#3_M9

Title	**Biopharmaceutics Classification System-Based Biowaivers ICH M9** **ICH M9 생물약제학적 분류체계 근거 생동면제**
Speaker 1	**James Mann** (Associate Principal Scientist In Vitro Product Performance, AstraZeneca)
Bio 1	with more than 14 years' experience in pharmaceutical industry specializing in all aspects of dissolution testing. At AstraZeneca, James is the global lead for the in vitro product performance scientific community with oversight of all dissolution related activities in product development. Prior to joining AZ, James was with Merck in the UK where he jointly led the global in vitro predictive technologies team as well as supervising a small team of product development analysts and more recently was the analytical manager at Molecular Profiles. James received his first degree from University of Strathclyde, followed by a PhD from the University of East Anglia.
Speaker 2	**Xavier Pepin** (Principal Scientist Biopharmaceutics, AstraZeneca)
Bio 2	Xavier is a pharmacist (University Paris XI). He has a Ph.D. in granulation technology where he studied powder surface energy and liquid bridges during wet high-shear granulation. He has more than 20 years' experience in the pharmaceutical industry and has occupied several positions from preformulation, clinical and commercial formulation development, industrial transfer, regulatory CMC and biopharmaceutics. He's worked in biopharmaceutical tools development for 10 years in transversal collaboration with scientists from CMC, Clin Pharm & MPK departments, using in vitro, in silico, and in vivo tools to support biopharmaceutical evaluation of drugs along the development value chain and post marketing. He was the co-leader of WP4 in silico tools for the OrBiTo IMI project 2012-2018. He has 35 publications in the field of powder surface energy, granulation technology and biopharmaceutics.
Summary	A walkthrough of the recent ICH M9 BCS-Based Biowaiver guideline from an industry perspective covering the topics of solubility, permeability, excipients and in vitro dissolution.

Biopharmaceutics Classification System- Based Biowaivers ICH M9

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2020 ICH Korea Training

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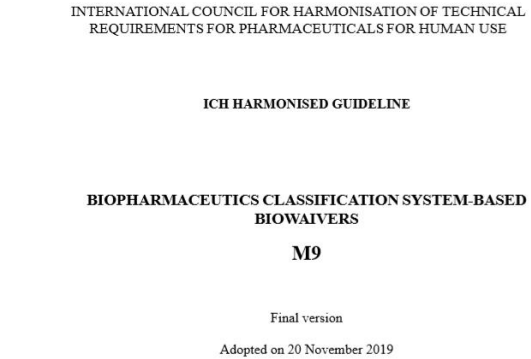
Overview

Introduction
- Background & Objective
- Scope

BCS Classification of the Drug Substance
- Solubility
- Permeability

Eligibility of a Drug Product for a BCS-Based Biowaiver
- Excipients
- In Vitro Dissolution

