

TDDS and Appendix I + II

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Disclaimer

The presentation reflects the personal opinion of the author and not necessarily the official policy of the EMA or national agency

Transdermal drug delivery systems (TDDS)



A TDDS or transdermal patch is defined as a flexible pharmaceutical preparation of varying size containing one or more active substance(s) to be applied on the intact skin for systemic absorption. Such TDDS are designed to provide a slow delivery of the active substance(s) through the intact skin resulting in a controlled systemic absorption rate.

Pharmacokinetic Studies required for TDDS of a new chemical entity



- Studies should be conducted to evaluate drug transport characteristics and the rate limiting step that determines systemic availability i.e. drug release and/or skin reservoir and/or other formulation related particularities
- Single-dose and multiple-dose investigations necessary.

Pharmacokinetic Studies required for TDDS of a new chemical entity



considering particular aspects:

- application site-dependent absorption
- fluctuation
- lag-times
- concentration time profile after patch removal

Studies required for TDDS of a new chemical entity

In addition to conventional phase I studies

- skin irritation, sensitization (see also appendix 1)
- Phototoxicity
- patch adhesion
- effect of sauna and sunscreen on the patch adhesion

should be investigated.

(see also Guideline on quality of transdermal patches
EMA/CHMP/QWP/911254/2011)

GENERICCS

Generics



- It is advisable to ensure comparable or better adhesion properties prior to bioequivalence investigations in volunteers since inferior adhesion could invalidate the pharmacokinetic results and question the acceptability of the product.
- The adhesion properties of the patch should not be altered by e.g. over-taping

Generic TDDS

dose	Single dose	Multiple dose
40 mg		
20 mg		
10 mg		

with accumulation

with no risk of accumulation

	Single dose study	Multiple dose study
C_{max}	yes	
$AUC_{(0-t)}$	yes	
$AUC_{(0-\infty)}$	yes	
partial AUCs		
$C_{max,ss}$		yes
$C_{\tau,ss}$		yes
$AUC_{(0-\tau)ss}$		yes



Bioequivalence should be assessed using the same pharmacokinetic parameters as for prolonged release formulations

	Single dose study	Multiple dose study
C_{max}	yes	
$AUC_{(0-t)}$	yes	
$AUC_{(0-\infty)}$	yes	
partial AUCs	yes	
$C_{max,ss}$		
$C_{\tau,ss}$		
$AUC_{(0-\tau)ss}$		

New recommendations

- To avoid medication errors that arise from poor visibility, the development of invisible patches should be considered conservatively. In these cases the usage of prominent ink as printing on the patches to increase noticeability is encouraged.
- Therefore adhesion tests should be performed in individuals with similar skin conditions as the expected patients.

in vivo skin adhesion

APPENDIX II

Patch adhesion



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



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EMA/CHMP/QWP/911254/2011
Quality Working Party (QWP)

Guideline on quality of transdermal patches
Draft

Annex 2 In vivo skin adhesion

The investigation of *in vivo* adhesive performance may be included as a component part of human clinical pharmacokinetic and efficacy studies (both single dose and multi dose), or may be an independent study with either patients or volunteers.

Patch adhesion

The scores for adhesion of transdermal patches should be scaled in 5 % increments as indicated below:

- more than 95 % of the patch area adheres
- more than 90 % of the patch area adheres
- more than 85 % of the patch area adheres
- more than 80 % of the patch area adheres
- more than 75 % of the patch area adheres
- more than 70 % of the patch area adheres
- less than 70 % adheres or patch detachment

In general, a mean adherence of greater than 90% should be expected

Patch adhesion

The results should be reported in explanatory tabular and graphical formats, including:

- frequency table showing the number of patches with each adhesion score at each evaluation time point.
- number of patches that are completely detached at each evaluation time

A critical assessment and statistical analysis should be provided.

FINAL VERSION

- Accidental transfer of a patch to the skin of a non-patch wearer
- poor-adhesion related risks

have to be prevented by ensuring acceptable adhesion characteristics by the patch.

