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Current practice and challenges in the evaluation of dissolution profile comparisons in support of minor/moderate product quality changes: A Health Canada Perspective

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Outline

- Dissolution within drug product specifications
- Justification of test conditions and discriminatory power
- Aligning expectations in drug product comparison
- Approaches to predicating clinical performance
- Examples to illustrate different approaches to dissolution profile comparison
- Challenges

Drug Product - Dissolution

- Should identify the critical quality attributes (CQA) and indicate the various control points in the manufacturing process (material attributes and/or process parameters) which contribute to effective control of each CQA …
- Dissolution is often used to qualify the impact of changes in material attributes or process parameters, and link changes at various stages of the product's lifecycle.
- The dissolution test's utility depends on its discriminatory ability and relevance to product performance.

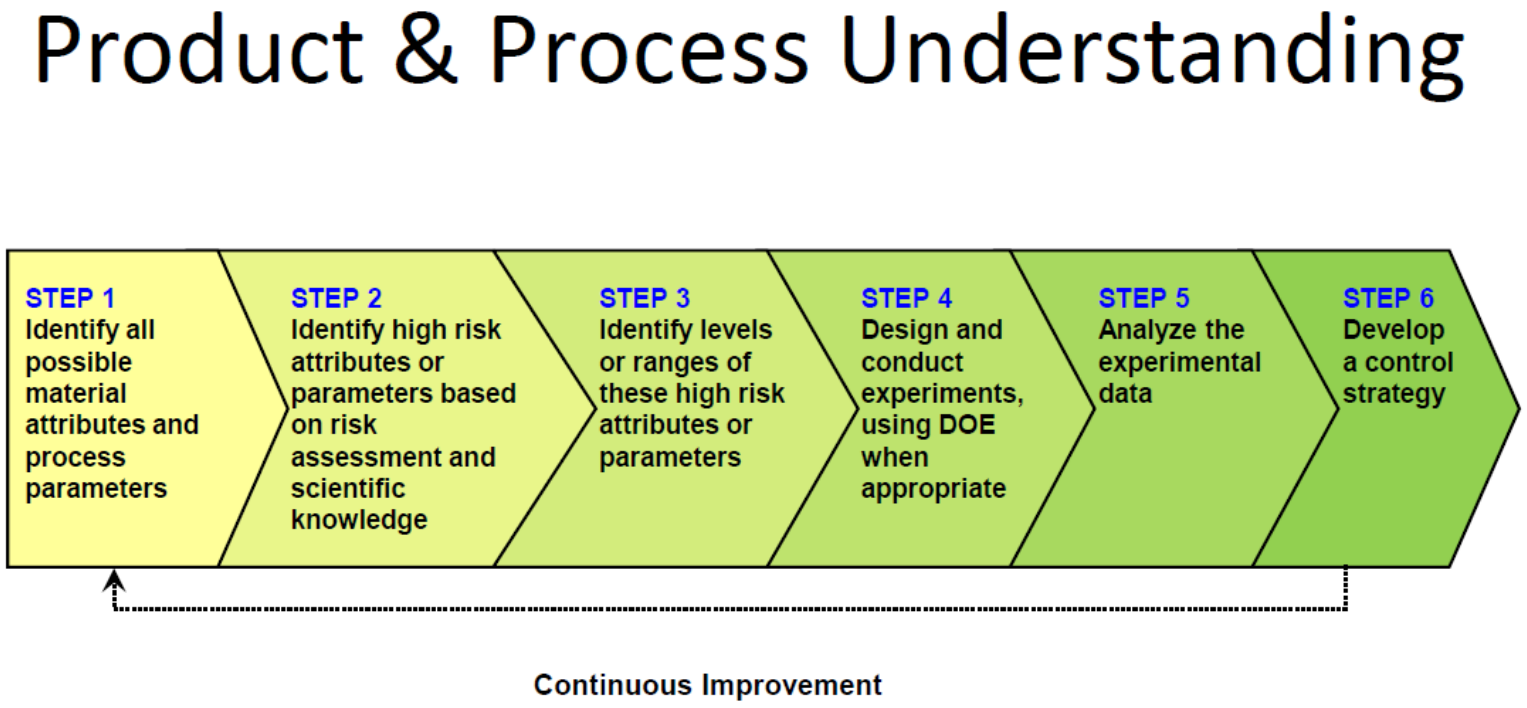
Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDS) and Abbreviated New Drug Submissions (ANDS), Health Canada, 2017

Dissolution Testing

- Health Canada's expectations on appropriate development of a dissolution method, test conditions and discriminatory power are aligned with EMA/CHMP/CVMP/QWP/336031/2017
- Developmental studies should confirm appropriate evaluation on sources of high variability, following USP<1092>
- f2 accepted in regulatory assessment, provided that the conditions above are verified
- Statistical interpolation/extrapolation based on poorly generated data is invalid.