Documentation


INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

M9

Final version

Adopted on 20 November 2019

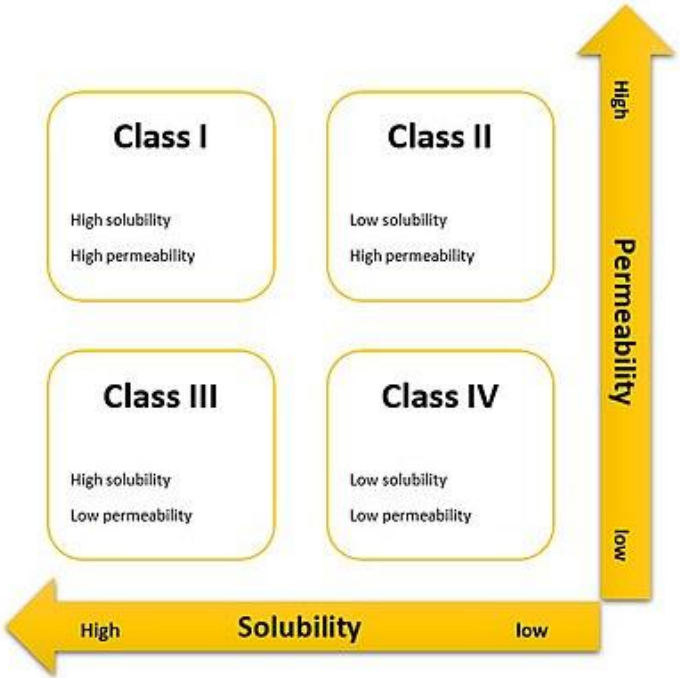
BCS Dissolution Guidance Before ICH M9

Dissolution	US	EU	WHO	Brazil	Canada	Australia	Russia	China	Japan
BCS	I & III	I & III	I & III II (weak acid)	I	I & III	I & III	I	I & III	No particular guideline for BCS based biowaiver. Dissolution for other biowaivers
Apparatus	App I @ 100 rpm App II @ 50 rpm (75 rpm)	App I @ 100 rpm App II @ 50 rpm	App I @ 100 rpm App II @ 75 rpm	App I @ 100 rpm App II @ 50 rpm	App I @ 100 rpm App II @ 50 rpm	App I @ 100 rpm App II @ 50 rpm	App I @ 100 rpm App II @ 75 rpm	App I @ 100 rpm App II @ 50 rpm (75 rpm)	App I @ 100 rpm App II @ 50 rpm (75 rpm)
Volume	500 mL	≤900 mL	900 mL	900 mL	900 mL	900 mL	900 mL	≤ 500 mL	900 mL
Media	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.8	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.8	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.β	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.8 or SIF w/o enzyme	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.8 or SIF w/o enzyme	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.8 or SIF w/o enzyme	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.8 or SIF w/o enzyme	0.1 N HCl or SGF w/o enzyme, pH 4.5, 6.8	Acidic drugs: pH 1.2, 5.5-6.5, 6.8-7.5, water Neutral or basic drugs & coated DF: pH 1.2, 3.0-5.0, 6.8, water
Rate & Similarity	BCS III: ≥85% in 15 min: No statistical test BCS I: ≥85% 15 ~ 30 min: F2 or other statistical tests	BCS III: ≥85% in 15 min: No statistical test BCS I: ≥85% 15 ~ 30 min: F2 or other statistical tests	BCS III: ≥85% in 15 min: No statistical test BCS I: ≥85% 15 ~ 30 min: F2 or other statistical tests BCS II (weak acid): ≥85% 15 ~ 30 min in pH 6.8: F2 or other statistical tests	≥85% in 15 min: No statistical test ≥85% 15 ~ 30 min: F2 ~~or other statistical tests~~	BCS III: ≥85% in 15 min: No statistical test BCS I: ≥85% 15 ~ 30 min: F2 or other statistical tests	BCS III: ≥85% in 15 min: No statistical test BCS I: ≥85% 15 ~ 30 min: F2 or other statistical tests	≥85% in 15 min: No statistical test ≥85% 15 ~ 30 min: F2 or other statistical tests	BCS III: ≥85% in 15 min: No statistical test BCS I: ≥85% 15 ~ 30 min: F2 or other statistical tests	Ref: ≥85% in 15 min: Test DP should be ≥85% in 15 min or within ± 15% of Ref mean at 15 min Ref: ≥85% in 15 - 30min: Test DP should be within ± 15% of Ref mean at two time points (60% - 85%) or F2 ≥42 Ref: <85% in 30min: F2
Units	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12	N = 12

Table courtesy of Xi Shao (Abbvie)

Background and Objective

- BCS-Based biowaivers approach is intended to reduce the need for in vivo bioequivalence studies = surrogate for in vivo BE studies.
- In vivo BE may be exempt if an assumption of equivalence on the in vivo performance can be justified by satisfactory in vitro data.
- BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance.
- Risk based approach.



Citation: Amidon, Gordon L.; Lennernäs, Hans; Shah, Vinod P.; Crison, John R.; (1995). "A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability." Pharmaceutical Research 12(3): 413-420.

Scope

- BCS-Based biowaivers may be used to substantiate in vivo BE.

