional dissolution studies that show that the dissolution method along with the proposed specifications are able to reject lots that are unacceptable from a CMC point of view
- Factors tested can include:
 - Hardness
 - Particle size
 - Manufacturing conditions outside the target process range
 - These lots should not be outside the proposed limits by more than 20 % if possible

Modified Release Formulations Irrespective of the BCS Classification

Manufacturing product variants with different release characteristics resulting in markedly different plasma concentrations is the most desirable way to establish the discriminating ability of the dissolution method and set clinically relevant specifications

Produce formulation variants with different release characteristics



Select optimal dissolution method with adequate discriminating power



Determine bioavailability for all formulation variants



Determine dissolution rates resulting in similar in vivo performance (safe space)



Set the dissolution specifications to reject formulations with bioinequivalent plasma levels

Case Study: Combination of **Drug A/Drug B**

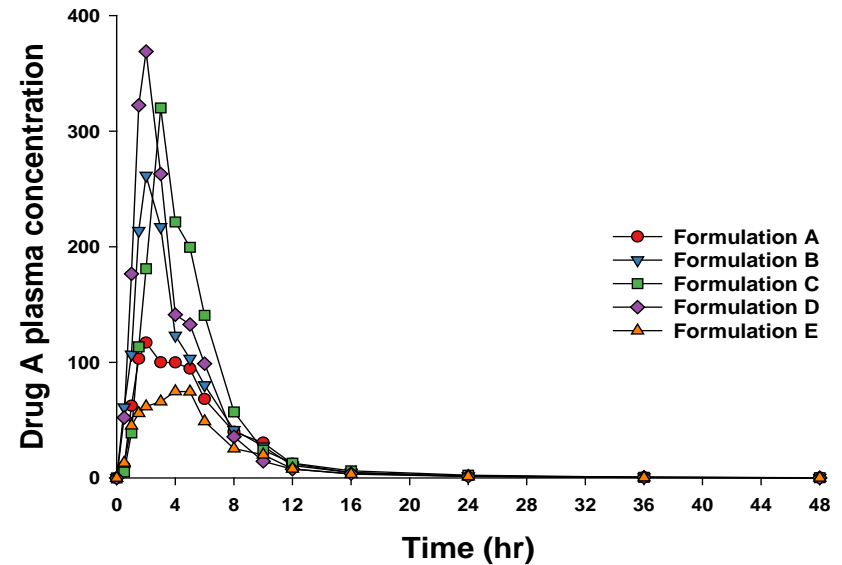
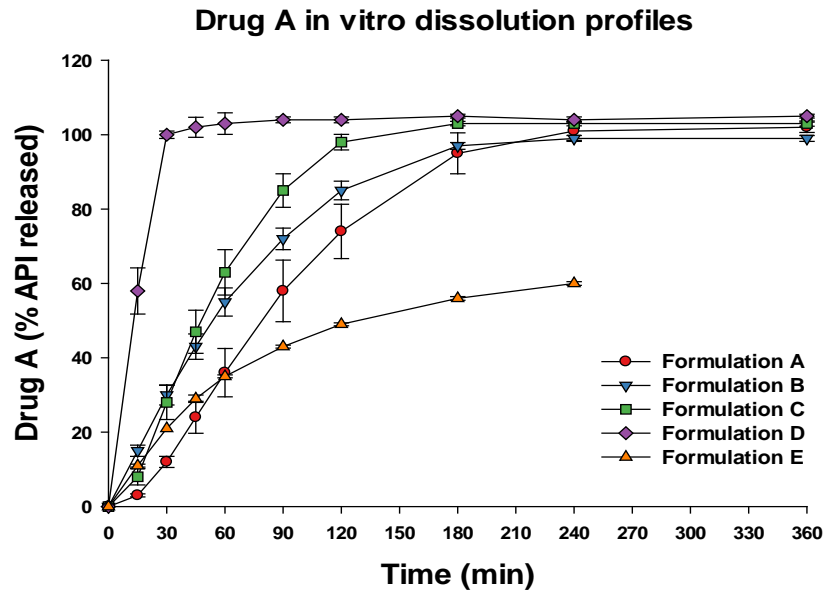
Both drugs are BCS class IV