Post-Notice of Compliance (NOC) Changes: Quality Document, Health Canada, 2018
Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDS) and Abbreviated New Drug Submissions (ANDS), Health Canada, 2017
ICH Q2(R1) Validation of Analytical Procedures, adopted by Health Canada: 2015

ICH Q8, Q9, Q10 (Q-trio)



Aligning expectations in comparison testing (1)

$$f_2 = 50 \times \log\{[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\}$$

- Results from pivotal clinical lots or acceptable commercial lots should be used as the basis for calculations – link to the product's quality target profile to deliver clinical performance
- f2 is not applicable when RSD of initial timepoint is > 20% or subsequent timepoint RSD > 10%
- Health Canada interprets "not more than 1 mean value > 85" as no further timepoint beyond the timepoint once ***either*** test or reference reaches/surpasses 85% should be used for comparison calculations

Quality Guidance: NDS and ANDS 2017, Post NOC 2018, Health Canada

Aligning expectations in comparison testing (2)

- Health Canada is open to considering alternative statistical methods to f2 calculations however this is not an invitation to provide poor data with high variability as a basis of a biowaiver
- Model dependent approaches have not been explicitly endorsed by other regulatory agencies
- Model dependent approaches are not accepted at present unless the model has a verified clinically relevant basis
- Physiologically based (PB)-IVIVC and PBPK model based in vitro – in vivo extrapolation (IVIVE) enable better correlation to clinical performance – in order for model predicted data to be considered to support a change, this should be adequately validated for the purpose

Aligning expectations in comparison testing (3)

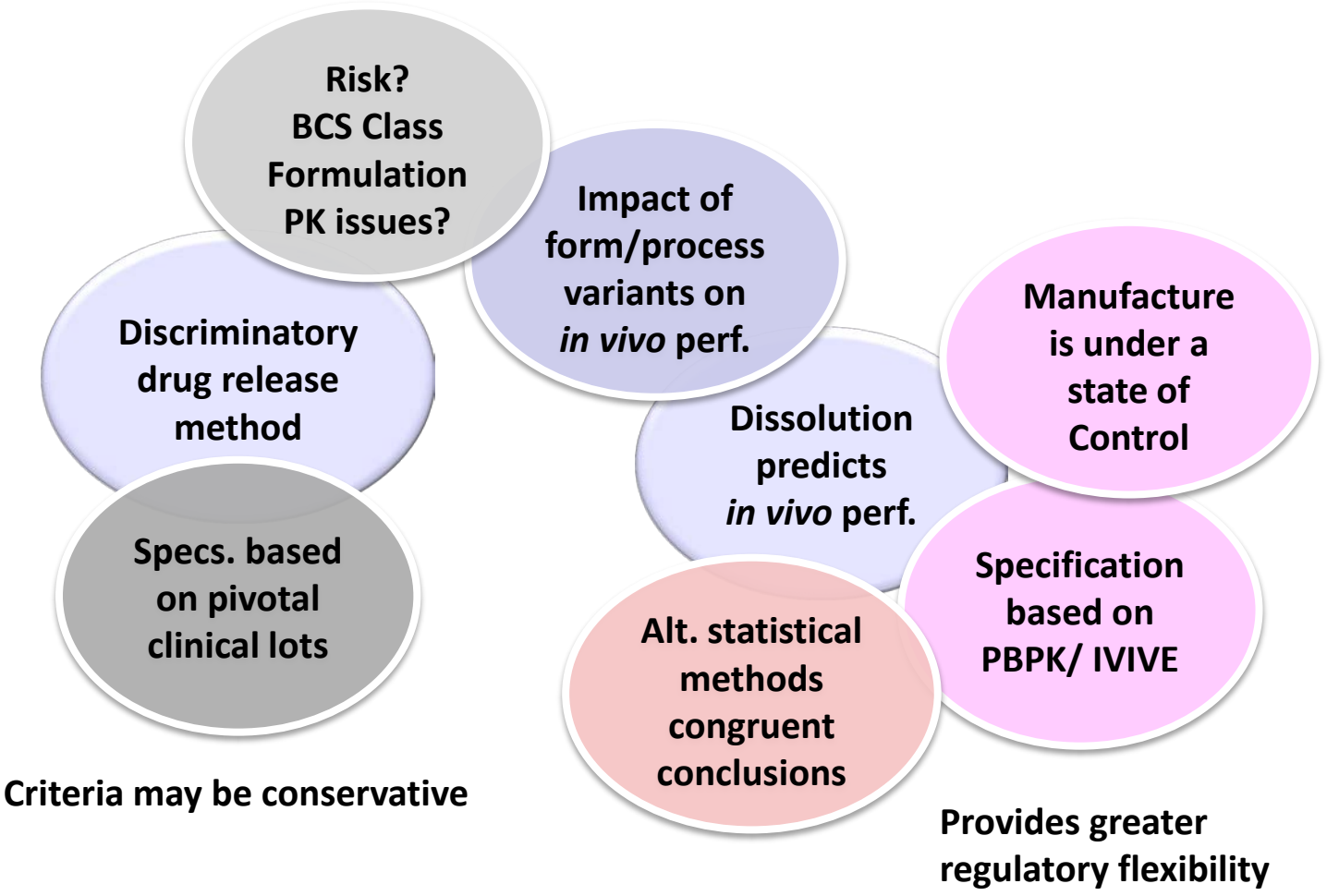
- Model Independent approaches may be applied with dissolution datasets where regular f2 may not be applied due to high variation (RSD or coefficient of variation is > 20% for the first timepoint or > 10% for subsequent timepoints):
  - f2 bootstrap (bias corrected and acceleration)
  - Mahalanobis Distance (MSD) method
- Health Canada's expectation is to use both methods to compare profiles and results should be congruent for both methods as evidence of similarity (statistical equivalence test – two methods to generate the same conclusion)

