The Role of Göttingen Minipigs in Dermal Drug Development

Andrew Makin

CEO, Andrew Makin Preclinical Consulting

www.andrewmakin.dk

Agenda

- Dermal drug development
- Species selection and dose route choice for dermal preclinical studies
- Minipigs as a preferred species for dermal studies
- Why Göttingen minipigs?
- Issues to consider for dermal studies

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Dermal drugs: Studies to support Phase 1 clinical

- Dose range finding and 4-week studies in rodent and non-rodent
- Genetic toxicology
- Safety pharmacology
- Local irritation
- Skin sensitisation
- Phototoxicity
- Pharmacokinetics/Metabolism

Dermal drugs – special considerations

- Application to skin = probable exposure to sunlight
- Potential for sensitisation
- Probable low systemic exposure (but also probable continual systemic exposure)
- Site of application not necessarily site of action

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Species and dose route choice for toxicology studies

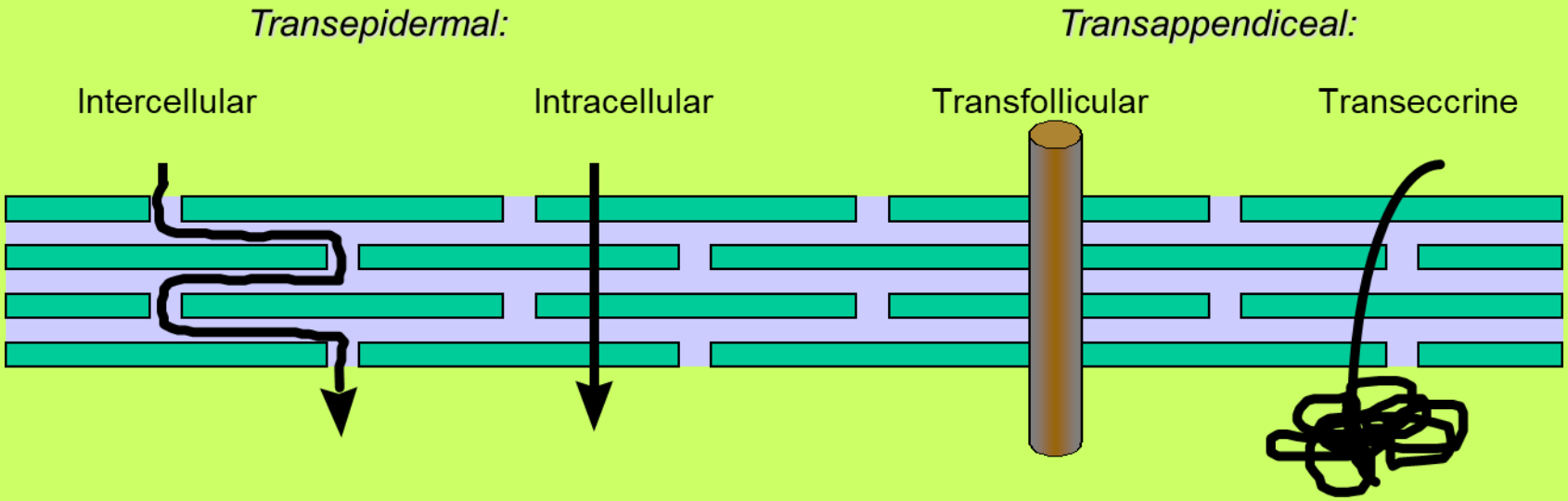
Non-rodent species should be minipig, dosed by the clinical route (see later slides)

Rodent (rat) studies; should consider e.g. oral or subcutaneous dosing.

Provides data on general toxicology profile of the compound

Route to provide good bioavailability. SC could be best route if there is a vehicle that does not induce local reaction.

Dermal absorption pathways



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Minipig skin - comparison to humans -1/2

(Relatively) sparse hair covering

Skin closely attached to underlying structures

Skin surface carved with fine intersecting lines

Epidermis has an identical number of cell layers in stratum corneum and viable zones

Pig has a rete ridge structure as do humans

Skin texture and thickness varies over the surface of the body

Epidermal thickness is 70-140 µm in pigs and 50-120 um in humans (10-20 µm in rats)

Pig (and human) wounds tend to heal by re-epithelialisation rather than contraction – useful in modelling wound healing.