Due to their insolubility, formulated as a Meltrex formulation using hot melt extrusion technology

Even though these are IR formulations, dissolution in vitro is slow and occurs over a time period of up to three hours

In vitro and In vivo Profiles for Drug A

In vivo rank order:
Formulation D > C > B > A > E

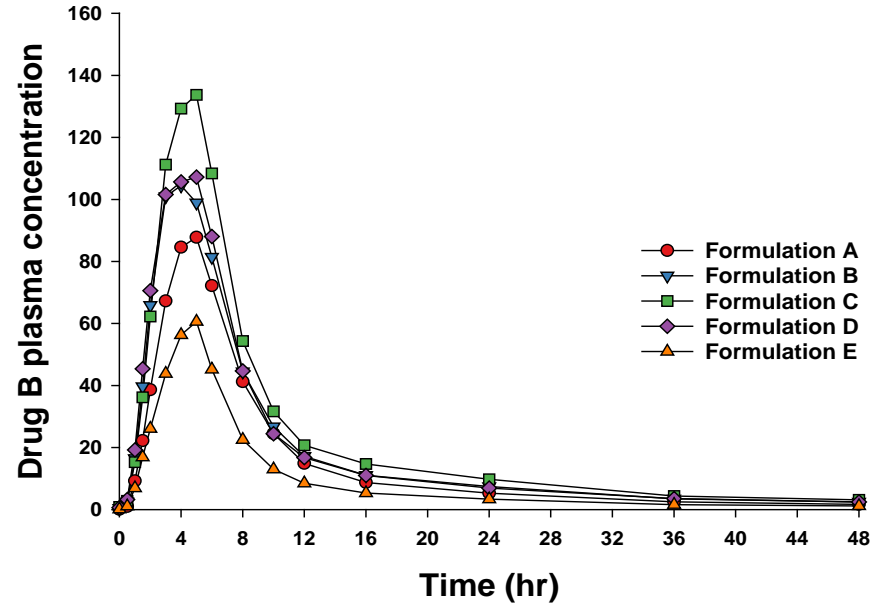
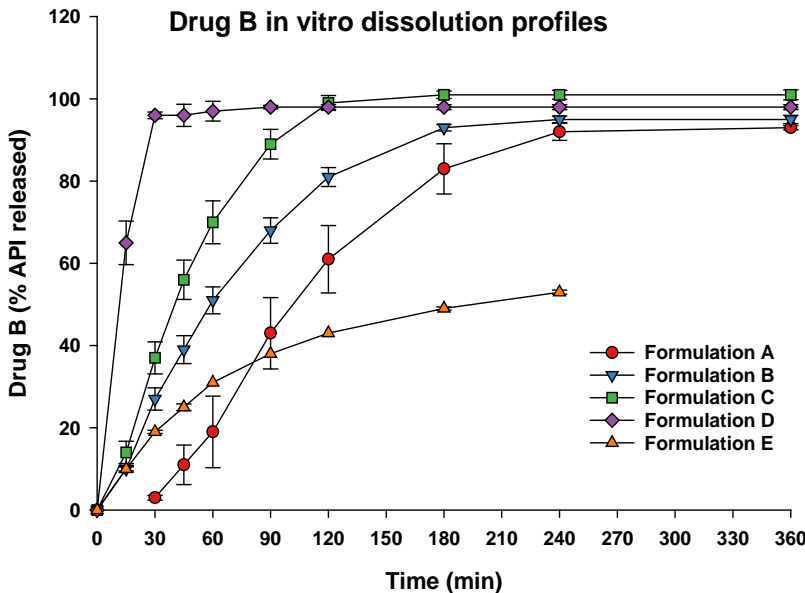


In vitro rank order:
Formulation D > C > B > A > E

Note: In vivo plasma concentration time profiles for drug A are absolute mean concentrations and do not account for relative bioavailability.

