BE assessment of transdermal patches

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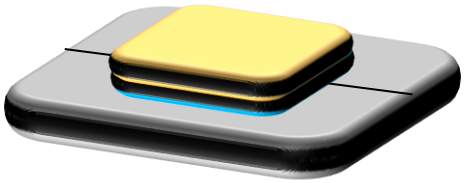
Topics

- 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

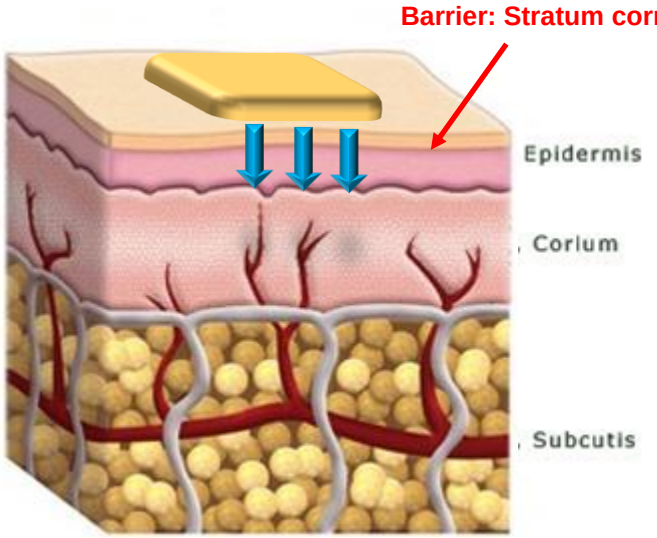


Backing layer = outer surface

Drug containing adhesive matrix

Release liner = protective film

Route of administration



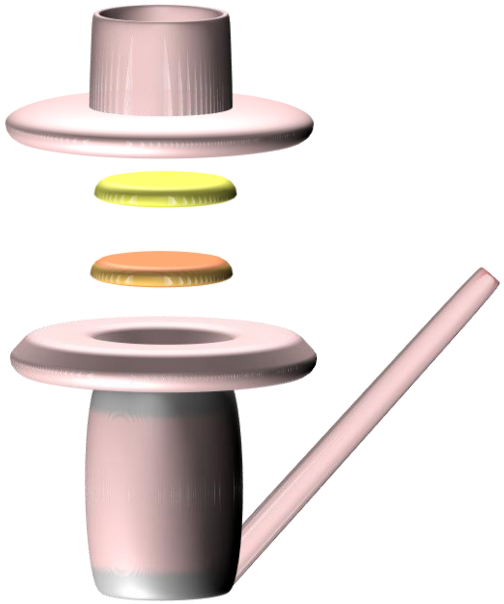
Relevant guidelines

- 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



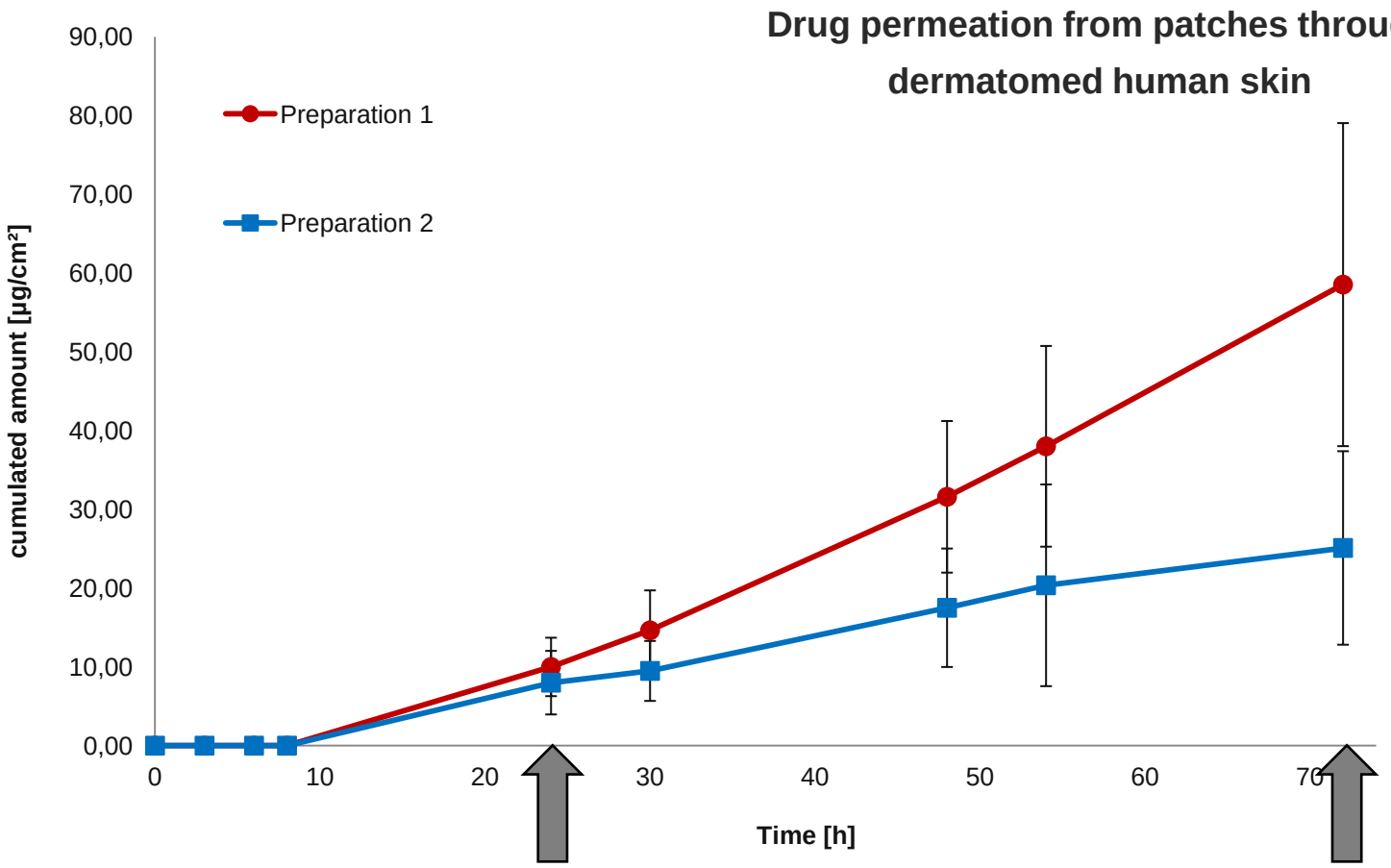
Franz cell experiments

- 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



