Health Canada Santé Canada

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Modified Release Products – A Health Canada Perspective

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**This presentation reflects the views of the author and should not be construed to necessarily represent Health Canada's official position

NTIs

- Assessment standards for these products (cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, theophylline, warfarin) are more stringent than those applied for uncomplicated drugs

	Modified release?	
Cyclosporine	**No (microemulsion in softgel)**	
Digoxin	No	
Flecainide	No	
Lithium	**Yes – tablet**	HPMC + mg stearate
Phenytoin	Extended only	
Sirolimus	No	
Tacrolimus	Yes - capsule	HPMC + ethylcellulose, lactose mg stearate
Theophylline	Yes – tablets	Only generics
Warfarin	No	

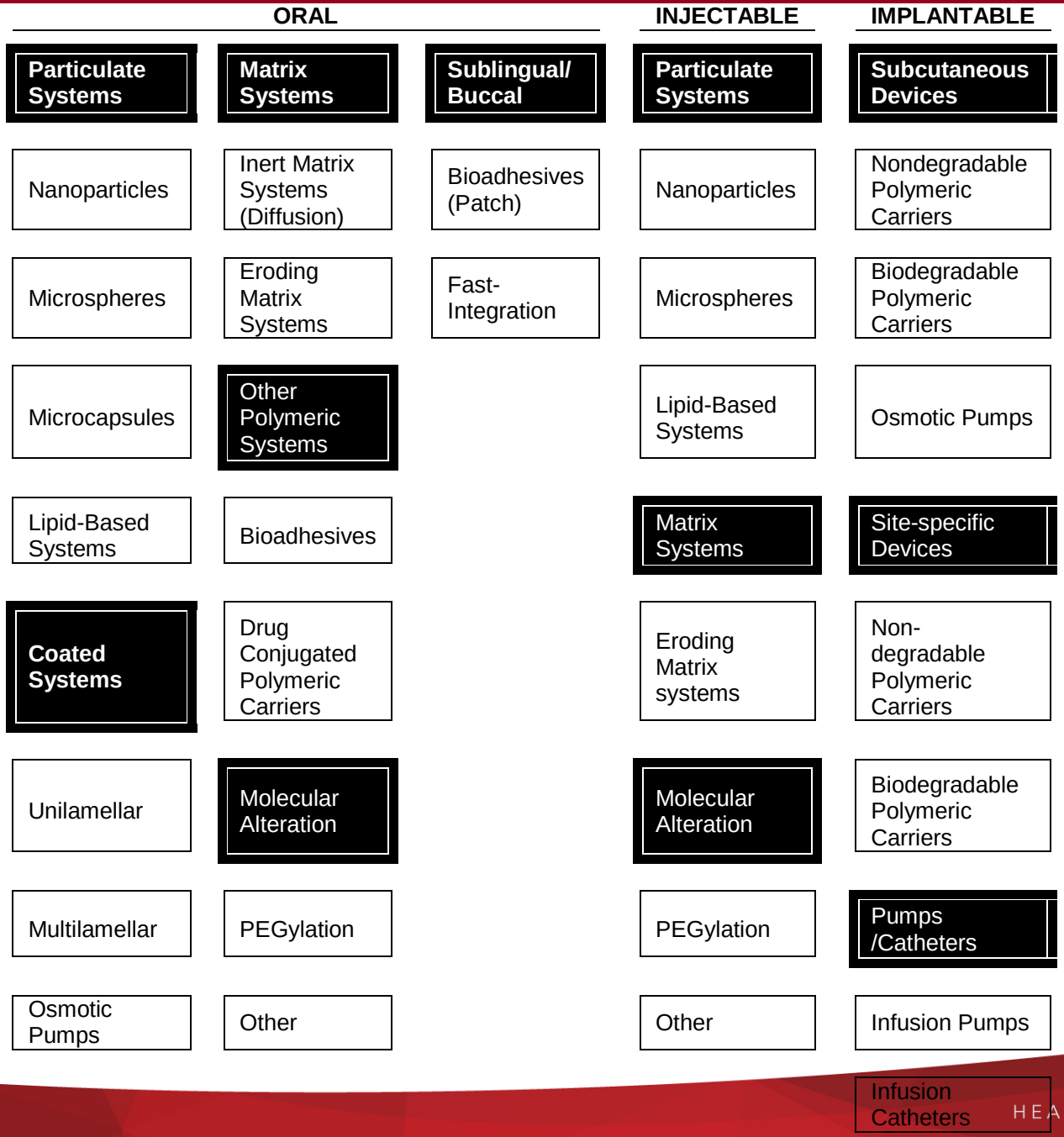
NTIs

- Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (2017) implemented January 2018 - for products where dose accuracy is considered clinical risk concern, more stringent in process controls are requested (instituted)
  - A product's dose is determined by the weight of the final tablet/capsule
  - Average: target ± 3 - 4 % (i.e., less than 5%).
  - Individual: target ± 5%
- Low dose drugs need more content uniformity testing than the USP <905> test
  - Sampling plans and statistical analysis of results within process validation protocols
  - Routine testing of content uniformity is requested for direct blending manufacture

- Size reduction and production of a redispersible biphasic system.
  - In process controls should include temperature monitoring for this key phase with known critical heat generation
  - Potential media attrition and potential contamination with assessment of risks with selected process (eg. ball-milling or microfluidization)
  - particle size or globular size distribution for suspended state
    - absence of aggregation, growth (Oswald ripening) or recrystallization on storage
    - Studies on aged samples
  - Confirmation that material containing the same polymeric form results at or near end of proposed shelf life
  - discussion on the potential for microbial and/or cross contamination from one batch to the next, and if media is not dedicated, then the potential for product cross-contamination
  - Softgel: "*Insufficient data to demonstrate suitability of the dissolution analytical methodology and specification limits to control product quality and assure consistency on routine testing; to detect manufacture and stability deviations by dissolution testing as a performance test. The general USP testing chapters pertaining to softgels including <1094> (USP General Chapter <1094> Capsules- Dissolution Testing and Quality Attributes , as first published in PF 38(1) and official in the first supplement of USP 37 in 2014. This was first developed for liquid filled capsules but is applicable to all types of capsule products*"