In vitro and In vivo Profiles for Drug B

In vivo rank order:
Formulation C > D > B > A > E

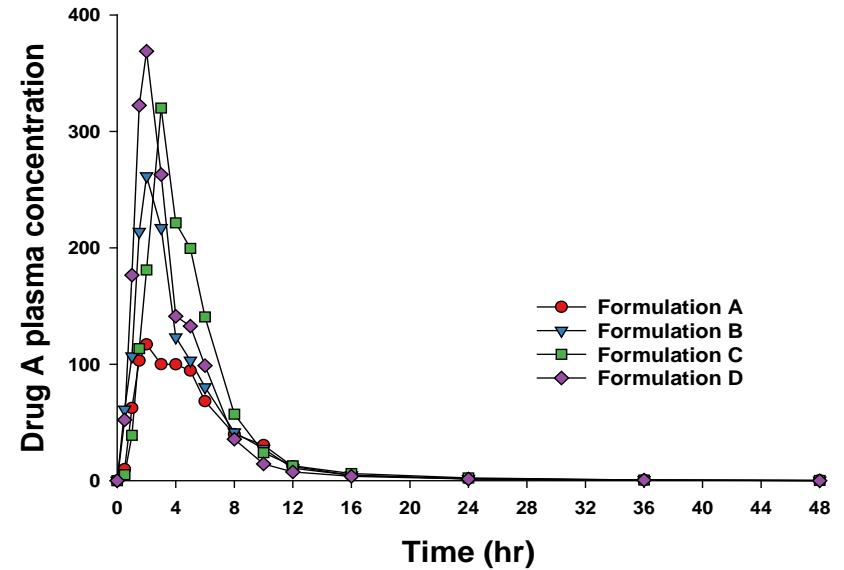
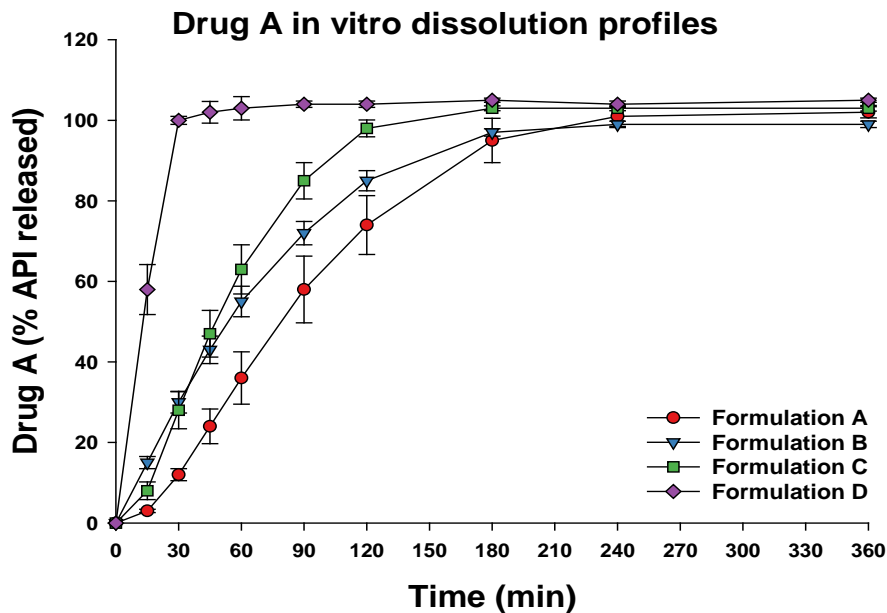


In vitro rank order:
Formulation D > C > B > A > E

Note: The in vivo plasma concentration time profiles for Drug B accounts for boosting by Drug A, whereas, in vitro dissolution profiles are obtained from Drug B alone without boosting by Drug A.

