BE assessment of transdermal patches

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Topics

- Transdermal patches – the basics
- In vitro approach to BE by Franz cell permeation
- First in vivo studies – pilot BE study
- Proof of BE – pivotal BE study
- New aspects from the draft guideline
Transdermal patches – the basics

**Composition of matrix patches**

- **Back ing layer = outer surface**
- **Drug containing adhesive matrix**
- **Release liner = protective film**

**Route of administration**

- **Barrier: Stratum corneum**
Relevant guidelines

- Guideline CPMP/EWP/QWP/1401/98 Rev1/Corr
  - Investigation of bioequivalence

- Note for Guidance CPMP/EWP/280/96 Corr
  - Modified release oral and transdermal dosage forms: Section II

- Draft Guideline EMA/CHMP/EWP/280/96 Corr1
  - Pharmacokinetic and clinical evaluation of modified release dosage forms
  - Update to former guidelines

- Draft Guideline EMA//CHMP/QWP/911254/2011
  - Quality of transdermal patches
Franz cell experiments

- In vitro model
  - Prediction of permeation behavior
  - No in vitro – in vivo correlation!
- For generics: comparison with reference
- Skin samples or artificial membranes

- Obstacles
  - Cell creates occlusive conditions
  - Sink conditions required
  - Additives
  - Selection of membrane
    - EVA, mouse, pig, human

Acceptation compartment
Skin sample/membrane
Patch (test preparation)
Lid
Franz cell experiments

- Integrity of the skin/membrane – Guideline requests proof
- Min. n=6 samples when using skin
- n=4 sufficient with artificial membranes (own experience)
- Duration of experiment: 72 h (state of the art)

- Draft guideline „Quality of transdermal patches“
  - Regular testing by in vitro skin permeation throughout shelf-life
  - Use as quality control parameter

- Own experience
  - Not useful as quality control parameter
  - Albeit highly standardized procedures high data scattering
Example permeation chart

Drug permeation from patches through dermatomed human skin

- Preparation 1
- Preparation 2

Cumulated amount [µg/cm²]

Time [h]

24 h: no difference detectable
72 h: difference detectable
BE study generals

- Number of test persons essential
  - Statistical significance
  - Depending on evaluation method and scope of study
  - Determines quality of results
  - Refer to experienced staff

- Randomized two-period, two-sequence cross-over studies
  - Single dose
  - Multiple dose
  - Open label
BE studies transdermal-specific

- Important evaluation criteria
  - AUC
  - \(T_{\text{max}}\)
  - \(C_{\text{max}}\)

- Identical application site for test and reference
  - Chest
  - Arm
  - Back

- Critical parameters during application in the clinic
  - Experience of the study nurse
  - Skin state (use of creams/lotions)
  - Hairy skin (removal by scissors)
Pilot Bioequivalence studies (I)

- Aim: first proof of BE for development/first indication on performance
  - One strength (highest or intermediate)

- Small number of test persons
  - Sufficient to show statistical significance
  - Usually about 10-25
  - Seek guidance of biometrics and medical staff

- Test patches often without application aid
  - Due to small scale origin
  - Challenging for clinical staff
  - Briefing prior start of study
Pilot Bioequivalence studies (II)

- **Application**
  - Chest preferred
  - Fixation possible, if proof of concept
    - Lifting of edges
    - non-conformance to guideline
    - Improvement of adhesive properties prior pivotal BE!

- **Extrapolation of patch size**
  - In case BE is not reached – adjustment of patch size
  - Only possible to certain extent
Limits of extrapolation – example (I)

First pilot study: due to safety concerns, test had half of the patch area of reference

BE not reached - estimation by extrapolation performed:
- Increase of patch size of test by 105% will be successful
Limits of extrapolation – example (II)

Second pilot study: patch area 105% of initial area

BE still not reached - estimation over the large range too imprecise
-> Increase of patch area should have been about 140%
Pivotal Bioequivalence studies (I)

- Designed to show bioequivalence – part of the dossier
  - guidelines fully applicable
  - Standard acceptance limits (80-125%; 90% CI, ANOVA)
    - $\text{AUC}_{(0-t)}$, $\text{AUC}_{(0-\infty)}$, $\text{C}_{\text{max}}$, partial $\text{AUC}$ (single dose)
    - $\text{AUC}_{(0-\tau)}$, $\text{C}_{\text{max,ss}}$, $\text{C}_{\tau,ss}$ (multiple dose)
Pivotal Bioequivalence studies (II)

- Guideline requirements on test product
  - Final equipment
  - 1/10 production scale or 100,000 units, whichever higher
    - For TDS often 100,000 units

- In the past, combination of sizes has been accepted
  - All sizes gained from 1 intermediate product (laminate)
  - total of 100,000 patches; per size smaller amounts acceptable
Pivotal bioequivalence studies (III)

- Further things to consider
  - Co-medication for healthy subjects (high potency drugs)
  - Additional fixation not possible -> final product approach
  - Testing of highest strength sufficient with dose proportionality
    - Lowest strength may be acceptable when safety concerns exist
      - exceptional cases, justification

- Choice of reference
  - Full dossier available?
  - Abridged/hybrid applications not acceptable as reference
    - Further studies requires
Pivotal bioequivalence studies (IV)

- Further things to consider
  - Comparability of batches
    - Assay of test shall not differ more than 5% from that of reference
    - Test procedure for test product to be used
      - Differences for reference possible!
  
- CRO location
  - Site visit
  - Pre-training with CTS
  - Study monitoring
Irritation/Sensitization testing

- Monitoring during study possible
- Data on previous experience required
  - Adhesives usually tested
  - ISO 10993 as guidance
- Equivalence or superiority to reference
Draft guideline „quality of transdermal patches“

- EMA/CHMP/QWP/911254/2011
- Addresses critical clinical parameters
  - Bioequivalence
  - Irritation/sensitization
  - In vivo skin adhesion

- New limits
  - Size for generics essentially identical
  - Size +20% acceptable in special cases, all other properties must comply
  - Increased adhesion testing protocol
Adhesion testing – critical issues (I)

- Assessment in 5% increments
  - Requires some matrixed positioning device
    - Transfer of loose sections to stencil
    - Photodocumentation
  - Assessment may be difficult with non-transparent patches
    - Fabrics/non-wovens
    - Adhesive overlays
Adhesion testing – critical issues (II)

- Mode of assessment /documentation
  - Manipulation for assessment – effect on adhesion?
  - Transfer of detachment-pattern to matrixed stencil

- Photography suggested by guideline
  - Resolution of images?
  - Significance with non-transparent patches?
Resume (I)

- Bioequivalence testing with TDS
  - essential part of patch development
  - challenging

- New guidelines increase requirements
  - Establishing common standards
  - Some requirements are difficult to adapt

- In vitro skin permeation (Franz cell experiments) give guidance
  - No in vivo in vitro correlation
Resume (II)

- Pilot bioequivalence studies are useful
  - Limits in extrapolation

- Adhesion must be monitored starting in early stage

- Pivotal bioequivalence studies must be carefully planned
  - Considering bioequivalence guideline
  - Adhesion
  - CRO choice
Thank you!