Pharmaceutical Development

- Quality specifications and end-product testing
  - with emphasis on the development of a discriminatory dissolution testing method

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Objectives of the presentation

- Role of quality specifications
  - Setting and justification of acceptance criteria
  - Selection of test procedures

- Establishment of a dissolution testing method
  - Discrimination of formulations
  - Discrimination of manufacturing performance
  - Identification of stability problems
Introduction

- **API**
  - Establishing *chemical equivalence* with Innovator API
    - Stress stability testing
      - Identify critical chemical quality attributes
      - Developing a stability indicating analytical method
        ✅ Establishing suitable acceptance criteria

- **FPP**
  - Establishing *equivalence of performance* with Innovator FPP
    - Dissolution testing
      - Developing a dissolution method with discriminatory potential for changes in formulation
        ✅ Establishing discriminatory testing conditions and acceptance criteria
Discriminatory power of a dissolution method

- Dissolution methods should be challenged during development to demonstrate that change in formulation effects change in dissolution profile

Quality specifications

- Specification
  - List of tests (test parameters) & reference to analytical procedures & appropriate acceptance criteria

- Specifications are critical quality standards

- Specifications are chosen to confirm the quality of the API / FPP

- Specifications are not intended to fully characterize the API / FPP

- Specifications are one part of a quality control strategy of the API / FPP
Quality of pharmaceutical products

Diagram:
- Design
- Development
- In-process controls
- Process validation
- Quality systems

Pharmaceutical GMP

Training Workshop on Pharmaceutical Development with a Focus on Paediatric Medicines / 15-19 October 2007
Quality specifications

- The quality of APIs and FPPs is determined by a well-controlled, validated manufacturing process
  - Critical quality attributes of input materials
  - Critical process parameters

- Quality specifications are established to ensure that APIs and FPPs meet the pre-determined acceptance criteria derived from thorough product characterization during development
Quality specifications of biological APIs

- The quality of APIs resulting from biological processes such as fermentation cannot be sufficiently ensured by quality specifications

- PQIF
  - Not suitable for evaluation of biological APIs

- Biological APIs are not subject of this presentation
Quality specifications

General concepts

- Periodic testing / skip testing
  - Pre-selected batches / predetermined intervals
    - Justification / less than full schedule testing / post approval

- Release versus shelf-life specification
  - Acceptance criteria / set of tests

- In-process tests
  - Conducted during manufacturing process / acceptance criteria

- Exclusion of tests
  - Supported by development data
    - Extractables / particle size / dissolution >> disintegration

- Revision of specifications based on sufficient batch data
Quality specifications

- **Pharmacopoeial standards**
  - If appropriate, pharmacopoeial test procedures and acceptance criteria should be used.
  - *Alternative test procedures (and acceptance criteria) may be used if comparability to or superiority to the pharmacopoeial procedure is demonstrated.*
  - If *pharmacopoeial finished product standards* are used compliance to each test parameter/procedure/acceptance criteria is understood.
Quality specifications

Specifications typically not included in official compendia

- Residual solvents
  - API and FPP (e.g. granulation, film coating)
- User requirements
  - Particle size
    - Potential critical quality attribute identified during pharmaceutical development
  - (Polymorphic forms)
Verification of compendial standards

Compendial assay methods

- API
  - Verification of applicability with the necessary accuracy and precision
  - Verification of specificity with regard to impurities/degradants identified during stress testing
    - comparable impurity profile

- FPP
  - Verification of applicability with the necessary accuracy (matrix!) and precision
  - Verification of specificity with regard to impurities/degradants identified during stress testing
Verification of comparability of in-house methods with pharmacopoeial standard

- **Abacavir sulfate PhInt**

- **In-house impurity profile should be verified by comparison with PhInt method**
  - Comparison of retention times of PhInt impurities with chromatographic profile of sample
  - Verification that impurities B and D-F are not present (e.g. spike with impurity standard)