Minipig skin - comparison to humans -2/2

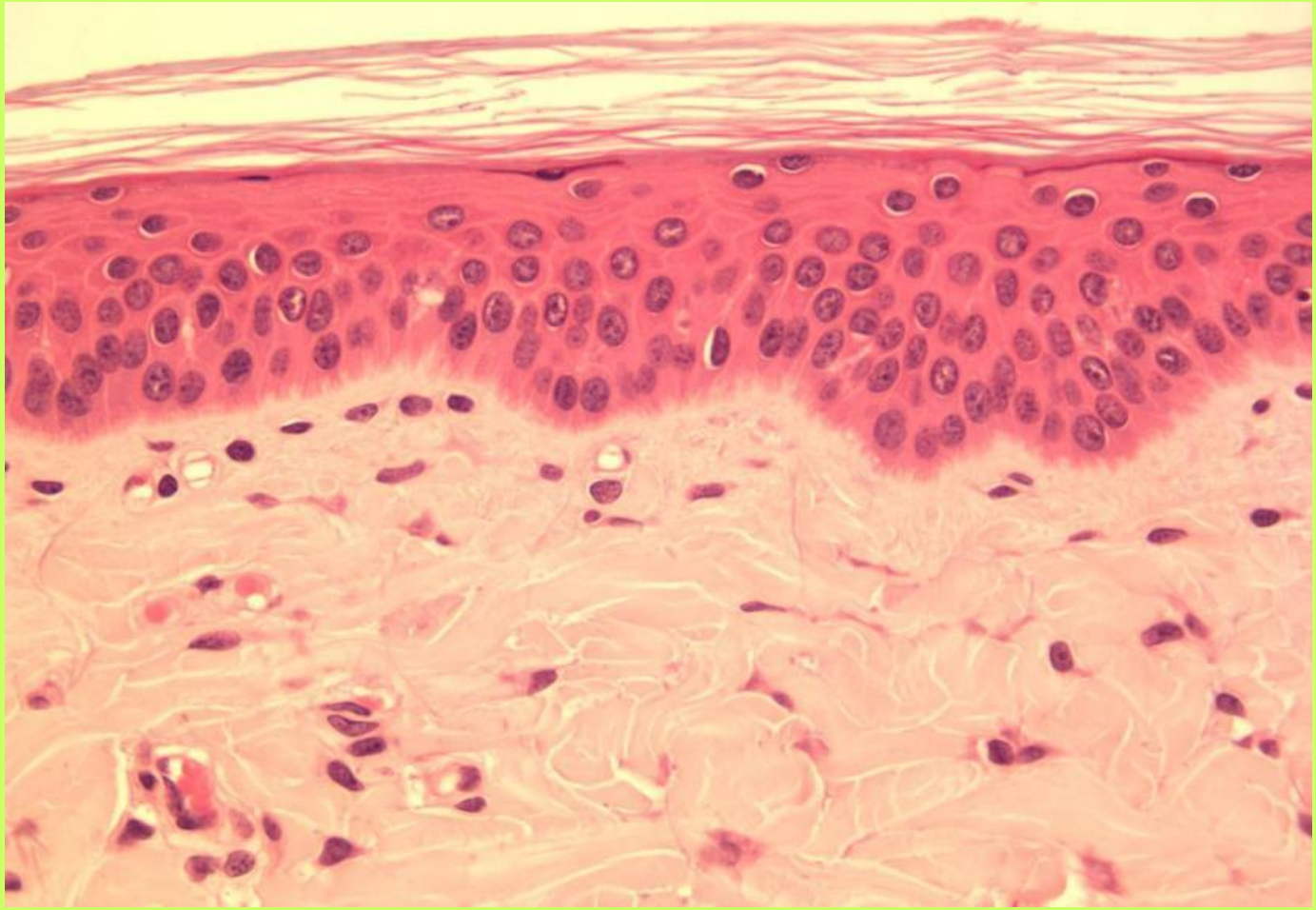
Pigs have few eccrine sweat glands; limited to snout and carpal glands. Humans have them all over; function in thermoregulation.

Pigs have apocrine sweat glands (in humans these are restricted to e.g. armpits); however they are not used in thermoregulation.