In vitro and In vivo Profiles for Co-formulated Drug A

In vivo rank order:
Formulation D > C > B > A

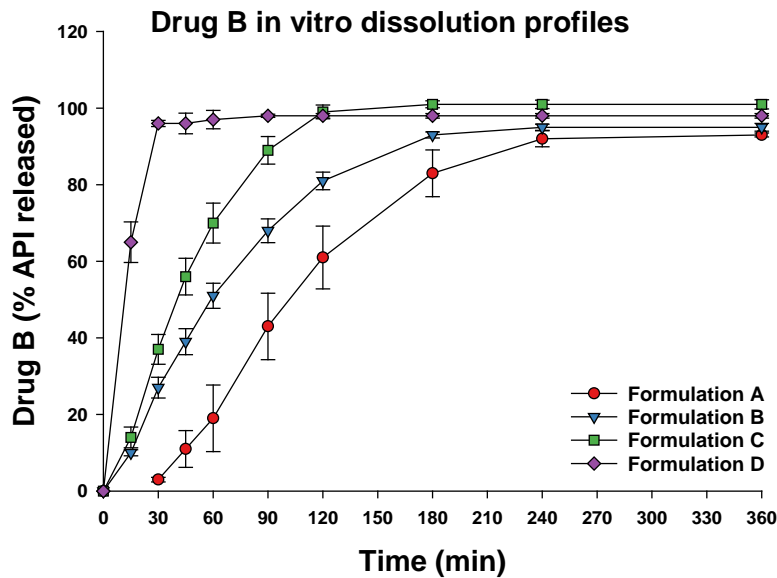
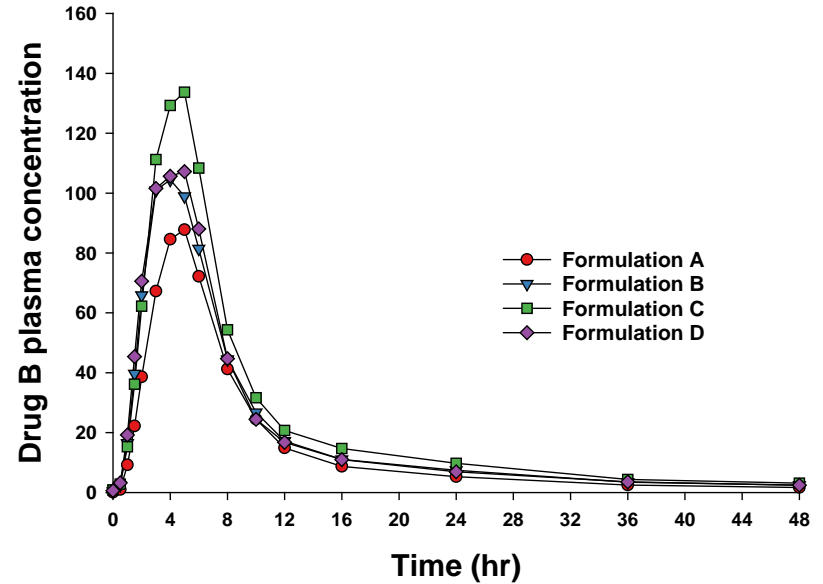