24 h: no difference detectable

72 h: difference detectable

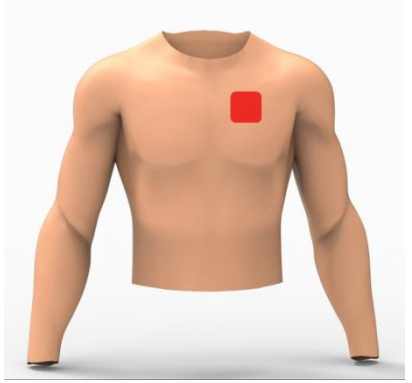
BE study generals

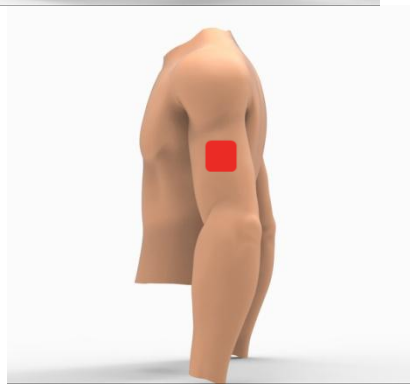
- Number of test persons essential
  - Statistical significance
  - Depending on evaluation method and scope of study
  - Determines quality of results
  - Refer to experienced staff

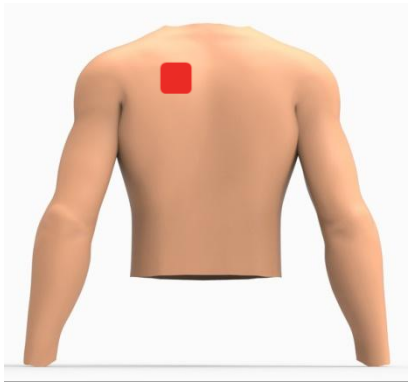
- Randomized two-period, two-sequence cross-over studies
  - Single dose
  - Multiple dose
  - Open label

BE studies transdermal-specific

- Important evaluation criteria
  - AUC
  - T_{max}
  - C_{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