Quality Guidance: NDS and ANDS, Health Canada 2017

Aligning expectations in comparison testing (4)

- Weight of evidence should be provided to contradict the assumption of dissimilarity (statistical equivalence test)
- Precautions
  - Dosage forms which release minimally at early timepoints may inadvertently bias results (reject replicates with < 5% drug release to prevent bias in MSD analysis)
  - f2 bootstrap simulations are based on resampling data from only 12 samples for CI based only on the mean of the values – bias correction is preferred
  - Similarity limit should be 10%.
- The Mahalanobis Distance (MSD) and bias corrected bootstrap (BCa) f2 results should be congruent, conclusive and calculations appropriate with a similarity limit of 10%.

Approaches to Dissolution Profile Assessment



Drug Product X

Modified release tablet, sealed and layered pareils, administered once daily.

- **the lower boundary of 90% f2 confidence interval (i.e. 5th percentile) all exceeds the critical value of 50 for the comparisons of the highly variable dissolution data**
- **multi media dissolution profiles**

BCa f2 data was provided to support the proposed biowaiver

			Bootstrap CI	
Batch comparison	Time Points Used	Method	5th Percentile	95th Percentile
one vs two	6	BC	53.15	62.91
		BCa	53.41	63.32
one vs three	4	BC	52.67	77.70
		BCa	52.67	78.05
one vs two	4	BC	52.96	75.65
		BCa	53.31	77.13
one vs four	4	BC	60.84	91.55
		BCa	64.91	94.05
one vs two	4	BC	59.41	90.52
		BCa	63.31	98.24

Drug Product Q

- Modified release tablet, water soluble drug:
  - manufactured by dry granulation,
  - core hardness and dimensions impacts release,
  - functional coating,
  - site change with multiple manufacture changes proposed

- Alternate statistical analysis was considered in view of the variability that precludes application of the f2 calculation:
  - dissolution data at 5 minutes, mostly zeros, ↑ max MSD value
  - MSD (weighted differences over all time points) biases to similarity without exclusion of 5 minute timepoint

Drug Product Q (1)

Table 2. Multivariate confidence region results exclude 5 min time point

Compare	Time Points	Dosage Unit	Mahalanobis Distance (MSD)	Lower 90% CR MSD	Upper 90% CR MSD	Max MSD	Similarity Result
Ref. one Vs. two	4	12	1.3432	0.0206	2.6659	1.7296	Non-Similar
Ref. one Vs. three	4	12	1.6624	0.3398	2.9851	1.5175	Non-Similar
Ref. one Vs. four	4	12	0.9404	-0.3823	2.2630	1.9702	Non-Similar
Ref. two Vs. three	4	12	1.1938	-0.1288	2.5165	1.2419	Non-Similar
Ref. two Vs. four	4	12	1.9740	0.6513	3.2967	1.5476	Non-Similar