- Optimization and control strategy for the three phase system (lipid:surfactant:stabilizer) should include control of heating, homogenization, and cooling rate which are also critical process parameters
- Viscosity is a critical quality attribute as it is reflective of the aggregation tendency of the dispersed phase within the lipid delivery system - provide dispersed emulsion stability data to justify a lower viscosity
- Temperature cycling or freeze thaw data for risk assessment
- Assessment of stability of the droplet size distribution, emulsion coalescence and for precipitation of the API within the emulsion by quantitative birefringence microscopy (image analysis) averaged over multiple frames for adequate statistical power (or equivalent)
- Emulsion stability upon dispersion or globular coalescence is a unique aspect of this drug delivery system. Phase separation on both microscopic and macroscopic scale are first line indicators of emulsion break down and is a critical quality attribute – provide assessment of globular coalescence or viability upon dilution (quantitative evaluation may include zeta-potential measurements)

Modified Release Systems



Transderms

- Drug in adhesive monolithic matrix systems – surface area / size of the patch determines the dose (selected mechanism delivers predetermined flux)
  - strength derived by cutting patches of various sizes from a common laminate
- CQAs
  - For patches that are intentionally designed and manufactured with fully dissolved API.
    - Precipitation of this API on storage is considered to be a critical quality concern; the appearance of API crystals in the patch is an occurrence which makes the product quality and performance variable and unpredictable
    - Appropriate evaluation as a routine test - absence of precipitation on storage (with potential difference in flux rate).
  - Limits on cold flow (size = dose)
    - Cases where embedded drug containing area of the patch may be affected as a result of adhesive migration (cold flow).
  - Drug release specification limits, as monitored on a quality control basis by in vitro dissolution testing, should be benchmarked to the lot used in the bioequivalence stud(ies) for assurance of consistency in intended manufacture as representative of the lot used in the bioequivalence stud(ies) per C.08.002.1.(2)(d). in vitro permeation studies with a discriminative method may be considered as supportive evidence of consistency of product performance on storage

