Regulatory Expectations of Presentation of Dissolution Data

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• Dissolution Method Development and Validation

• Dissolution Data for Marketing Authorisation Applications

• Dissolution Data to Support Post-Approval Changes

• Setting Release and Shelf Life Specification Limits for Dissolution
Why Use Dissolution Testing?

- **Ultimate objective:** to ensure adequate and reproducible bioavailability without need for *in vivo* testing – need IVIVC [IVIVC covered by later presentations]

- **More common objective:** to test drug release characteristics of a formulation or batch under standard *in vitro* conditions

- **Product development:** formulation and process optimisation

- **Routine QC:** to demonstrate consistency of manufacture of each batch and similarity to pivotal clinical batches

- **To support changes** in manufacture, formulation, site, pack or scale-up
Dissolution Method Development & Validation

• Pharmacopoeial method, unless justified
  - PhEur 2.9.3 solid dosage forms
  - PhEur 2.9.4 transdermal patches
  - PhEur 2.9.25 medicated chewing gum
  - PhEur 2.9.42 lipophilic solid dosage forms
  - PhEur 2.9.43 apparent dissolution – powders & granules

• PhEur 2.9.3 (= BP Appendix XII B1)
  - Text harmonised with USP and JP
  - Linked PhEur 5.17.1: Recommendations on dissolution testing
    • Experimental testing conditions
    • Recommended dissolution media
    • Qualification and validation
    • Expression of dissolution specifications for oral dosage forms
Choice of Apparatus

- Depends on physicochemical characteristics of dosage form
- Apparatus 1: basket – capsules, tablets
- Apparatus 2: paddle - tablets, capsules
- Apparatus 3: reciprocating cylinder - bead-type MR dosage forms, soft capsules, suppositories, poorly-soluble drugs
- Apparatus 4: flow-through cell – if change of pH needed; also as Apparatus 3
Dissolution Method Development & Validation (continued)

• Investigate pH/media and sink conditions
  - Drug substance solubility across physiological pH range
  - Sink conditions: Dissolution medium volume $\geq 3 - 10 \times$ saturation vol.
  - Recommended media listed in PhEur
  - For QC testing:
    – Discriminatory and physiologically-relevant media
    – Water to be used only if no pH influence on dissolution characteristics
    – If drug poorly aqueous soluble, surfactant (e.g. SLS) is permissible (lowest concentration to obtain sink conditions). Justify alternative additives (e.g. enzymes). Avoid organic solvents!

• Investigate rotation speed
  - ↓ speed $\rightarrow$ ↑ discrimination
  - Too slow may lead to variable results (poorer hydrodynamics, coning)
  - Apparatus 1: basket 50 – 75 – 100 rpm (BP prefers 100 rpm)
  - Apparatus 2: paddle 50 – 75 – 100 rpm (BP prefers 50 rpm)
  - Apparatus 3: reciprocating cylinder – dip rate
  - Apparatus 4: flow-through cell – flow rate of medium
• Demonstrating Discrimination
  - Above work may already demonstrate this
  - Formulation and/or manufacturing process development work
    - Tablet hardness trials
    - Varying quantity of lubricant and/or lubricant mixing time

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<th>Cap no.</th>
<th>Bloggeline released, %</th>
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**Mean**

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<tr>
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<td>RSD %</td>
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**Bloggeline hard capsules 10 mg batch no. ABC999**

**Bloggeline hard capsules 10 mg batch no. XYZ123**

**Dissolution conditions:**
PhEur apparatus 1 (basket), 100 rpm, 1000 ml 0.1 M HCl
Potential Pitfalls

- For generics, US FDA Dissolution Database helpful, but...
  - Check if applicable to formulation and justify suitability
  - Example 1: Escitalopram oxalate tablets
    - FDA database: Paddle, 75 rpm, 0.1 N HCl, 900ml
    - Applicant’s data: > 90% dissolution after 5 minutes
    - No discussion of why 50 rpm not investigated
    - Escitalopram Tablets USP monograph method: 50 rpm
  - Example 2: Lamivudine tablets
    - FDA database: 100 & 150 mg – Paddle, 50 rpm, H₂O (deaerated), 900 ml
    - FDA database: 300 mg – Paddle, 75 rpm, 0.1 N HCl, 900 ml
  - FDA database may simply reflect US originator formulation
Dissolution Method Development & Validation (continued)

• Method Development Documentation:
  - Describe above development work
  - Justify conditions/method adopted
  - Justify any method modifications during pharmaceutical development