<table>
<thead>
<tr>
<th>PhInt profile (PhInt method)</th>
<th>In-house profile (in-house method)</th>
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<tbody>
<tr>
<td>Impurity A</td>
<td>Enantiomeric impurity</td>
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<tr>
<td>Impurity B</td>
<td>-</td>
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<tr>
<td>Impurity C</td>
<td>Amino-impurity</td>
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<td>Impurity D</td>
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<td>Impurity E</td>
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<td>Impurity F</td>
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<tr>
<td>-</td>
<td>Chloro-impurity</td>
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<tr>
<td>-</td>
<td>Pyrimidine-impurity</td>
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</tbody>
</table>
Quality specifications

„A specification establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use“ (ICH Q6A)

…Justification should be presented for each procedure and each acceptance criterion included (ICH Q6A)

− Development data, pharmacopoeial standards, test data from preclinical and clinical studies, results from stability studies
− Range of expected analytical and manufacturing variability
Quality specifications (FPP)

**General Characteristics and Tests**

- **Description**
  - Size, shape, colour

- **Identification**
  - Identity of API (discriminatory)

- **Assay**
  - Specific, stability-indicating

- **Purity**
  - Degradation products (single un-identified and identified; total)
  - Residual solvents
Quality specifications (FPP)

Particular Characteristics and Tests

- Oral solid dosage forms
  - Dissolution
    - Disintegration (dissolution > 80% in 15 min at pH 1.2 – 6.8)
  - Hardness/friability
  - Uniformity of dosage units
  - Water content
  - Microbial limits
Quality specifications (FPP)

Particular Characteristics and Tests

- **Liquid dosage forms for oral use**
  (& powder and solution for reconstitution)
  - Uniformity of dosage units
  - pH
  - Microbial limits
  - Antimicrobial/Antioxidative preservative content
  - Antimicrobial preservative effectiveness
  - Extractables
  - Dissolution (suspensions)
  - Particle size distribution
  - Redispersibility (time required)
  - Water content (powder and solution for reconstitution)
Quality specifications (FPP)

Particular Characteristics and Tests

- **Parenteral** drug products
  - Uniformity of dosage units (powders for reconstitution)
  - pH
  - Sterility
  - Endotoxins
  - Particulate matter (visible /subvisible particulates)
  - Water content (powders for reconstitution)
  - Antimicrobial/Antioxidant preservative content
  - Antimicrobial preservative effectiveness
  - Extractables
  - Osmolarity
  - Particle size distribution (suspensions)
  - Redispersibility (suspensions)
  - Reconstitution time
Particular aspects – FDC-FPPs

- WHO TRS 929, Annex 5, Guidelines for registration of fixed dose combination medicinal products
  - Emphasis on **homogeneity of APIs** in dosage form (≤ 25 mg/%)
    - Homogeneity of blend before compression (content uniformity, PhInt, PhEur, USP)
    - Homogeneity of finished dosage form (content uniformity, PhInt, PhEur, USP)
  - Emphasis on **adequate impurity specifications**
    - Calculation with reference to the parent API or API with lowest peak area percentage
    - Particular attention to adequate validation of analytical procedure
    - **Stability testing**
      - Impurity specifications based on adequate stress testing (Appendix 3)
  - Emphasis on **adequate dissolution testing**
    - More than one dissolution medium may be necessary
Quality specifications - limitations

- Quality specifications are applied to a relatively small proportion of a batch and rely on representativeness of samples for a batch
  - Well controlled manufacturing procedure (dosage forms)

- Acceptance criteria of quality specifications are limited by the performance/capability of the method used for testing
  - Specifications (assay, impurities) based on inadequate validation
    - Impurity specifications and LOQ / response
    - Assay specification and peak purity
    - Impurities not covered by an analytical method
Quality specifications - potential

- Unravel unexpected related quality problems
  - Quality problems identified by non-conformance to organoleptic parameters/appearance
    - Odour (discovery of genotoxic esylates)
    - Turbidity \([\text{Ba}^{2+}\text{(type I-glass !)}\) and \(\text{SO}_4^-\)-containing FPP-solution]\)
    - Color (formation of degradation products)
Pediatric formulations in PQ

- Isoniazid + Pyrazinamide + Rifampicin tablet
  30mg+150mg+60mg
  - Uncoated dispersible tablet with break line
    • 7th EOI, antituberculosis medicines

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Quality specifications - Dissolution