- Examples mentioned:
  - Comparison between products used in clinical development and commercialisation
  - Post approval changes
  - Applications for generic drug products

- Only applicable for:
  - Immediate release, solid oral dosage forms or suspensions designed to deliver drug to systemic circulation.

- Guideline applicable to drugs with non linear PK
- Locally acting drug products are excluded.
- Narrow therapeutic index drug products are excluded.
- Fixed-dose combinations are eligible if all drug substances meet the criteria
- Products with buccal or sublingual absorption are not eligible
- Only products which are administered with water are eligible
  - If admin without water is also intended (e.g. orodispersible) a BE study will be required in which the product is does without water

Scope (continued)

- BCS-Based Biowaivers are applicable to drug products where the drug substance exhibit high solubility and either high permeability (BCS 1) or low permeability (BCS 3).
- Drug substance in test and reference products must be identical.
- Drug product must be the same strength and dosage form as reference
- A biowaiver may be applicable if test and reference products contain different salts provided they both belong to BCS Class 1.
- Biowaiver not applicable when the tested product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product.
- This is due to the differences may lead to different bioavailabilities not deducible by the experiments defined in ICH M9 BCS-Based biowaivers.
- Prodrugs may be considered when absorbed as the pro-drug.

Solubility

- Large debate during ICH M9 as to whether high solubility classification should be based on highest single therapeutic dose or highest strength.

	FDA (2017)	EMA (2010)	WHO (2015)	Canada (2014)
Unit studied	Highest formulation strength	Highest single therapeutic dose	Highest single therapeutic dose	Highest single therapeutic dose

- Settled on:
  - High solubility classification: when the highest single therapeutic dose is completely soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8 at 37±1°C

- However:
  - In cases where the highest single therapeutic dose does not meet this criterion but the highest strength of the reference product is soluble under the aforementioned conditions, additional data should be submitted to justify the BCS-based biowaiver approach
  - Later on it discusses the used of dose proportional PK over a dose range that includes the highest single therapeutic dose

Solubility

Details

- At least 3 pH including buffers at pH 1.2, 4.5 and 6.8
- Solubility at pH of lowest solubility should be evaluated
  - Important for zwitterions.
- Solubility should be maintained over a relevant timeframe to accommodate expected duration of absorption.
- Equilibrium solubility experiments may be performed using a shake flask or an alternative method if justified.
  - Small volumes of solubility media may be employed if apparatus will allow (AZ approach)
- pH should be measured after addition of DS and at end of experiment
  - pH should be adjusted if necessary – within ± 0.1 is acceptable
  - Not in guidance but best practice to also confirm form at end of experiment.
- Suitable timeframe should be used to reach equilibrium (at AZ typically 24 hrs)
- An option exists:
  - Alternatively, solubility experiments where the highest therapeutic single dose is examined in 250 mL volume, or proportionally smaller amount in a proportionally smaller volume of media, can be considered.
  - Important when drug is very highly soluble or self buffers when present in excess.
- Lowest measured solubility will be used to classify the drug substance.

Solubility

Details

- Minimum of 3 replicates at each solubility condition/pH using appropriate compendial media is necessary.
  - Does not specify which compendia – recommend USP buffers as most commonly used in dissolution method development
  - The mean of the replicates will be used to make the determination
  - High variability is not expected for a highly soluble drug substance

- A suitably validated method must be employed
  - Recommended to use the assay/degs method as should be stability indicating

- Adequate stability in the solubility media must be demonstrated.
  - In cases where more than 10% degradation over the course of the assessment is observed drug substance cannot be classified due to being unable to adequately determine the solubility.

- An option is provided to use literature data to substantiate and support solubility determinations.
  - This is in addition to experimental data not as a substitute.
  - It is cautioned that journal articles may not contain the necessary detail level needed to make a judgement on the quality of the studies.