Table 3. Multivariate confidence region results include 5 min time point

Compare	Time Points	Dosage Unit	Mahalanobis Distance (MSD)	Lower 90% CR MSD	Upper 90% CR MSD	Max MSD	Similarity Result
Ref. one Vs. two	5	12	1.6003	0.1048	3.0958	23.3271	Similar
Ref. one Vs. three	5	12	1.7044	0.2089	3.1999	58.4682	Similar
Ref. one Vs. four	5	12	1.0199	-0.4756	2.5154	49.9331	Similar
Ref. two Vs. three	5	12	1.3382	-0.1573	2.8337	23.7793	Similar
Ref. two Vs. four	5	12	2.1065	0.6110	3.6019	23.2821	Similar

Drug Product Q (2)

Table 4. Bootstrap f2 and BCa bootstrap f2 results exclude 5 min time point

Compare	Bootstrap mean f2	Lower Limit of f2	Similarity Result	BCa Bootstrap mean f2	Lower Limit of f2	Similarity Result
Ref. one Vs. two	55.603	42.389	Non-Similar	55.503	55.955	Similar
Ref. one Vs. three	49.261	36.801	Non-Similar	49.198	37.666	Non-Similar
Ref. one Vs. four	57.140	40.672	Non-Similar	56.984	41.378	Non-Similar
Ref. two Vs. three	48.397	34.398	Non-Similar	48.330	35.578	Non-Similar
Ref. two Vs. four	46.174	34.999	Non-Similar	46.140	36.325	Non-Similar

- **Similarity was not demonstrated:**
  - **re-analysis with MSD excluding data from the 5 min timepoint demonstrates non-similarity**
  - **bootstrap f2 and BCa bootstrap f2, regardless of inclusion or exclusion of 5 min data except for one comparison, also concludes non-similarity**

Drug Product Y

BCS Class II drug substance, IR capsule, layering process.

- High variability in manufacture: drug loading and seal coating, differ in PSD of granules
- PK data from one study
- QC dissolution method

Reanalysis of the MSD and BCa f2 results are not congruent with the conclusion of similarity. MSD alone would not respect that similarity limits should not be > 10% different at any timepoint.

Drug Product	Modified Mahalanobis Distance (MSD)			Bias-corrected and accelerated bootstrap f2		
Test Product	Upper Limit M-Distance	Max Limit M-Distance	Conclusion according to modified MSD	Bootstrap mean f2	Lower Limit of the Confidence interval of f2	Conclusion according to BCa Bootstrap
one vs. two	1.96	0.81	Non-Similar	65.42	37.61	Non-Similar
one vs. three	4.66	6.41	Similar	66.09	39.31	Non-Similar

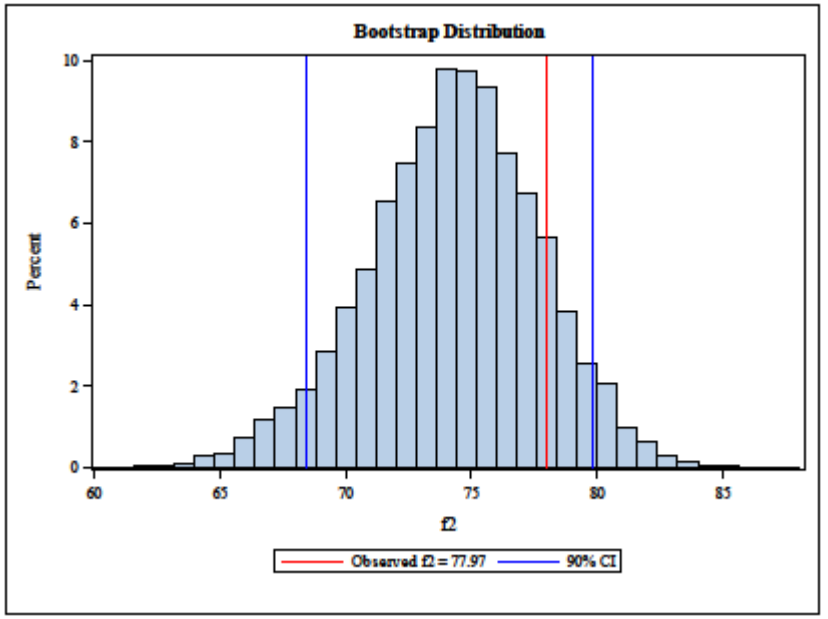
Drug Product Z (1)

Narrow therapeutic index drug, IR tablet, direct compression process.