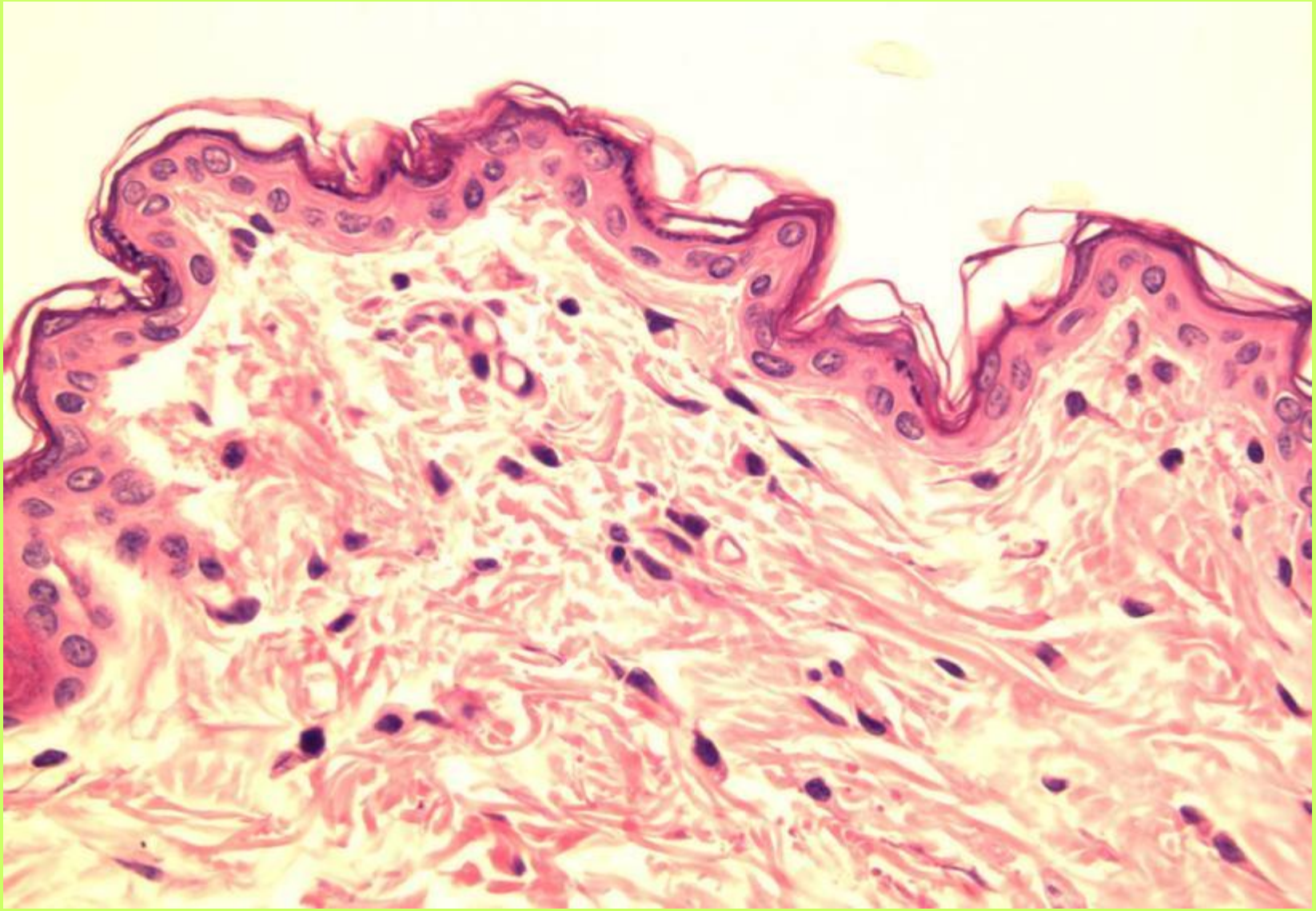
Skin is less vascular than human skin.