In vitro rank order:
Formulation D > C > B > A

Note: In vitro rank order follow in vivo rank order

In vitro and In vivo Profiles for Co-formulated Drug B

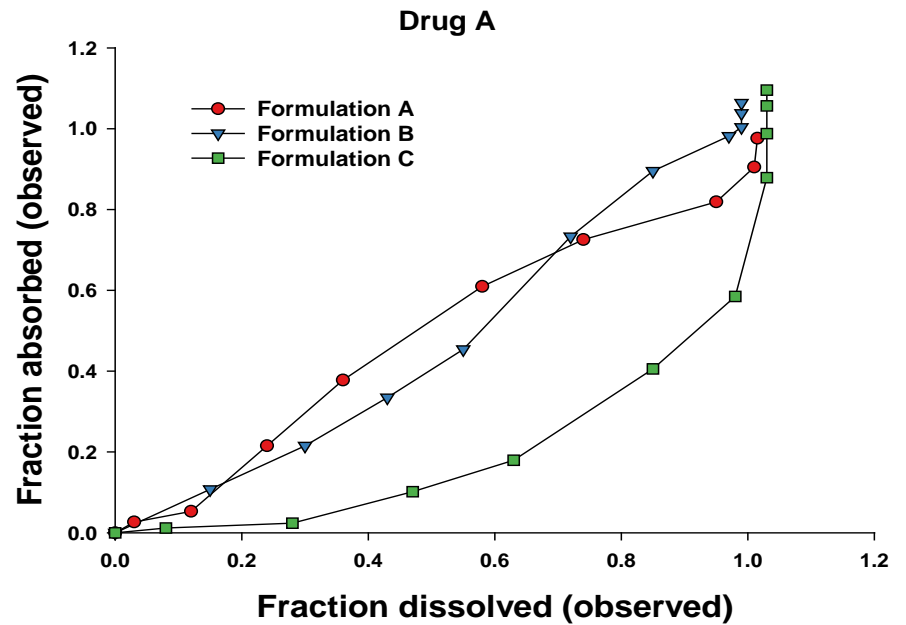
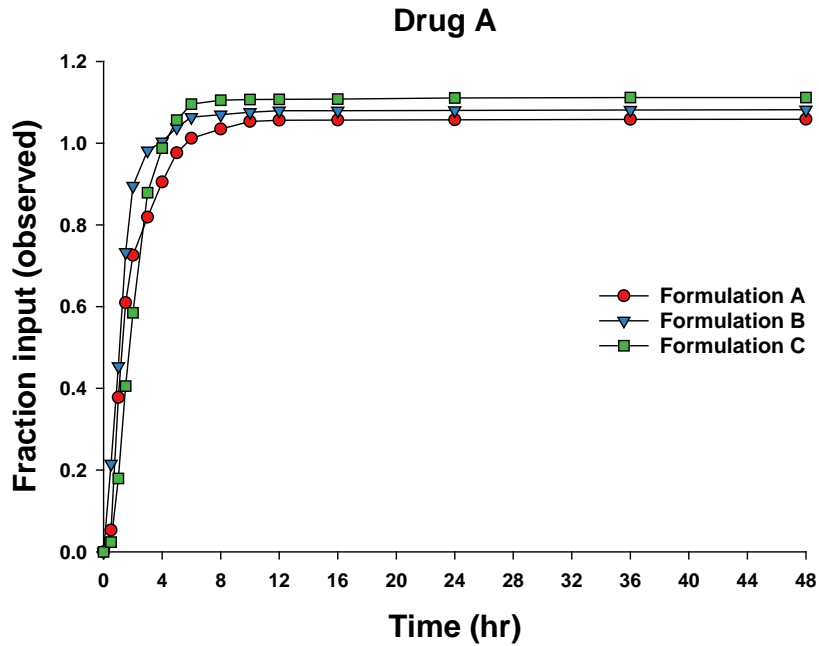
In vivo rank order:
Formulation C > D > B > A