• Method Validation (ICH Q2 (R1), CPMP/ICH/381/95)

<table>
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<th>Type of analytical procedure characteristics</th>
<th>IDENTIFICATION</th>
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<td>+</td>
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<td>+ +</td>
<td>+</td>
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<tr>
<td>Detection Limit</td>
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<td>- (3) +</td>
<td>-</td>
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<td>Quantitation Limit</td>
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<td>+ -</td>
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<tr>
<td>Range</td>
<td>-</td>
<td>+ -</td>
<td>+</td>
</tr>
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</table>

...considered a method development issue, but do not forget robustness

(1) in cases where reproducibility (see glossary) has been performed, intermediate precision is not needed
(2) lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s)
(3) may be needed in some cases
Dissolution Data for Marketing Authorisation Applications (MAAs)

- **All relevant applications** (new chemical entities & generics)
  - Dissolution method development
  - Dissolution method validation
  - Dissolution data within batch analyses and stability studies
  - Description and justification of any changes (dissolution method, dissolution results, formulation, manufacture) through development
  - Comparison of strengths
  - Modified-release tablets/capsules: Effect of alcohol on dissolution rate
    (EMA Q&A http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&mid=WC0b01ac058002c2b0#section6)

- **Generics**
  - Comparison to reference medicinal product
  - Biowaivers for multiple strengths
  - BCS biowaivers [covered by next presentation]
Dissolution Data for Generic MAAs - Comparison to reference medicinal product

- Advisable to investigate more than one batch of test and reference products; must include bioequivalence batches
- Aim: To show similar *in vitro* dissolution under physiologically relevant experimental pH conditions
- Investigate within pH 1 - 6.8 (normally pH 1.2, 4.5 and 6.8) and QC media (if different)
- Additional investigations may be required at pH values in which the drug has minimum solubility
- Use 12 units to enable statistical evaluation
- For each condition, present comparative dissolution profiles (mean values vs. time) together with statistics (max, min, mean, RSD; f2 similarity factor if calculated; individual values)
Dissolution Data for Generic MAAs - Comparison to reference medicinal product
(continued)

- **Immediate Release Tablets/Capsules**
  - $> 85\%$ dissolved within 15 minutes: test and reference similar without any further calculation
  - $\leq 85\%$ dissolved within 15 minutes: calculate $f_2$ similarity factor (see next slide)

- **Modified Release Preparations**
  - Calculate $f_2$ similarity factor (see next slide)
  - More information later

- If comparative *in vitro* dissolution results of biobatches do not reflect bioequivalence as shown *in vivo*, latter prevails.
  BUT: address and justify possible reasons for discrepancy
- Final QC specification reflects biobatch dissolution value
Similarity Factor ($f_2$)

Defined as:

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

- $n$ is the number of time points
- $R_t$ is the mean % drug dissolved for the current formulation
- $T_t$ is the mean % drug dissolved for the changed formulation

- Minimum of 3 time points each of 12 individual values
- Not more than one mean value of >85% dissolved
- Relative standard deviation or C of V to be <20% for the 1st time point and <10% from 2nd to last time point
- An $f_2$ value of 50-100 suggests similar dissolution profiles
- Alternatively, can use model-dependent or model-independent methods (to be justified & validated)
Similarity Factor \((f_2)\) – Prolonged Release Preparations

- Minimum of 3 time points, but may be prudent to do more
  - Particularly important if desired release profile not uniform
    (e.g. immediate release outer coat and prolonged release core)
- If only 3 time points: expected to mirror final specification time points (20-30\% (dose dumping), 50\% (defines profile), >80\%)
- More time points = \(\uparrow\) confidence of bioequivalence
  - e.g. for once daily preparations (1, 2, 4, 8, 12, 16, 20 & 24 hours)
Dissolution Data for Generic MAAs – Comparison to reference medicinal product: Gastro-resistant preparations

- Compare dissolution profiles at PhEur conditions (2 hrs, pH 1.2 → 45 min pH 6.8) and at more neutral pHs (2-5)
- Hence, at least two dissolution tests in two steps:
  - 2 hrs pH 1.2 (‘fasted state’) → 45 min pH 6.8
  - Higher initial pH (‘fed state’), e.g. 2 hrs pH 4.5 → 45 min pH 6.8
- Initial step (pH 1.2 or 4.5): ≤ 10% dissolved
- Second step: Comparison of dissolution profiles to be performed even if > 85% before 15 min. Hence, tight sampling schedule recommended as profile comparison (e.g. f2 calculation) required.