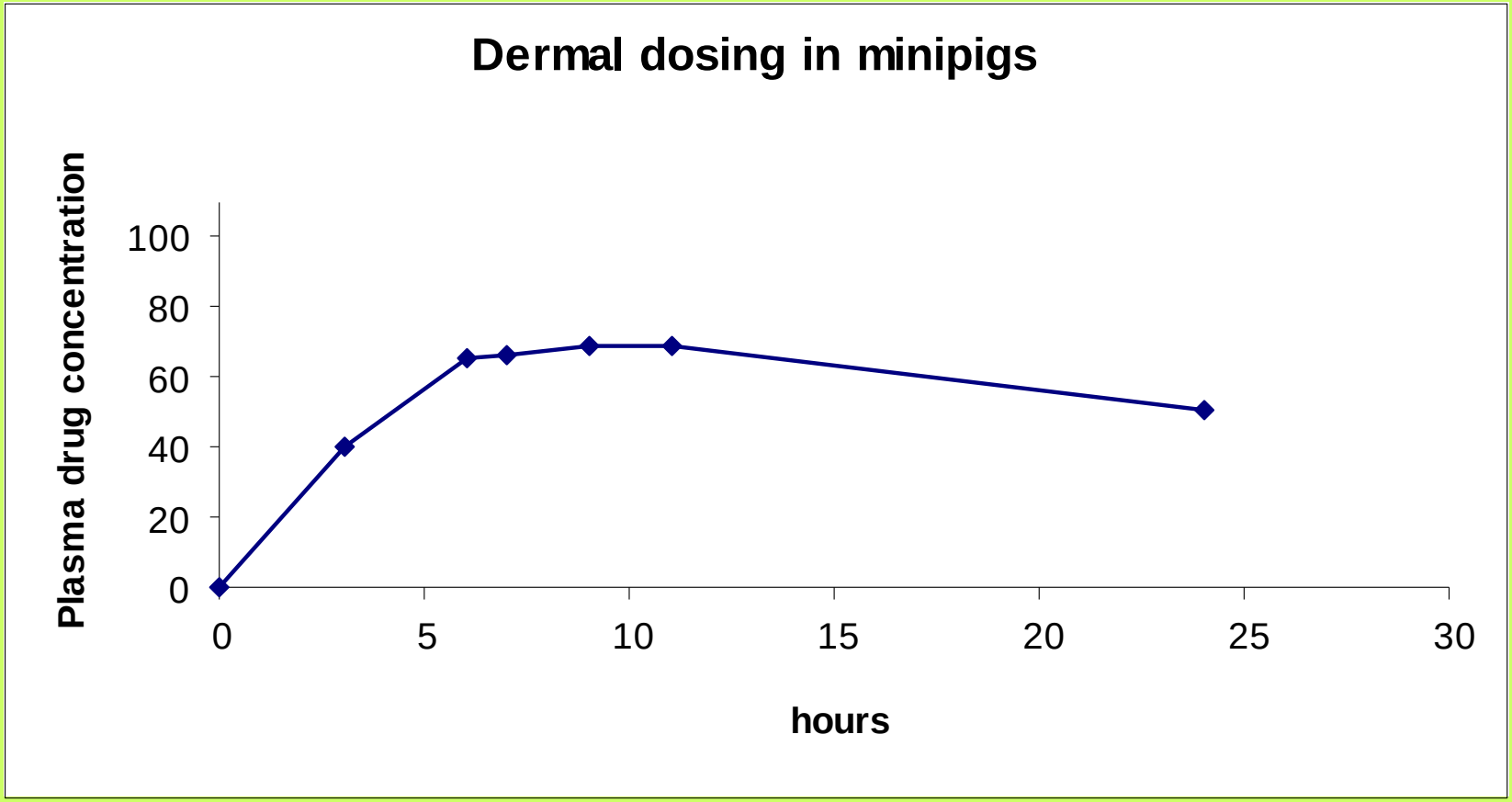
Pigs tend to develop substantial amounts of subcutaneous fat.