- **Performance Testing (ICH Q8)**
  - **Performance** can be considered as an indicator of the delivery of a drug from the dose to the target site (type of dose/route of administration)
  - **Performance monitoring** of unit solid dosage forms is usually addressed as the disintegration of the preparation and the dissolution of the active substance in a suitable medium

- **Disintegration testing** should demonstrate the effective break up of the solid formulation after administration (performance of disintegrant)

- **Routine performance of disintegration testing** may not be necessary if a dissolution test with acceptable discriminatory power is included in the finished product specification
Dissolution - ICH Q8

- The actual amount of drug liberated from the dose form into an aqueous reservoir in vitro is intended to reflect the in-vivo behaviour of the product.

- In-vivo behaviour is dependent on several factors making in-vitro / in-vivo correlation difficult.

- Investigation of dissolution characteristics should routinely be applied to all solid dosage forms at the development phase.

- From such studies a decision can be made as to the relevance of the dissolution test to the in-vivo behaviour and its ability to discriminate between formulation changes.
Preliminary considerations

- Physical parameters of APIs demonstrated to be variable and critical for the quality of the product need to be controlled
  
  - Additional physical tests beyond scope of a monograph
    
    - Water content (crystal properties/particle size/stability)
    - Particle size (bioavailability/content uniformity/solubility/stability)
    - Crystal properties and polymorphism (solubility / bioavailability / stability)
Development of Dissolution Testing

- Consideration of physicochemical characteristics of the API in formulation
  - Solubility of API (at 37 °C)
    - choice of formulation/choice of analytical method
  - Physical properties of APIs and excipients
    - Differing properties may lead to uneven distribution/alteration in drug delivery

- To be addressed in development studies
  (WHO TRS 929, Annex 5, (6.3.2.3, 6.3.2.5, 6.3.3, Appendix 3)
  - Homogeneity
  - Performance characteristics (e.g. dissolution testing)
    - Establishing pharmaceutical equivalence to innovator
Development of Dissolution Testing

- Establish a dissolution method
  - Apparatus
  - Dissolution medium
  - Test conditions

- Expectations
  - discriminating sufficiently rugged
  - Reproducible for day-to-day operation
  - Capable to be transferred between laboratories
  - Acceptance criteria representative of multiple batches
    - Same composition, same manufacturing procedure including key batches (clinical studies/stability studies)
Development of Dissolution Testing

- **Discrimination (balance)**
  - Distinguishing significant changes in a composition or a manufacturing process – *likely to affect bioavailability*
  - Distinguishing between batches - *without significant difference observed in vivo*
  - Reflect relevant *changes in drug product over time* (by temperature / humidity / photosensitivity and other stresses)

- **Characterize discriminatory power of the procedure**
  - Assessing results from multiple batches (typical variability in composition and manufacturing parameters)
  - Intentional variation of manufacturing parameters (e.g. lubrication, blend time, compression force) or drying parameters
Development of Dissolution Testing

- Separate development of different dissolution methods for different purposes
- Discrimination between different concentrations of a functional excipient (sodium laurylsulfate) in preformulation experiments

Variability of dissolution data is discouraged
- because it is difficult to identify trends or effects of formulation changes on highly variable data
  - RSD ≥ 20% at ≤ 10 min, RSD ≥ 10% at > 10 min

Root cause investigation on variability (prerequisite)
- Variability of formulation itself
  - Content uniformity, process inconsistency, excipient interactions, film coating capsule shell aging, hardening/softening of dosage form (stability)
- Artifacts associated with test procedure (coning, sticking)
- No free dispersing of contents throughout vessel
  - Change of apparatus, agitation speed, deaeration
  - Sinker type, composition of medium
Development of Dissolution Testing

- **Selecting a suitable dissolution medium**
  - Solubility of drug
  - Solution state stability
  - SINK conditions
    - Dissolution volume 3 – 10 times saturation volume (PhEur; USP)
    - Physiologic pH range 1.2 – 6.8, aqueous

- **Selection of appropriate conditions for routine testing**
  - discriminatory capability
  - stability of the analyte
  - relevance to the in-vivo performance
Development of Dissolution Testing