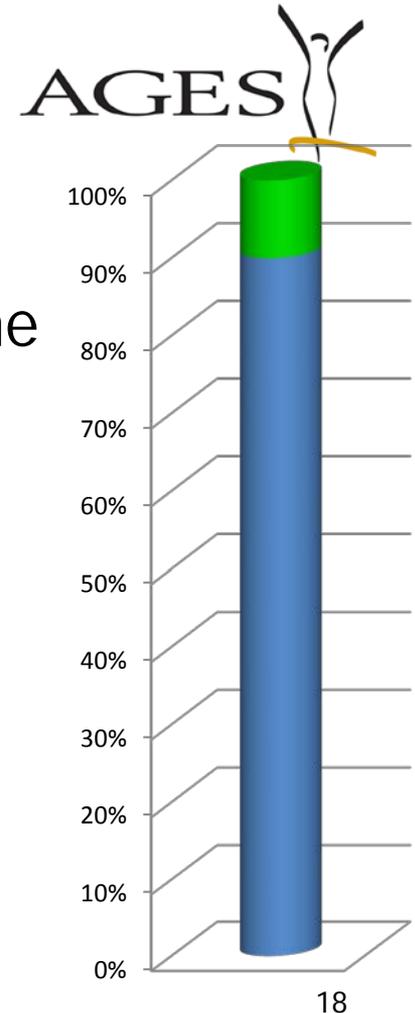


descriptive presentation of the study results

Adherence	Evaluation time point							
	..h		..h		..h		..h	
	Ref.	Test	Ref.	Test	Ref.	Test	Ref.	Test
	Nr.(%)	Nr.(%)	Nr.(%)	Nr.(%)	Nr.(%)	Nr.(%)	Nr.(%)	Nr.(%)
≥ 90%								
≥ 80%								
≥ 70%								
≥ 60%								
≥ 50%								
0% to < 50%								

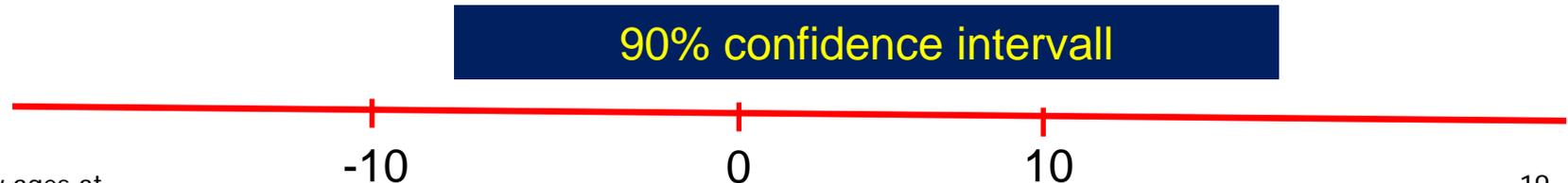
Patch adhesion

- The adhesion should be measured as the percentage of area that remains adhered at the end of the dosing interval.
- In general, it is expected that the 90% confidence interval of mean adherence for the test product at the end of the dosing interval should lie above 90%. This should therefore normally be the primary comparison.



Patch adhesion

- non-inferiority of the test product to the reference product, if the reference product has poor adherence ($< 90\%$).
- The lower limit of the 90% confidence interval for the difference of adhesiveness (test – reference), using the percentage of adhesion as continuous variable, should not be less than -10% .



sensitisation and irritation test for transdermal products

APPENDIX I

sensitization and irritation test



- to fully evaluate the equivalence of a generic transdermal product to the reference product similarity has also to be shown for skin irritation and sensitization unless otherwise justified by e.g. very similar quantitative and qualitative composition.
- intended to recommend study designs and scoring systems to test skin irritation and sensitization during development of transdermal products.