Permeability

- Ideally human data
  - Absolute bioavailability study F ≥85%
  - Mass balance study
    - Urine dose recovered : unchanged drug + Phase 1 oxidative + Phase 2 conjugative metabolites ≥85%
    - Faeces dose recovered : Phase 1 oxidative + Phase 2 conjugative metabolites ≥85%
    - Metabolites produced by reduction or hydrolysis post absorption can be included
    - Unchanged drug in Faeces can only be counted if it can be demonstrated it was secreted or metabolized from previously absorbed moieties

- In vitro assessment : Caco-2 cell lines
  - Validated and standardized assay
  - Need to demonstrate that compound in stable in GI tract (less than 10% degradation)

Permeability – Caco-2

- Restricted to passively transported drugs
  - Caco-2 may not express biorelevant efflux and influx transporters levels
- Suitability :
  - Transepithelial electrical resistance (TEER) to demonstrate integrity + zero permeability compound
- Correlation established with min 5 reference compounds + 0 permeability marker : Fa% = fn (permeability)
- Min 3 cell replicates, measure Apical → Basal and Basal → Apical
- Passive transport demonstrated by varying concentration 0.01, 0.1 and 1 times the highest drug strength/250mL. Efflux ratio < 2
- Use probes to verify functional expression of efflux transporter substrates
- Investigate recoveries <80%
- Success criterion : Drug Papp should be higher than that(those) of the high permeability marker(s) chosen

Permeability – Caco-2

- Reference compounds

- Published data on human jejunal effective permeability

  – Lennernäs, H., Intestinal permeability and its relevance for absorption and elimination. Xenobiotica, 2007. 37(10-11): p. 1015-1051.

  – Lennernäs, H., Human in vivo regional intestinal permeability: importance for pharmaceutical drug development. Mol Pharm, 2014. 11(1): p. 12-23.

Group	Drug
High Permeability ($f_a \geq 85\%$)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability ($f_a = 50\text{-}84\%$)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low Permeability ($f_a < 50\%$)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol Chlorothiazide Polyethylene glycol 400 Enalaprilat
Zero Permeability	FITC-Dextran Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux Substrates	Digoxin Paclitaxel Quinidine Vinblastine

Permeability - Questions

- Why only Caco-2 ? : Most experience even if this classification can be done with other cell lines. Other methods may be considered in the future when regulators have gained confidence in these new models

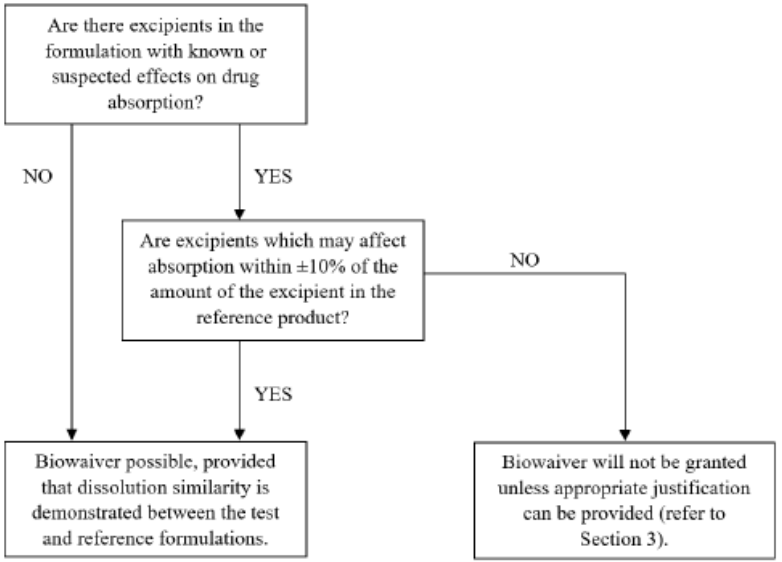
- How to demonstrate high perm :
  - Tested drug should have permeability higher than high permeability reference chosen from Guideline table

- Does it help to have moderate permeability ?
  - No: only high permeability marker is needed. If a drug cannot be demonstrated as high permeability, then it is considered a low permeability drug as per the BCS classification

Excipients

- Use of BCS-based biowaivers subject to composition similitude between test and reference formulations
  - Differences between excipients should not impact drug substance properties or physiological functions