Transderms

- If nucleation (crystallization) occurs –propensity for propagation is a CQA
  - In vitro permeation studies with a discriminative method for patches with and without crystals using the proposed formulation should be provided. Ideally crystals should be achieved via stress studies. However, if this is not possible, implantation may be used however the size and dispersion of implanted crystals should adequately represent true crystallization. Data should include the following,
    - Evidence of discriminatory ability and validation of the selected permeation method should be confirmed and provided.
    - Results from (historical) in vitro permeation studies (i.e. flux rates through human skin) for batches used in bioequivalence studies.
    - The plot of the cumulative amount of drug permeated per unit area (mass/cm2) as function of time should be presented. Data from all diffusion cells should be reported and the mean flux reported together with the corresponding standard deviation (SD), coefficient of variation and the validity, variability and reproducibility of the results should be discussed. Outliers may be excluded from the statistical analysis, if satisfactorily explained and justified.
    - Flux data should be statistically compared with an analysis of variance. The 90% confidence interval for the ratio of the biolot and the aged lots /lots containing crystals (above the proposed limit) should be determined and should be contained within the ratio of 0.8 to 1.25 unless justified. The method should be based upon a null hypothesis of non-equivalence.

KPP/CPPs/CQAs

- Coating density or architecture critical quality attribute as controlled by weight gain and spray coating parameters. Weight gain alone is inadequate to assess coating density which directly affects drug release.
  - provide the detailed calculations to derive the surface area the relative difference in tablet surface area to tablet volume ratios between strengths as a ratio to the coating weight gain should be addressed
  - variation in target average coating thickness, which directly correlates to coating density, may affect drug release rates even if appropriate coating weight has been applied to the tablet surface
- Mechanical integrity of the semipermeable membrane is the critical attribute in the prevention of dose dumping or release of the entire daily dose as a bolus in patients.
  - Quantitative data should be provided on the evaluation of the mechanical strength of the semipermeable coating selected for your product to withstand the hydrostatic pressure generated by the core osmogen and to prevent rupture and failure both in the absence of an orifice and in the presence of several holes drilled into the coated core
  - Confirmation of the mechanical strength of the proposed semi-permeable membrane is requested for an additional lot processed at the lowest coating range (thickness)

Tamper resistance

- In vitro studies, appropriately powered to quantitatively assess mechanical fractionation, extraction in common household solvents, time and temperature extraction, vaporization, insufflation and syringeability
- relevant forms of tampering (across range of particles sizes, tampering methods) should be investigated with respect to potential impact on in vitro dug release profiles
  - Evaluation of several strata of rendered particle sizes including distribution and dissolution testing to provide conclusive evidence of equivalence of test and reference products (between whole tablets as well as manipulated tablets)
  - Extraction studies with multiple solvents, with and without thermal cycling over short durations
  - Data from the proposed test product and the reference product should be statistically compared. The 90% confidence interval for the ratio of the means of two products, for the relevant parameters, and should meet the appropriate regulatory criteria.

Tamper resistance

- In exceptional cases where extremely high levels of rate controlling polymers are present, dissolution methods may not be demonstrated to be suitably discriminating based on *in vit*ro data alone.
- Dissolution specification limits may be adopted based upon IVIVC model-predicted pharmacokinetic parameters to increase the assurance of similar in vivo lot to lot performance if a Level A IVIVC is in effect.
  - For NTIs or critical dose drugs, IVIVC modelling is the default
- In cases where no biowaiver is requested, in vitro dissolution data demonstrating the boundary of failure relative to the lot used in the successful bioequivalence stud(ies) (eg. batches that would fail the drug product dissolution specifications) may provide justification on the robustness and the acceptability of the modified release formulation containing very high levels of high molecular weight polymer

Modified release systems - dissolution

- Quality Control in vitro dissolution test and limits are established in order to ensure manufacture deviations are suitably identified on commercial manufacture
- However, in extended release products with very high levels of one or more rate controlling polymers, if the polymer concentration to effect extended release greatly exceeds a threshold, the rate control may approach a plateau.
- In lieu, tablet dissolution data where the amounts of the main critical rate controlling polymer within the core is varied below target while delivering API at target may be provided for consideration
  - maintaining target levels of auxiliary rate controlling polymers
  - the drug loading level, the other polymer levels and the lubricant levels as well as the size and shape of the tablets should be invariant to ameliorate interpolation of the data
  - Corollary data on the robustness of the proposed formulation