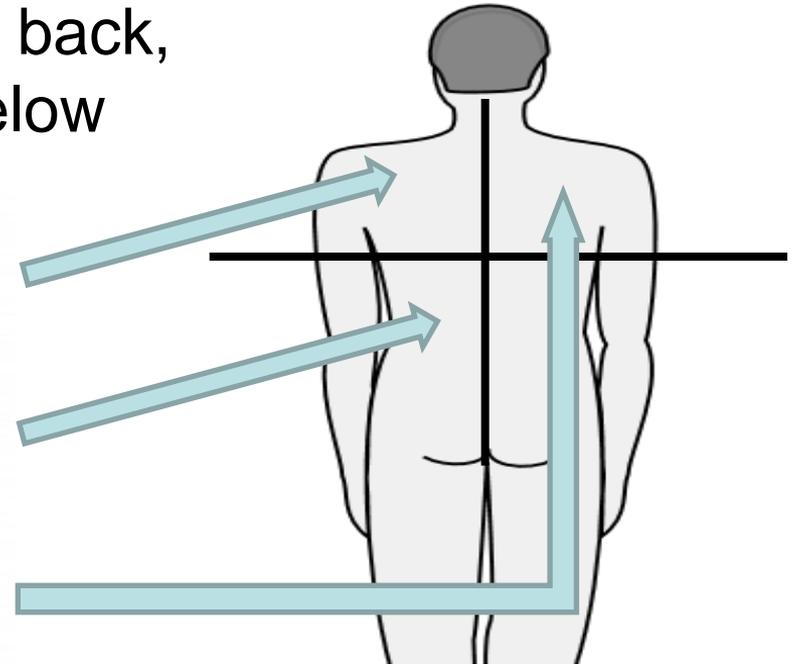
sensitization and irritation test

Application areas are upper left back, upper right back, or left back below

Referenz

Test

Placebo



sensitization and irritation test



Overall Study Design for a generic application

- Induction/Cumulative Irritation Phase
- Rest Phase
- Challenge Phase

Induction/Cumulative Irritation Phase

- Group 1 subjects apply test, reference, and placebo patches to randomly assigned treatment areas for 21 consecutive days.
- Group 2 subjects apply test, reference, and placebo patches to randomly assigned treatment areas three times weekly over a period of 21 days (a total of nine applications). In Group 2, the patches remain in place for 48 hours (on weekdays) and 72 hours (on weekends). The new patch should be applied to the same site as the previous patch

sensitization and irritation test

Induction/Cumulative Irritation Phase

Group 1



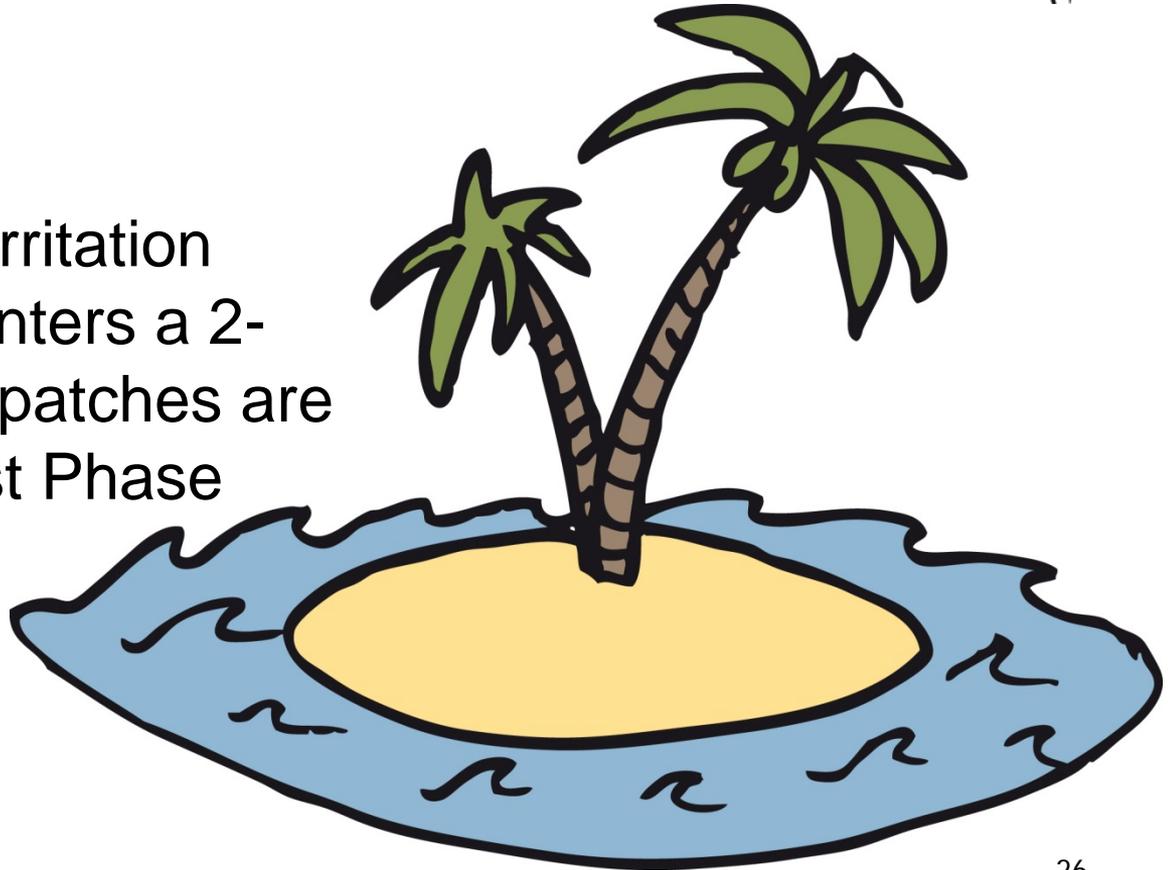
Group 2



sensitization and irritation test

Rest Phase

Following the Induction/Cumulative Irritation Phase, each subject enters a 2-week Rest Phase. No patches are applied during the Rest Phase