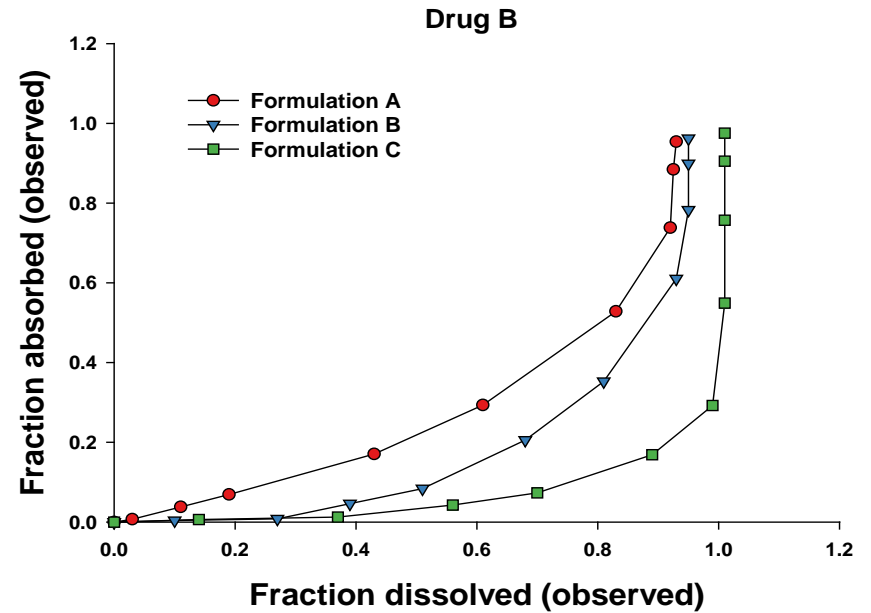
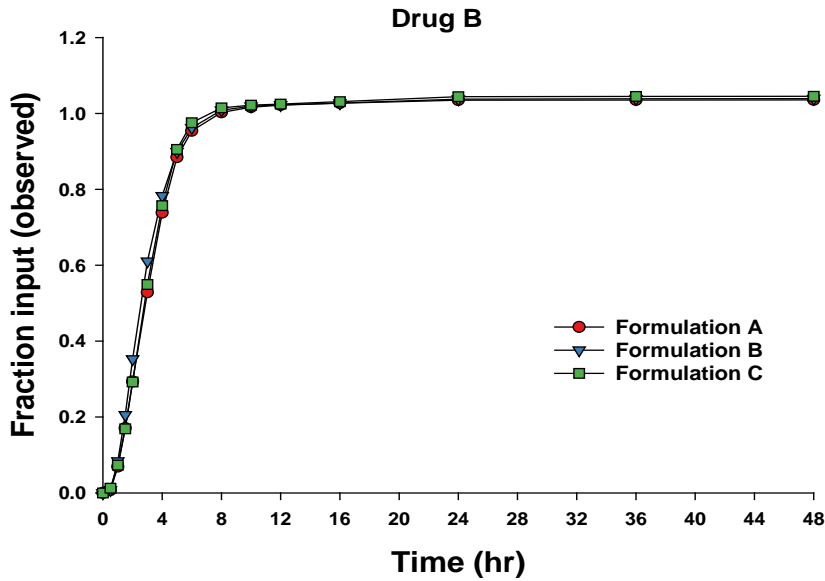
In vitro rank order:
Formulation D > C > B > A

Note: In vitro rank order does not follow in vivo rank order

Fraction Input and Fraction Absorbed for Drug A



Fraction Input and Fraction Absorbed for Drug B



Possible Reasons for Failure to Develop IVIVC

Data obtained from various Phase-I studies leading to increasing variability of the results

Rate limiting step is not the release of the drug from the formulation in vivo despite the slow release observed in vitro

The boosting effect of Drug A on the plasma levels of Drug B that cannot be accounted for in vitro

Setting the Dissolution Specifications

Since the dissolution profiles were slow, more than 1 time point was selected to achieve the optimal control of the dissolution profile

The first time point was selected in such a way that the release of the drugs from the formulation was not too slow to achieve adequate exposure levels to assure the efficacy of the product

- Not less than specification was chosen
- An upper bound was not required as there was no safety concern if the release was fast leading to higher plasma levels and the formulation was IR not intending to control the release of the drug

The last time point was chosen in such a way to assure complete release of the drug from the formulation

Setting the Dissolution Specifications

Average of all the lots that were used in the clinical trials along with validation batch was calculated

Value for the first time point was set as -10 % of the overall average

The proposed specification would not allow the release of lots that were not bioequivalent to the lots that were used in the clinical trials

The proposed specification also did not reject any lots with acceptable safety and efficacy profile

Proposed specifications were deemed clinically relevant

Dissolution method and specifications accepted by FDA.

Summary and Conclusions

Clinically relevant specifications are crucial in providing the optimal therapeutic benefit and reducing inter and intra lot variability

Multidisciplinary effort required to achieve this objective

The availability of different variants with different release characteristics and different bioavailability will provide the necessary information to establish the link between the in vitro release characteristics and the in vivo bioavailability that is needed to set clinically relevant specifications

Patient centric specification is increasingly becoming a regulatory expectation if not a requirement

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