Modified release systems - dissolution

	% w/w Biolot 50mg	↓ 35%, %w/w 50 mg	↓ 30%, %w/w 50 mg	%w/w Biolot 100 mg	↓ 35%, %w/w 100 mg	↓ 30%, %w/w 100 mg
API	20	20	20	40	40	40
Rate Controlling Polymer A	40	35	30	50	35	30
Diluent	299	304	309	269	284	289
Rate Controlling Polymer B	1	1	1	1	1	1
Core tablet (mg)	360	360	360	360	360	360

- Demonstrate robustness of the formulation
- A single common dissolution drug product specification should be declared as benchmarked to pivotal in vivo study lot(s)
- Dissolution specifications acceptability criteria should not exceed +/-10% of the target limit per Quality Chemistry and Manufacturing Guidance: NDSs and ANDSs (2017) - MR products minimum of 3 timepoints including a mid-point where approximately 50% of drug release occurs, dissolution should continue until at least 90% of the drug is dissolved or an asymptote is reached

- Considerations for a biowaiver include:
  - Pharmacokinetics (fasting and fed studies are required for modified release products) with guidance documents updated and in effect 2018
  - Comparable dosage form for the purposes of establishing pharmaceutical equivalence
  - Manufacturing process and controls
  - Proportionality of formulations

- Pharmaceutical development should link *in vitro* dissolution through *in vivo* drug release to *in vivo* product performance

- Under certain conditions, the results of a comparative bioavailability or clinical study can be extrapolated to all strengths in a product series, for biowaivers based on proportionality

- The requirements are described in the Policy: Bioequivalence of Proportional Formulations – Solid Oral Dosage Forms (1996).
  - The criteria include both proportionality of formulations as well as comparative dissolution profiles.
  - Additional recommendations: Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology, 2013.

Excipient type core weight	% Difference in
Filler	±5.0
Disintegrant	
Starch	±3.0
Other	±1.0
Binder	±0.5
Lubricant	
Ca or Mg stearate	±0.25
Other	±1.0
Glidant	
Talc	±1.0
Other	±0.1

% Difference is assessed relative to the biobatch

Multi-functional excipients: most conservative limits

Excipients which affect dissolution and drug release may not be considered as an inactive filler

- Incremental changes: proportions of ingredients increase or decrease successively from the lowest to the highest strengths.
  - Bracketing approach for incremental changes that exceed limits specified in the Proportional Formulations table (section 1.1.2 may apply on a case by case basis)
  - *In vivo* equivalence studies on the lowest and highest strengths.
- Modified-release products: no changes in the proportions of release controlling excipients are permitted.
  - Non-proportional strengths to modified-release dosage forms containing "complicated" drugs will require at least one biostudy on each strength
  - Delayed-release products with enteric coating: proportions of coating components may be based on the tablet surface area ratio (coating thickness expressed as mg per mm squared)
  - For functional coats, changes in proportion relative to core tablet (surface area to volume ratio) may influence the rate of drug release (coating thickness and architecture)

Biowaivers for Solid Orals

- The comparative dissolution profiles in three media should be conducted against the lot used the in the bioequivalence study
- Proportionality of multiple strengths - excipient variability compared to the biolot exceeds the allowable criteria as per the policy “Bioequivalence of Proportional Formulations”
- If a common blend is used to manufacture the drug product, the comparative dissolution profiles (in the three media) are required for all strengths which are manufactured from a second lot of granulation (i.e. a different lot than the one used to manufacture the biolot)

Dissolution

- Dissolution methods (discriminatory)
  - Acceptance criteria should be tied to the bioequivalence study
  - The method should be shown to be appropriate for the product
    - I.e. discriminatory – shown to be able to detect modest changes in formulation and manufacturing processes such as levels of disintegrant, binder, mixing time after addition of lubricant per recommendations from the SAC-PSCP (2013)
    - Use of a compendial method without showing that it is appropriate for a product is a common reason for sending a deficiency comment
    - Emphasize possible differences between the product strengths
      e.g. pH of the medium close to the transition pH of the critical rate controlling polymer if pH dependent