- BCS 1 : Individual and sum of excipients that may affect absorption should not vary by more than 10% w/w between test and ref

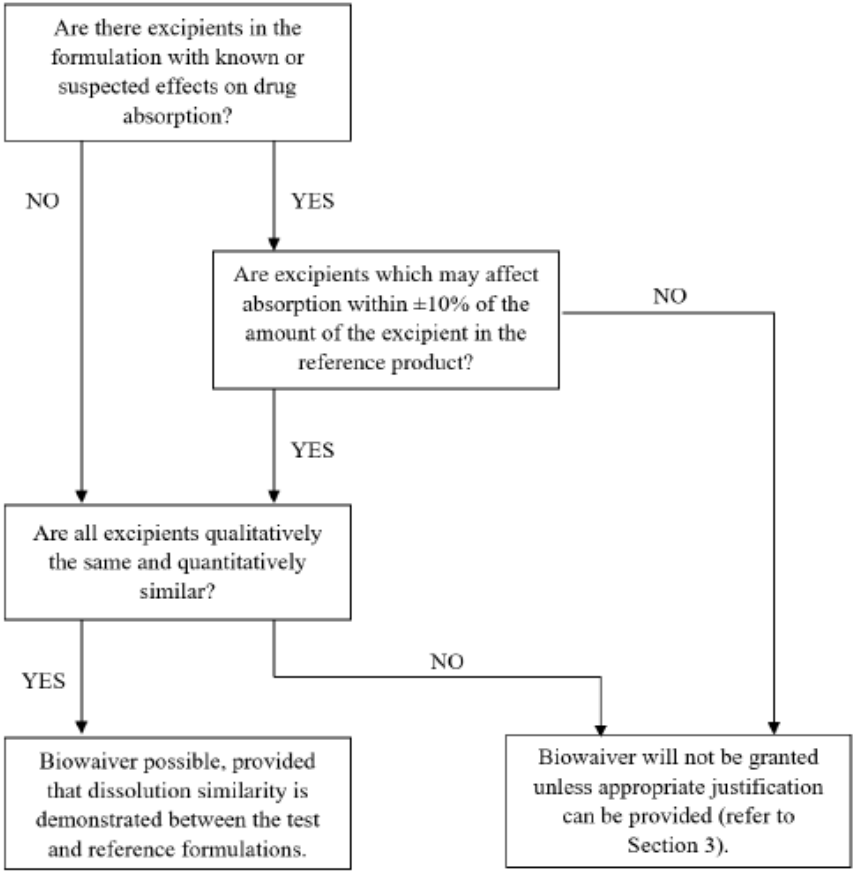


Excipients

- BCS 3 : Individual and sum of excipients that may affect absorption should not vary by more than 10% w/w between test and ref. In addition, qualitative similarity needed and stricter quantitative changes allowed

Within the context of quantitative similarity, differences in excipients for drug products containing BCS Class III drugs should not exceed the following targets:	
Excipient class	**Percent of the amount of excipient in the reference**
Excipients which may affect absorption	
Per excipient:	**10%**
Sum of differences:	**10%**
	Percent difference relative to core weight* (w/w)
All excipients:	
Filler	**10%**
Disintegrant	
Starch	**6%**
Other	**2%**
Binder	**1%**
Lubricant	
Stearates	**0.5%**
Other	**2%**
Glidant	
Talc	**2%**
Other	**0.2%**
Total % change permitted for all excipients (including excipients which may affect absorption):	**10%**

*Note: Core does not include tablet film coat or capsule shell



Excipients - Questions

- FDC :
  - if all BCS class 1 → Excipients criteria for BCS 1
  - If mix of BCS 1 and 3 → Excipients criteria for BCS 3
  - If all BCS 3 → Excipients criteria for BCS 3

- Can we bridge different formulations of the same drug
  - Can be done using the principles of this guideline during development with additional human data
  - BCS-based biowaivers cannot be used exclusively for two different formulations

- Can we use a Physiologically Based Biopharmaceutics Model (PBBM) to support excipient changes beyond those recommended ?
  - Only in certain cases where the mechanism of action is understood and the PBBM has been validated