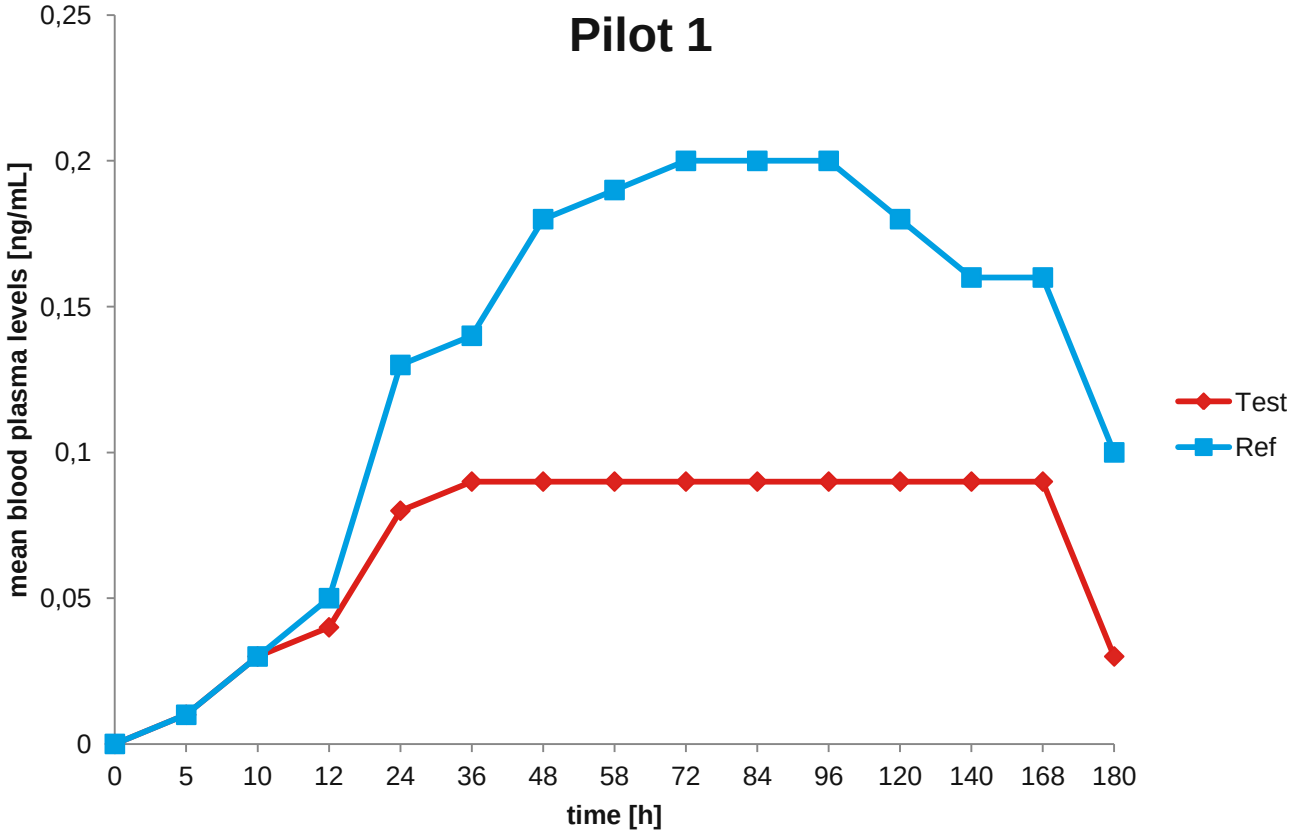
Pilot Bioequivalence studies (II)