  "*A dissolution method for a drug product should be formulation specific and should have discriminatory ability to exclude the batches which did not or potentially would not meet bioequivalence criteria, particularly for extended release formulations. The dissolution method is considered to be discriminatory when modest changes in the formulation (composition) and modest changes in the process should be differentiated by the dissolution test method. The information provided to date on the discriminatory ability of the proposed method is considered to be inadequate*"

- Analysis of dissolution results
  - Calculation of f2 similarity factors are not considered suitable when there is incomplete release or high RSD results for dissolution studies
  - Use of alternative statistical methods may be considered within review with appropriate due diligence in dissolution methods evaluation

- , Matrix modified release core combined with immediate release

	mg	%	mg	%	mg	%
API X (ER)	**500**	46.3	**500**	51.3	**250**	29.4
Excipients	50	4.6	50	5.1	50	5.9
Rate controlling polymer	320	29.6	320	32.8	325	38.2
API Y (IR)	**100**	9.3	**50**	5.1	**50**	5.9
Excipients	30	2.8	15	1.5	15	1.8
Polymer (binder)	80	7.4	40	4.1	40	4.7
Total Core	**1080**	100	**975**	100	**850**	100

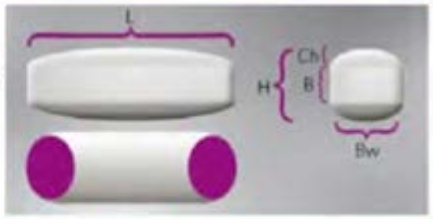
- Delayed release systems are modified release systems, therefore manufacture variability in the core affects the critical surface area and therefore thickness of the critical delayed release coat
  - Confirm minimum and range where weight per area (mg per mm squared)

$$X = 2\pi \cdot (rB + r^2 + Ch^2)$$

$$Y = 2 \cdot \sqrt{Bw^2 + \left(\tfrac{16}{3}Ch^2\right)} \cdot (L - 2r)$$

$$Z = 2B \cdot (L - 2r)$$

$$A = X + Y + Z$$



The individual calculation steps are based on the hatched areas in the schematic drawing:

X = round ends
Y = 2 x top-hat segment
Z = band (2 x faces)

- If there are differences between the lots used in clinical safety and efficacy or the lots used in bioequivalence studies and the proposed commercial drug product manufacture, supporting data should be provided to ensure compliance with C.08.002.(2) (m)
  - Setting specifications for drug release testing (eg. dissolution limits) which are reflective of the pivotal lot(s)

Modified Release Drug Product

- Dissolution testing is not typically a predicator of mechanical failure *in vivo*.
  - hardness in modified release matrix tablets will result in lower cohesive strength and increased risks of mechanical failure of these hydrogel matrices in vivo. Notably, dissolution testing is not a predictor of mechanical failure in vivo; this in vitro test may not be considered as a surrogate to address the risks of mechanical failure
- Swelling tests which measures the extent of hydration does not address the strength of the swollen hydrogel and potential for shear failure (unintended sectional erosion rather than controlled intended surface erosion). Testing in uniaxial compression is not worse case and does not address shear failure.

Drug Product

- If there are differences between the lots used in clinical safety and efficacy or the lots used in bioequivalence studies and the proposed commercial drug product manufacture, supporting data should be provided to ensure compliance with C.08.002.(2) (m)
  - Setting specifications for drug release testing (eg. dissolution limits) which are reflective of the pivotal lot(s)

Process validation

- BPS ensures protocols to be used for process validation are appropriate and can be used for subsequent changes after marketing authorization
  - Completed process validation reports are not provided to Health Canada
  - No pre-approval inspection
- Blend uniformity vs Content uniformity
  - Low dose drugs need more content uniformity testing than the USP <905> test
  - Sampling plans and statistical analysis of results should be planned carefully
  - Routine testing of content uniformity is probably necessary for direct blends
- The protocol should confirm extremes of critical process parameters
  - Testing should be more rigorous during process validation
    - Hardness during compression – high and low press speeds, dwell times
  - Plan testing to get as much information as possible about what is important (i.e. QbD or “QbD light”)

Risk-based approach in review