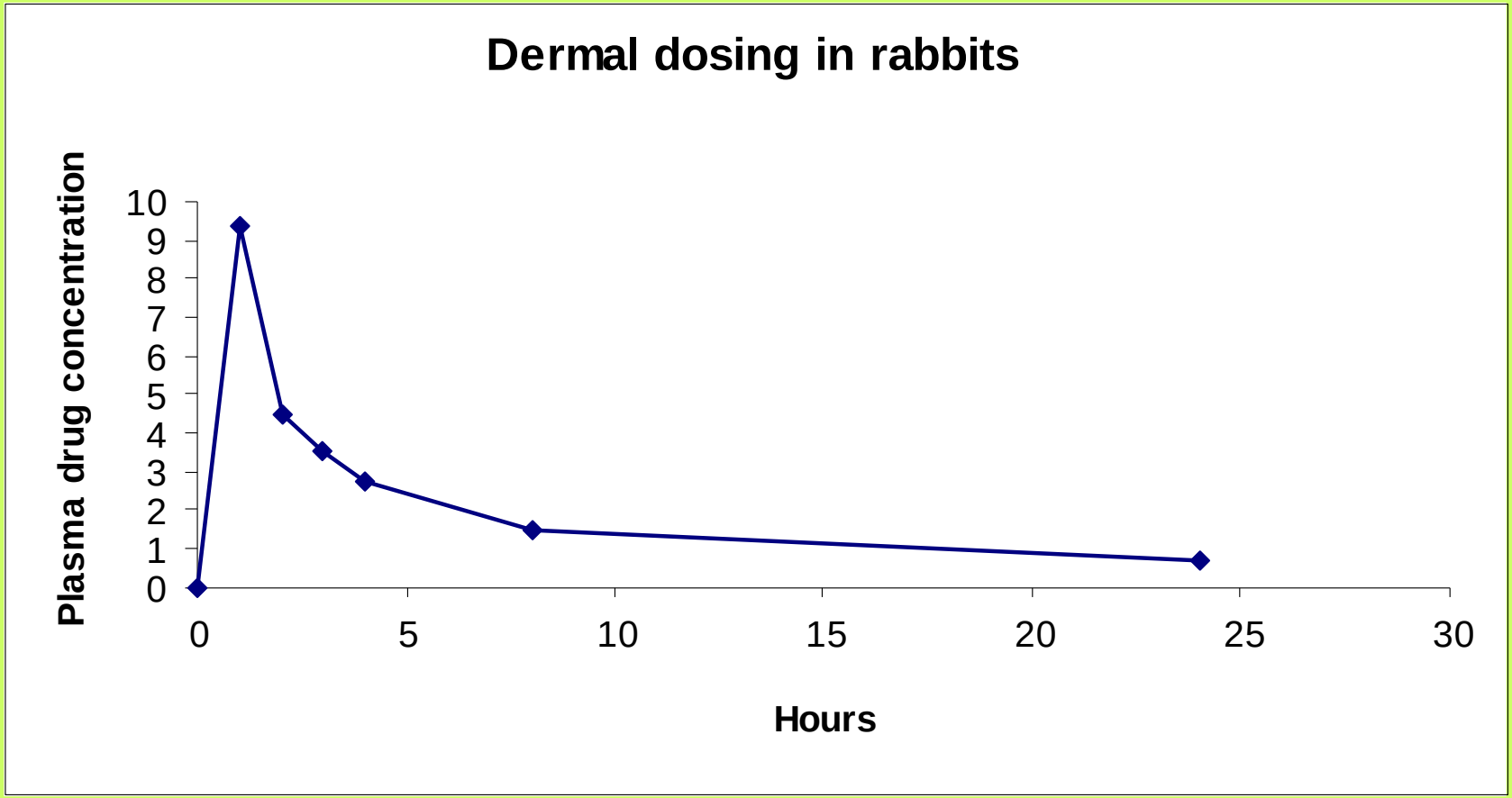
Skin, male minipig, dorsum, x 40



Skin, male rabbit, dorsum, x 40




Dermal dosing in minipigs
Plasma drug concentration
100
80
60
40
20
0
0
5
10
15
20
25
30
hours


Dermal dosing in rabbits
Plasma drug concentration
10
9
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
30
Hours

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Why Göttingen minipigs?

- Size
- Skin colour
- Ease of handling
- Genetically well-defined

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Dermal studies – items to consider

Formulation / vehicle(s)

Dosage (Amount to administer), Dosing area

Local tolerance

Abrasion

Occlusion of the dose site (covering/bandaging)

Contamination

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Formulation / Vehicle(s)

Should be the same as the formulation intended for use in humans

Consider effects of

- Carriers
- Absorption enhancers
- Preservatives, etc

Nature of formulation

- Creams
- Ointments
- Gels
- Patches
- Plasters, wound dressings, etc

Consider need for vehicle treated animals

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Dosing

Amount to administer

- Depends on the nature of the material, ointments can be dosed at greater volumes that gels, for instance

Dose administration

- Use sides and back – avoiding ridge of back
- Normally up to 10% of the body surface; up to 15% is also possible, but use with care
- Dosing duration – consider up to 20/22 hours per day

Dose formulations (see also next slide)

- Consider use of formulations of different concentration.
- Could be limited by maximum feasible concentration
- Formulations to be same as human formulation as far as possible

Control groups

- Consider inclusion of both vehicle and untreated control groups.