- 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

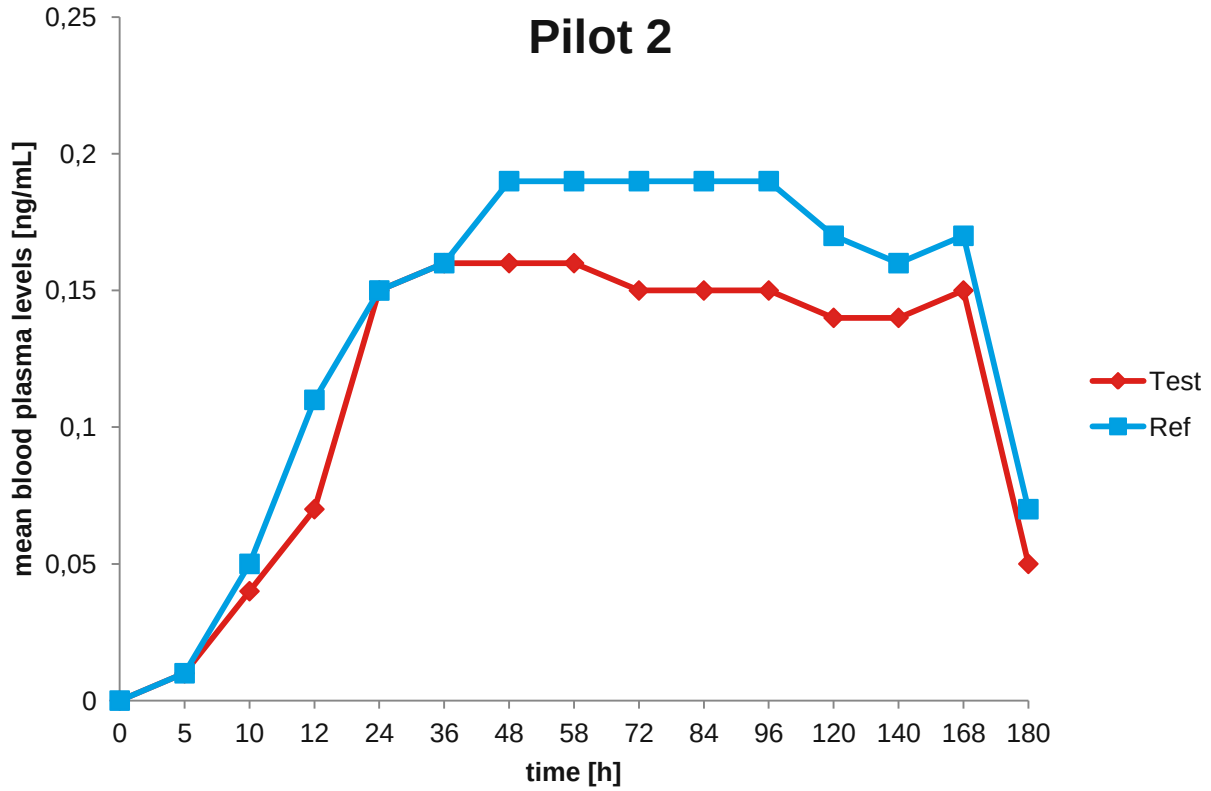


BE not reached - estimation by extrapolation performed:

-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

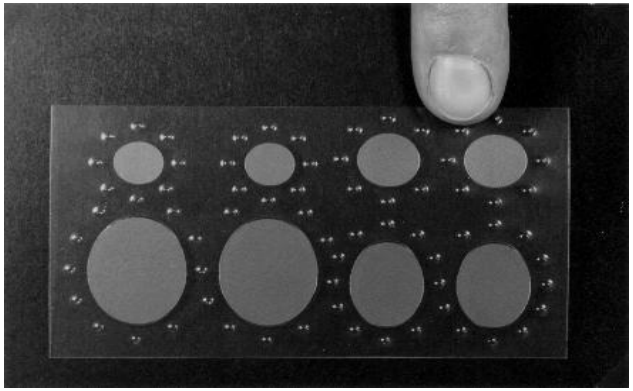
-> Increase of patch area should have been about 140%

Pivotal Bioequivalence studies (I)

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

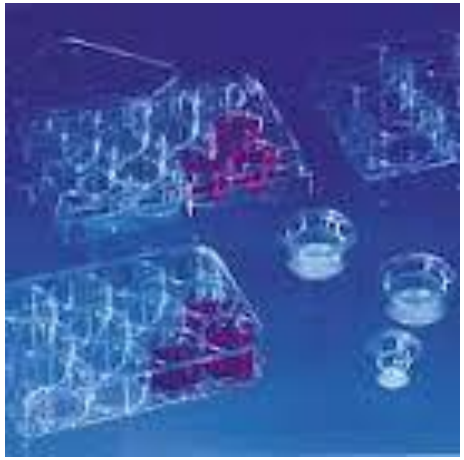
- Further things to consider
  - Co-medication for healthy subjects (high potency drugs)
  - Additional fixation not possible -> final product approach
  - Testing of highest strength sufficient with dose proportionality
    - Lowest strength may be acceptable when safety concerns exist
      - exceptional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

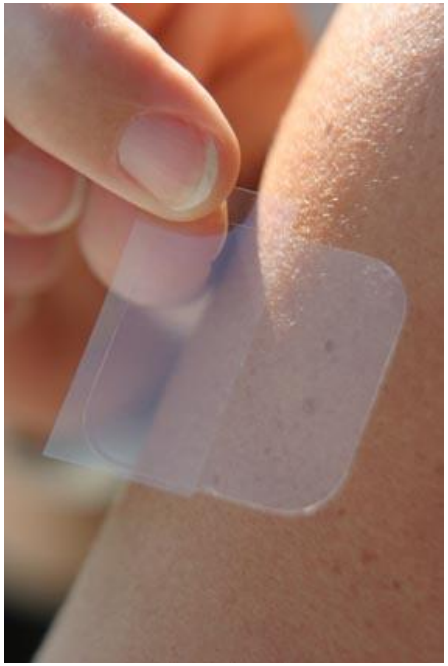


Draft guideline „quality of transdermal patches“

- 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

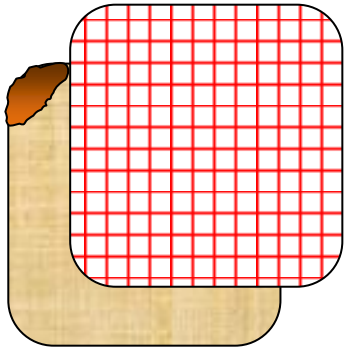
Adhesion testing – critical issues (I)

- 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!