Ref. PKWP Q&A EMA/618604/2008 Rev.4
Dissolution Data for Generic MAAs - Biowaivers for multiple strengths: Prerequisites

- Manufactured by same manufacturing process
- Compositions qualitatively same, quantitatively proportional
  - i.e. ratio between weight of each excipient to active(s) same
  - Immediate release products: coating components, capsule shell, colour agents and flavours not required to follow this rule
- If deviation from quantitatively proportional, still considered fulfilled if i) and either ii) or iii) below apply to strength used in biostudy and strength(s) for waiver:
  i. weight of active substance < 5% of tablet core / capsule content weight
  ii. weights of different tablet core / capsule content excipients are the same and only active substance weight changed
  iii. weight of a filler is changed to account for change in amount of active substance. Amounts of other tablet core / capsule content excipients should be the same.
- Linear pharmacokinetics (Non-linear: See guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)
Dissolution Data for Generic MAAs - Biowaivers for multiple strengths: Investigations

• Investigate dissolution at same conditions as above (i.e. as performed for test and reference biostudy batches)
• Demonstrate similarity at all conditions between additional strengths and strength (i.e. batch) in biostudy.
  - > 85% dissolved ≤ 15 min.
  - > 85% dissolved ≤ 30 min (but not 15 min), ≥ 3 time points: 1st < 15 min, 2nd at 15 min and 3rd when release close to 85%; calculate similarity factor (f2 or other justified)
• At pH values where sink conditions not achievable for all strengths, dissolution may differ between strengths. Demonstrate drug substance not formulation related by comparing respective strength of reference product.
  - In addition, similar profiles at same dose (e.g. two tablets of 5 mg versus one tablet of 10 mg) could be compared.
Dissolution Data for Generic MAAs - BCS biowaivers

- Covered by next presentation
Dissolution Data for Generic MAAs – Post authorisation requirements (if not in submission)

- Comparative dissolution profile testing on first three production batches
  - batch cannot be marketed until comparative dissolution profile testing completed.
- Results to be provided at Competent Authority’s request, or if dissolution profiles not similar, together with proposed action to be taken

![Graph showing dissolution data for reference and test products]
Dissolution Data for MAAs
– Potential Pitfalls

• Record dissolution conditions on all documentation
  - Development over years, but personnel change or confusion on inter-departmental transfer
  - Same pH but different results due to non-documented changes
    • e.g. presence of surfactant, change in agitation speed or buffer composition

  - Example: Dissolution results for clinical batch presented in pharmaceutical development section (mean 98% (n=6), min 97%, max 99%)
    ≠ batch analysis section (mean 86% (n=6), min 74%, max 94%)
    (Narrow therapeutic index drug, explanation currently awaited.)

• If reference = tablet, but generic = capsule (or v.v.), paddle data at x rpm cannot be assumed to be equivalent to basket data at same speed (different hydrodynamics)
Dissolution Data for MAAs
– Potential Pitfalls (continued)

• Check consistency of data, consistency of story and therapeutic relevance
  - Example 1. 18 month batch stability results very consistent: n=6; min 100%, max 103%; yet 6 months: 66%, 77%, 79%, 81%, 88%, 103%
     • Specification set at ‘≥ 60% (Q) at 45 min’ simply to meet results?
     • Any account taken of nature of drug (narrow therapeutic index, anti-epileptic)?
     • Any comment on inconsistencies between data sets?
     • Any cross-reference to development work findings (‘almost complete release at 30 min’; test biobatch 103 – 107% at 30 min)?
     • Any relevance of USP monograph limit of ≥ 85% (Q) in 30 min?
Check consistency of data, consistency of story and therapeutic relevance (continued)

- Example 2. Innovator 600mg & 800mg: 100% dissolution, 45 min; Test 600mg biobatch 63%, 45 min
  - Lab scale test 600mg, 98% dissolution after 45 min
  - What caused change? Scale-up issues?
  - 800mg test biobatch (common blend) showed little difference on scale-up. Non-homogeneous blend (one strength made first)? Difference in tablet punch tooling?