- MSD results returned with incorrect max for similarity
- Verification of bootstrap results since bias corrected should differ from uncorrected

Site manufacture change.

5th and 95th percentile histograms from bias corrected bootstrap



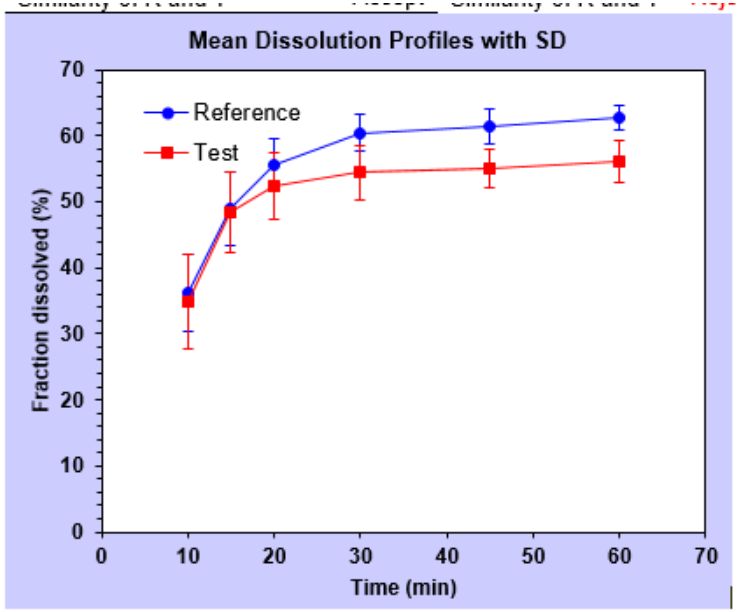
Drug Product Z (2)

Post-approval change of site of manufacture, Drug Z is a NTI drug

BCa f2 does not concur with MSD Observed variability for the clinical batches is evident.

Fit for purpose?
Currently in review.

Dissolution – overlay of site one vs site two



Statistics	Value	Statistics	Value
p (sampling points)	6	p (sampling points)	6
K (scaling factor)	0.7727	K (scaling factor)	0.7727
F_(p,n1+n2-p-1,0.9)	2.1524	F_(p,n1+n2-p-1,0.9)	2.1524
Hotelling's T^2	61.4432	Hotelling's T^2	61.4432
Mahalanobis Distance (MSD)	3.2001	Mahalanobis Distance (MSD)	3.2001
Lower_90_CR_MSD	1.5311	Lower_90_CR_MSD	1.5311
Upper_90_CR_MSD	4.8690	Upper_90_CR_MSD	4.8690
Max_Diff_Mean Fraction (%)	11.6000	Max_Diff_Mean Fraction (%)	11.5000
Max_MSD	4.8980	Max_MSD	4.8558
Is Upper_90 ¡Ü Max_MSD	Yes	Is Upper_90 ¡Ü Max_MSD	No
Similarity of R and T	Accept	Similarity of R and T	Reject

Summary

Examples presented:

- **Model independent approaches may result in different conclusions on the same datasets**
- **Convergence in similarity assessment**
- **BCa f2 bootstrap predicted data for a high solubility drug MR product supported a conclusion of similarity (Drug Product X)**
- **MSD and f2 bootstrap data was provided to support a change in site manufacture for a low solubility IR product (Drug Product Z, in review)**

Challenges

- Not many submissions include appropriately generated analysis
- While advances in modelling methods enable better correlation to clinical performance, regulatory experience is limited, and standards and acceptance criteria are not well established or agreed upon across regulatory agencies and industry
- Use and selection of minimum levels of non-biologically relevant surfactants for dissolution testing of poorly soluble drugs creates artefacts – where formulation and manufacture strategies may result in lower energy forms upon in vitro testing

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- ICH Q6A: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, adopted by Health Canada: 2016
- Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDS) and Abbreviated New Drug Submissions (ANDS), Health Canada, 2017
- Post-Notice of Compliance (NOC) Changes: Quality Document, Appendix 5: Recommendations for Conducting and Assessing Comparative Dissolution Profiles, Health Canada, 2018
- Bioequivalence of Proportional Formulations policy, Health Canada, 1996
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- EMA Question and answer on the adequacy of the Mahalanobis Distance to assess the comparability of drug dissolution profiles EMA/810713/2017
- EMA Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (2017) EMA/CHMP/CVMP/QWP/336031/2017