Obtaining a high enough dose in dermal studies

Consider to include expected clinical strength formulation as low- or mid-dose treatment and highest meaningful dermal formulation as top-dose

Adjust concentration of active ingredients in vehicle – but without changing vehicle properties!

Adjust applied volume – but do not apply a ridiculously thick layer!

- Consider that for dermal formulations with poor absorption characteristics, only that part that is in direct contact with the skin will have an effect; the rest is waste

Adjust size of treated skin area within practical limits

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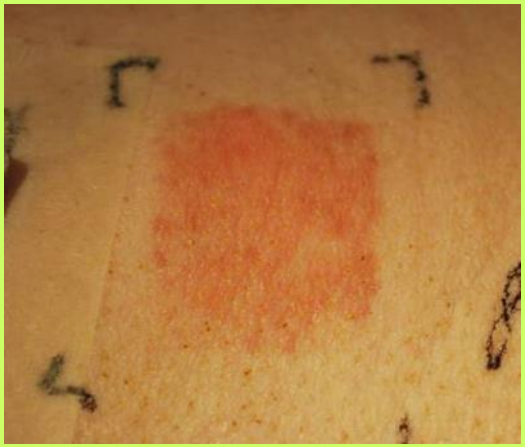
Local tolerance

- Local tolerance is normally measured as a part of the safety studies
- For screening of drugs/formulations the minipig is ideal because multiple formulations can be tested at the same time on one animal using small dosing fields (e.g. 3 x 3 cm)
  - Reduces animal use and minimises formulation requirements



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- Diseased human skin has altered properties
  - Altered permeability/absorption characteristics
  - Altered systemic bioavailability
- Abraded skin models
  - Tape stripping
  - Surgical intervention
    - Wound healing models
- Practical considerations
  - Animal welfare
  - Analgesia/anaesthesia
  - Infection risks

Dermal studies – items to consider

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Contamination

Occlusion of the dose site (bandaging)

Variety of options

Occluded vs non-occluded

Degree of occlusion can be varied e.g. we recommend a light gauze covering in all cases to prevent the animal interfering with the dose site. We recommend full occlusion on days when animals are subject to blood sampling. This prevents contamination of the site.

Duration – typically up to 20 hours per day. May use multiple dosings per day. A ”rest” period is normally used to allow for accurate scoring of reactions.


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Contamination

- Cross-contamination is potentially a big problem in dermal dosing studies.

- Strategies to avoid problems include:

  Separate areas for preparation of formulations containing drug vs controls

  Dosing of test-article treated animals performed by different staff from dosing of controls

  Blood sampling of test-article treated annimals performed by different staff from those sampling controls.

  Staff taking blood samples are different from those doing the dosing.

  Blood samples from treated animals are separated in different centrifuges that controls

  Blood samples from treated animals stored in different boxes from controls

  Analytical procedures need to take similar precautions

Conclusions

- For dermal safety studies the minipig is first choice
- Göttingen minipigs are ideal models
  - Size
  - Temperament
  - Uniformity

Acknowledgements

- Thanks to former colleagues at Charles River Copenhagen for pictures

References

Swine as Models in Biomedical Research and Toxicology Testing. Swindle, M.M, Makin, A., Herron, A.J., Clubb, F.J., Frazier, K.S; *Vet Pathol* 2012 **49**

Makin, A., Mortensen, J.T., and Brock, W.J., in The Minipig in Biomedical Research. McAnulty, P.A., Dayan, A.D., Ganderup, N-C., Hastings, K.L. eds. 2012 CRC Press

Toxicological and Pre-clinical Considerations for Novel Excipients and New Chemical Entities. Makin, A., Mortensen, J.T, in Topical and Transdermal Drug Delivery, Benson H.A. and Watkinson A.C. eds 2012 Wiley