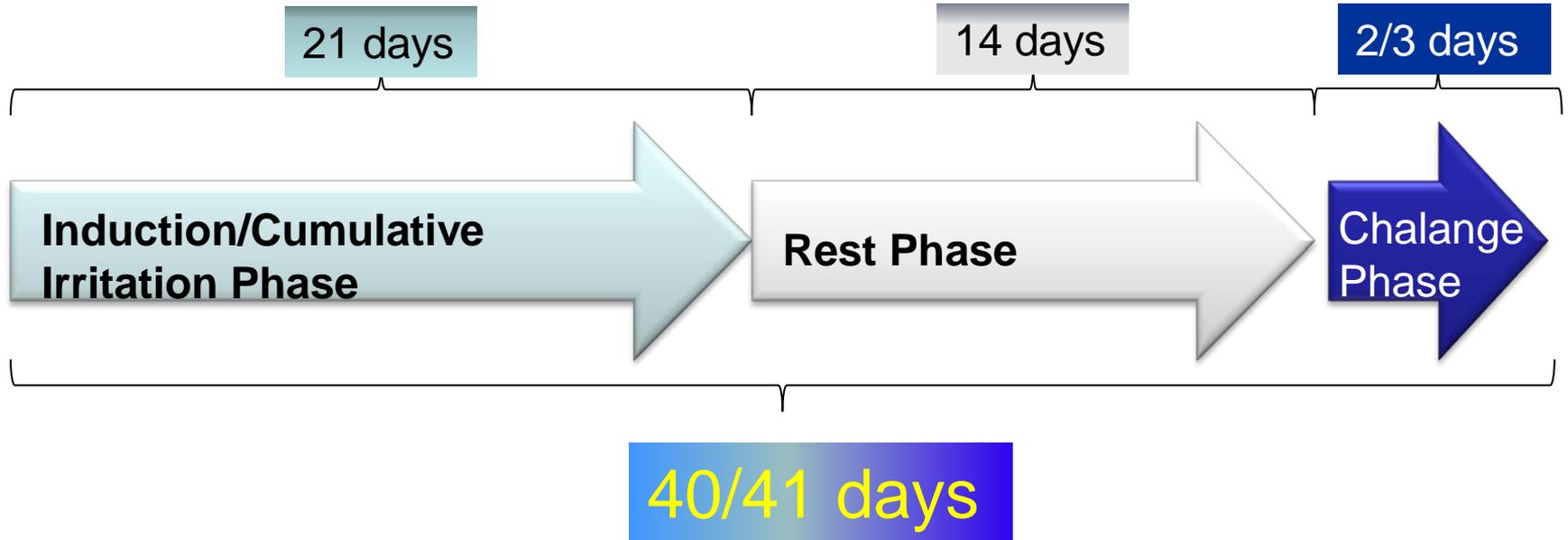
sensitization and irritation test



Challenge Phase

- Following the Rest Phase, patches are applied to new skin sites within the designated areas for 48 hours.
- In addition to dermal assessments at 0.5 and 24 hours after patch removal, subjects participating in the Challenge Phase also return for examination on Days 40 and 41 for additional dermal assessments at 48 and 72 hours after removal of the last patch.

sensitization and irritation test



sensitization and irritation test

Table 1 Dermal Response Score	
Score	Definition
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

sensitization and irritation test

Table 2	
Other effects	
Score	Definition
0	None observed
1	Slight glazed appearance
2	Marked glazing
3	Glazing with peeling and cracking
4	Glazing with fissures Film of dried serous exudates covering all or part of the patch site Small petechial erosions and/or scabs

sensitization and irritation test

Group	Phase	Evaluation by observer	Assessment of Test, Reference and Placebo
Group 1	Cumulative Irritation Phase	Dermal Response Score Other Effects Score	<ul style="list-style-type: none"> • Mean Irritation Score = average of Dermal Response Scores • Total Cumulative Irritation Score sum of Dermal Response Scores • Combined Dermal Response Score sum of Dermal Response Score and Other Effects Score • Mean Combined Dermal Response Score
Group 1 + Group 2	Challenge Phase (Contact Sensitization)	Dermal Response Score Other Effects Score	-Combined Dermal Response Score ≥ 2

sensitization and irritation test



The primary analysis compares the test and reference treatments for the mean irritation scores (average numeric dermal response over the observations) and the total cumulative irritation scores (sum of the numeric dermal response scores over the observations).

The assessment of contact sensitization consists of tabulations of dermal response scores ≥ 2 during the Challenge Phase. No statistical analyses has to be performed on these data.

Thank you!