- **Typical media**
  - Dilute HCl, buffers in the pH range 1.2 – 6.8, simulated gastric/intestinal fluid, water

- **Volume**
  - 500 – 1000 ml (900 ml)
    - Extendable to 2 – 4 L (sink conditions) with justification, validation

- **Apparatus**
  - Basket or paddle (most frequently for solid oral dosage forms)
  - Reciprocating cylinder or Flow through cell (special dosage forms)

- **Agitation**
  - Baskets: 100 rpm / Paddles: 50 – 75 rpm
    - Decreasing or increasing (25 – 150 rpm) justified if supported by data/profiles/results
Development of Dissolution Testing

Design of dissolution studies

- Immediate release dosage forms
  - For routine release purpose
    - Single time point specification
  - For product **comparability/performance**
    - Profiles with NLT 5 time points
      - Characterise ascending and plateau phase
      - Calculation of similarity factors
    - Exception
      - Release of more than 85% of API within 15 min
Development of Dissolution Testing

- Assay
  - Spectrometric determination (fast/simple/no solvents)
  - HPLC
    - no interference from excipients, stability indicating, specific

- Validation of assay
  - Specificity / Linearity and Range / Accuracy/Recovery / Precision / Robustness / Solution stability
Acceptance criteria (see also ICH Q6A)

- Typical range Q=75 – 80%
  - Assay and content uniformity ranges are considered
- To be established on the basis of evaluation of profile data
- Consistency with historical data
  - Acceptable batches will fall within the acceptance criteria
    - No significant differences in in vivo performance, composition, manufacturing procedure
  - Unacceptable batches should be outside the acceptance criteria
    - Batches from the development phase that showed poor bioavailability, different composition, difference in manufacturing procedure
Acceptance criteria II

- Discriminating stability problems
  - Disintegration rate affected by change in hardness, friability
    - Dissolution rate subsequently revealing change

- Discriminating manufacturing problems
  - Dissolution affected by alternative manufacturing procedure/alternative manufacturing site?
    - Variation No. 5, Doc. No. 9
    - (Supplement I, Generic Guideline)
Formulation investigation by dissolution

<table>
<thead>
<tr>
<th>API</th>
<th>Filler</th>
<th>Binder</th>
<th>Disintegrant</th>
<th>Lubricant</th>
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</table>

- **Objective:** Develop a formulation which is pharmaceutically equivalent to the innovator (capsules)

- **Direct filling**
  - Improper flow, poor uniformity of content

- **Wet granulation (with water)**
  - Dissolution inferior to innovator

- **Sieving at different mesh size, disintegrant partly extragranularly**
  - Dissolution higher than innovator

- **Decreasing the quantity of disintegrant**
  - Dissolution slightly faster than innovator

- **Adding binder intragranularly**
  - Dissolution still slightly faster than innovator

- **Decreasing disintegrant**
  - Final formulation; dissolution performed without sinker
Dissolution Testing and in-vivo performance

- Dissolution and potential in vitro / in vivo correlation
  - Biorelevant medium (USP; Medium with some relevance on the in vivo-performance)
    - Absorption site (if known)
    - Rate-limiting step to absorption
      - Dissolution or permeability?
    - Case A: quick dissolution in the stomach, high permeability
      - Rate limiting step to absorption may be gastric emptying time → acidic dissolution medium
    - Case B: poorly soluble drug, weak acid
      - dissolution mainly in the intestine → pH 6.8 dissolution medium
Dissolution Testing and in-vivo performance

  - Relationship of rate of disintegration versus rate of dissolution
Dissolution testing and in-vivo performance

- Discriminatory potential of dissolution test conditions and acceptance criteria
  - Physical characteristics of the APIs
    - Relation between solubility and permeability of the drugs
  - Influence of formulation on performance

- Dissolution test conditions and acceptance criteria must be developed individually for each particular formulation
Summary

- A well controlled manufacturing process is the essential prerequisite for FPPs
- Quality specifications will help to ensure that manufacturing has been performed under well-controlled conditions to meet predetermined acceptance criteria
- Dissolution testing can help to develop a suitable formulation and manufacturing process during development
- Established discriminatory dissolution testing will consequently identify FPP-problems
THANK YOU