- Changes of excipient beyond recommended ranges : Human PK data generated with formulations comprising excipient changes beyond those recommended + mechanistic understanding can be used to support these changes

In Vitro Dissolution

- Large debate during ICH M9 as to whether to include water and whether to allow 75 rpm when coning is observed.
- Water not included ✓
- 75 rpm when coning observed not specifically specified ✗

Details

- Comparative dissolution should be conducted on **one batch** representative of the proposed commercial manufacturing process for the test product relative to the reference product.
- The test product should originate from a batch of at least 1/10th production scale or 100000 units whichever is greater unless otherwise justified.
- During clinical phases, smaller batch sizes may be acceptable if justified.
- Compendial apparatus and suitably validated analytical methods should be used.

In Vitro Dissolution

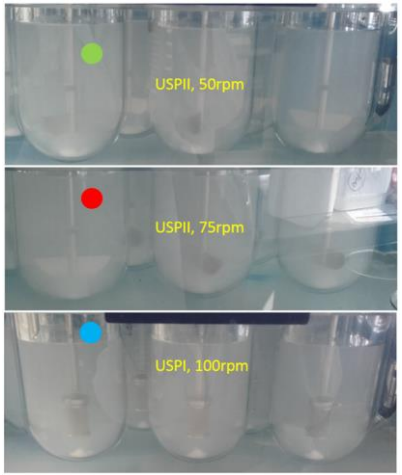
Conditions

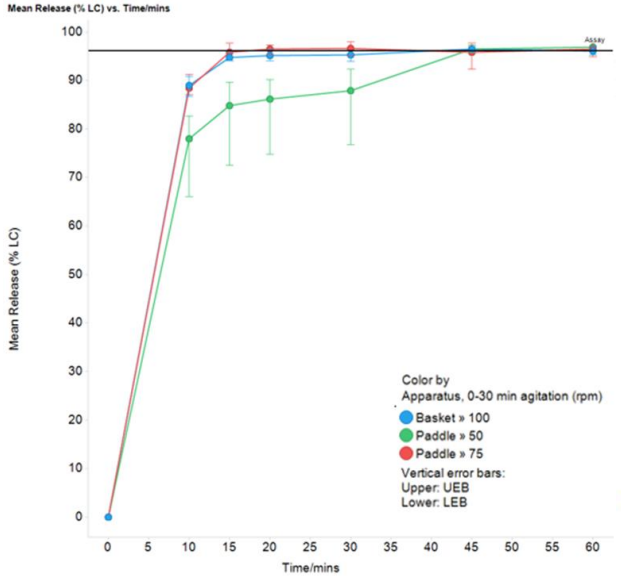
- Apparatus: paddle or basket
- Volume: 900 mL or less (recommended to use the volume of the QC method)
- Temperature: 37±1°C (wider than most pharmacopoeia requirments)
- Agitation: paddle = 50 rpm, basket = 100 rpm
- No. of units: At least 12 units of both test and reference products
- Buffers: pH 1.2, pH 4.5 and pH 6.8 (pharmacopoeia buffers)
  - Minimum solubility may need to be investigated (e.g. zwitterions)
- Organic solvents and surfactants are not permitted
- Samples must be filtered immediately after collection unless in-situ analysis (e.g. fibre optics are used)
- For gelatin capsules, where crosslinking is demonstrated the use of enzyme may be acceptable if justified

In Vitro Dissolution

Coning

- 75 rpm is not explicitly allowed
- Currently states: *When high variability or coning is observed in the paddle apparatus at 50 rpm for both reference and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally, alternative methods (e.g., the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically substantiated. All experimental results should be provided*
- Baskets often do not improve the situation.
- Sinkers have no evidence that I am aware of for improvement in coning.
- Strategies that work: 75 rpm paddle or apex/peak vessels
- Question: Can a global justified approach work?