<table>
<thead>
<tr>
<th>Product</th>
<th>Cumulative % drug dissolved (Time in minutes)</th>
</tr>
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<td></td>
<td>15</td>
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<tr>
<td>Bloggatin Tablets 600 mg (Lab-scale batch)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>42</td>
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<tr>
<td>Bloggatin Tablets 600 mg (Biobatch)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<tr>
<td>Bloggatin Tablets 800 mg (Lab-scale batch)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>36</td>
</tr>
<tr>
<td>Bloggatin Tablets 800 mg (Biobatch)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>28</td>
</tr>
</tbody>
</table>
Dissolution Data to Support Post-Approval Changes / Variation Applications

• What type of changes?
  - Any change which could impact dissolution!
  - Good starting point: EU Commission classification guidance on variations
    - Which changes need comparative dissolution profiles
    - Number and size (pilot or production scale) of batches required
    - Type IA and IB changes (not Type II)

• Examples of changes
  - Formulation
    - Quantitative changes including coating weight
    - Qualitative: Change of functional excipient (i.e. other than flavour or colour)
    - Shape or dimensions of dosage form changed
  - Manufacturing process
  - Active or excipient specifications (e.g. particle size parameters)
  - In-process controls or product specifications (e.g. tablet hardness)
  - Source of active substance (case-by-case basis)
Dissolution Data for Post-Approval Changes
– Potential Pitfalls

• Example: Orodispersible tablet
  - Bitter tasting active
  - Formulation not acceptable to patients
  - Solution:
    – Reformulate to minimise drug release in the mouth
    – Claim (supported by data): Rapidly dissolves at gastric pH (1.2) releasing drug, but does not dissolve at higher pHs, such as that of saliva (pH 6.8), preventing release of the bitter drug in mouth

| pH 1.2 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Product**     | **Cumulative % drug dissolved (Time in minutes)** |
|                 |      5 |      10 |      15 |      30 |      60 |
| Old Formulation |   92  |     94  |     94  |     94  | n/a    |
| Mean            |   92  |     94  |     94  |     94  | n/a    |
| New Formulation | 100  |    100  |    100  |    100  | 100    |
| Mean            | 100  |    100  |    100  |    100  | 100    |

Conclusion: Similar, > 85% dissolved in 15 min.
Dissolution Data for Post-Approval Changes – Potential Pitfalls (continued)

Taste masking issue solved, but…?
Dissolution Data for Post-Approval Changes  
– Potential Pitfalls (continued)

- Taste masked, but now absorption issue?
- Dosing instructions – with or without food
  - Based on old formulation
  - Inadequate bioequivalence and bioavailability data to support non-applicability of dissolution findings *in vivo*

- Product status: not yet marketed in EU
- Solution: revise dosing instructions – take without food
Setting Release and Shelf Life Specification Limits for Dissolution

PhEur limits for oral dosage forms

- Conventional-release
  - usually 1 time point
  - \( \leq 45 \text{ min, } \geq 80\% \text{ (Q } \geq 75\%) \)

- Prolonged-release dosage forms
  - \( \geq 3 \text{ time points:} \)
    - 20 - 30\% (to exclude ‘dose dumping’) 
    - 50\% (defines dissolution pattern)
    - > 80\% (ensures almost complete release)
  - Guideline allows \( \pm 10\% \) limits at each time point
Setting Release and Shelf Life Specification Limits for Dissolution (continued)

PhEur limits for oral dosage forms (continued)

- Delayed-release, gastro-resistant dosage forms: \( \geq 2 \) points in a sequential test or 2 different specifications in a parallel test
  - In a sequential test, 1st point represents an upper limit (\( \leq 10\% \)) set after 1 h or 2 h in acidic medium (0.1 M HCl) and the 2nd (\( \geq 80\%, \ Q \geq 75\% \)) after a pre-set time (usually 45 min) in an adequate buffer solution (preferably pH 6.8)
    - PhEur 2.9.3: 2 h acidic medium, PhEur 5.17.1: 1 or 2 h acidic medium
    - BP gastro-resistant monographs: 45 min – 2 h acidic medium
  - Note omeprazole story (formulation: no protection in fed state)
    - Need for pH 4.5 for 1st stage? (additional / alternative test?)

Limits should reflect pertinent data

- Development, scale-up, pilot & production-scale batches, stability data
- Also consider therapeutic use, therapeutic index, drug substance solubility
Additional Considerations for Generics

- Must reflect bioequivalence study batch(es)
  - Supported by batch analyses and stability data
- Note BP monograph conditions, e.g. Gastro-resistant Lansoprazole and Omeprazole Capsules/Tablets: 1st stage pH 4.5, not pH 1.2
- USP monograph limits – not binding in EU, but may indicate what originator product is capable of and could influence regulator
Thank you for your attention

Acknowledgements: Mr Malcolm Dash