Most common drug product transfer issues from a competent authority's point of view

Dedicated to your information and advancement.

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1

Disclaimer

Introduction Swissmedic

- Swiss agency for therapeutic products, founded 1/02, affiliated to Federal Department of Home Affairs
- Core units: marketing authorisation, market surveillance, licenses
- Legal basis: Swiss National Law on Therapeutic Products (LTP)
- Our website: http://www.swissmedic.ch

Agenda

- Pre-approval issues
- Post-approval adaptions
  - Improved methods
  - New manufacturing site
- Trouble shooting
- General comments
  - Future and current situation
  - Consistent quality documentation
  - Facilitated review

Pre-approval issues

- The **rationale** of the development (target product profile, TPP) is unclear
- Formulations used in early phases of the development are not properly **bridged** to the formulation intended to be marketed
- **Setting of specifications** is often erratic

Likely missing development data (1)

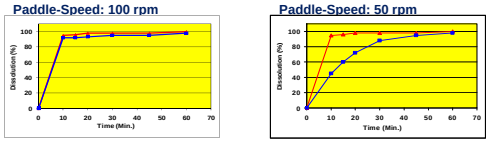
- **Discussion** of drug substance characteristics, which may impact the manufacturing process and/or drug release (e.g. solubility, polymorphism, particle size)
- Justification of manufacturing-**overages**

Likely missing development data (2)

- Discussion on the chosen type **and amount** of excipients
- Justification of key excipients **with impact on the in-vivo performance** (e.g. solubilizer)
- Inadequate excipients /API **compatibility data**, e.g. for combination products

Bridging (1)

- Bridging between drug used in clinical trials and for commercial purposes is often not discussed
- Be aware**: In-vitro dissolution studies may not be supportive**, if method has no discriminatory power



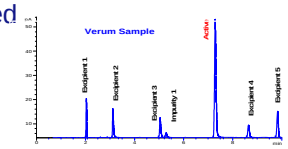
Hardness 45 and 60 KN

Bridging (2)

- Bridging by quality / in-vitro data only („Biowaiver“) may not be possible, e.g. for:
  - Narrow therapeutic index drugs
  - BCS Class 2/4 compounds
  - Modified release products
  - Dermal formulations
- In such cases a BE study, PD study or PK study will be required

Common deficiencies in DP control

- To control degradation, analytical methods need to be **selective**, **LOD/LOQ , SST** are often not addressed



- Formulations tested with pharmacopoeial methods (e.g. KF titration for water content in tablets) require product specific validation

Justification of DP Specification

- Respect pharmacopoeia (law)
- Evaluate development data / batch data / stability data
- Follow Guidelines (e.g. ICH Q3B: Identification- and Qualification-Thresholds for Degradation Products
- Utilize preclinical and/or literature data

DP specifications pitfalls

- Avoid **inconsistencies** between either
  - API and DP specifications or
  - DP data and DP specifications
- **Explain differences** between testing during development and release/stability
- Microbiological **purity testing** for non-sterile drugs is often missing / skip testing not justified

New manufacturer

- To introduce an **additional manufacturer** is quite common
- Represents majority of approvable changes in Switzerland
- Often associated with further, however not necessarily consequential changes (e.g. increase in batch size, changes in manufacturing method)

DP Manufacturing process

- Guideline text:

  „It is in the interest of both the applicant and the regulatory authorities to avoid unnecessary applications for variations. **Very detailed descriptions of the manufacturing process, apparatus and in-process controls should therefore be avoided“**
- Describe operating ranges; for type of equipment used see e.g. SUPAC Manufacturing Addendum
- Good flow diagrams are very helpful

Trouble shooting issues

- **Changes in formulation** may be required due to
  - Feedback from market
  - Technical failure and/or unexpected physical and/or chemical instability
  - Unavailability of an excipient
- **Specification** may turn out to be unsuitable (e.g. limits for micronized drug particles in formulation)

Feedback from market

- Typical market complaints, followed by change applications, are:
  - Primary packaging or dosage form difficult to handle
  - Aesthetics/appearance unsatisfactory
  - Different odor or taste preferences than expected (tested?)

A selection of more serious defects (1)…

- A new, more stable polymorph with lower solubility is formed in a product where oral absorption is solubility limited. Such alteration is noticed during scale up and/or after long term stability only
- Sticking of tablets during production, not noticed during small scale manufacturing at low speed

A selection of more serious defects (2)…

- Phase separation of semisolids during real time/real condition storage occurs
- Drug substance recrystallises in transdermal systems
- Alternative packaging material or excipients from a new source lead to instability of the product

Excipients selection criteria

- Regulatory status (more than 1000 excipients are in pharmaceutical use):
  1. Compendial excipients
  2. Noncompendial excipients with precedence of use (e.g. Inactive List, U.S.A. Excipient Directory by JPEC)
  3. Food/cosmetic/pharmaceutical excipients with new use (GRAS Status, CIR)
  4. Novel excipients
- Second source!

Motivation..

- .. to use uncommon excipients:
  - Solubilization of new potent drug substances
  - New dosage forms
  - Unique drug product properties
  - Drug targeting
- Consider uncommon excipients!
- Consider **increased risk** for specific excipients (e.g. TSE/BSE, e.g. genotoxic impurities from reagents)

ICH Q8 - Quality by Design

- Quality by Design means
  - Designing and developing formulations and processes to **ensure a predefined quality** (TPP)
- Quality by Design requires
  - **Understanding** how formulation and process variables influence product quality = more work for applicant and agency
- Quality by Design ensures
  - **Product quality** = less changes?

Current situation summary

- **Scientific understanding** as foundation for any drug product transfer is key
- Companies could probably benefit from a more structured feedback from issues resolved in the past (**lessons learned**). Work based on prior knowledge is well accepted
- **A close contact** between development/ production/regulatory experts and compentent authority should facilitate improvements

Consistent quality documentation

- **CTD format** is well established
- **DMF procedure** is widely used especially for generic drugs
- Proper **maintenance** of module 3 is advisable (regulatory compliance)
- **Track of changes** does not need to be submitted to CA, however…

Facilitated review

- Review is facilitated by a clear understanding and a **sound scientific justification**
- Changes should be adressed indicating the **present and proposed situation** in tabular format
- e-CTD hopefully reduces readability issues
- A good documentation speeds up approval time significantly!