In Vitro Dissolution

Criterion

- For BCS 1 both test and reference should display either
  - very rapid dissolution (≥ 85% for the mean % Dissolved in ≤ 15 mins)

  OR
  - rapid dissolution(≥ 85% for the mean % Dissolved in ≤ 30 mins) and similar in vitro dissolution characteristics (i.e. based on f2 comparison)
- Under all of the defined conditions (i.e. all pH conditions).

- In cases where one product has rapid dissolution and the other has very rapid dissolution similarity of the profiles should be demonstrated as below:

- Use f2: $f2 = 50 \bullet \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$

- Evaluation of f2 is based on the following:
  - A minimum of 3 timepoints (zero excluded)
  - Matching timepoints for both products
  - Mean individual values for every timepoint for each product
  - Not more than one mean value ≥ 85% dissolved for either of the products.
  - Coefficient of Variation should not be more than 20% at early timepoints (e.g. up to 10 min) and not more than 10% at other timepoints

In Vitro Dissolution

Criterion

- Two dissolution profiles are considered similar when the f2 value is ≥ 50

- When both test and reference products demonstrate ≥ 85% in 15 minutes comparison with f2 is not required and the dissolution profiles are considered similar.

- When the %CV is too high, f2 calculation is considered inaccurate and conclusion on similarity cannot be made.
  - No allowance is made for alternative statistical tools (e.g. f2 bootstrapping, MSD, TOST, etc)
  - Rationale is given that high variability is not expected for highly soluble drug substances
  - If variability is related to coning then that should be overcome

- For BCS 3 both the test and reference product should display very rapid dissolution (≥ 85% for the mean % Dissolved in ≤ 15 mins)

Notes

- For Fixed Dose Combinations criteria should be met for all drug substances to allow a BCS-based biowaiver.
- For products with more than one strength – the approach should be applied for all strengths.
  - i.e. it is expected to produce in vitro dissolution comparison at all strengths

Documentation

Expected Information

- Complete information on the critical quality attributes of the test drug substance and product
- As much information as possible on the reference product including but not limited to
  - Polymorphic form
  - Enantiomeric purity
  - Any information on BA or BE problems with the drug substance or product, can include literature and sponsor derived studies.
- All study protocols and reports
- Information on validated test methods – appropriately detailed as per current regulatory guidance

- Should include tabular and graphical presentations showing individual and mean results and summary statistics.

- Report should document all excipients, their qualitative and, where appropriate, quantitative differences between the test and reference product.

- A full description of the analytical methods employed, including validation and qualification of the analytical parameters, should be provided.

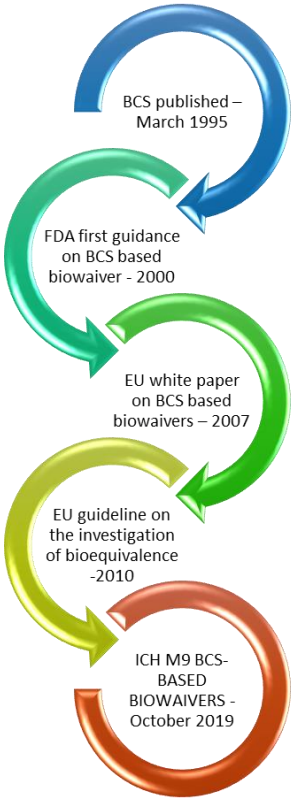
- A detailed descriptions of methods, media, test and reference batch information.

- Dissolution method should describe information on apparatus, de-aeration, filtration during sampling, volume, etc

- Complete information on the method applied for Caco-2 cell permeability assay method, if applicable

Conclusion

- ICH M9 is welcomed by industry and is a great stride forward
- Need to ensure that global acceptability is achieved especially in situations where guidance allows some flexibility/scientific justification
- Watch keenly as countries update their guidance and implement ICH M9
  - Canada implemented on 26th Aug 2020
- Welcome in particular the acknowledgement of the references to pre-approval BCS-based biowaivers rather than fully focused on post approval.



Links

Link to Guideline

- https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf

Link to Q and A Document

- https://database.ich.org/sites/default/files/M9_QAsAnnex_Step4_2019_1116_0.pdf

Q and A

Thankyou for your attention

Confidentiality Notice