



Photosafety Evaluation of Pharmaceuticals since Implementation of ICH S10

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Training on ICH Guidelines

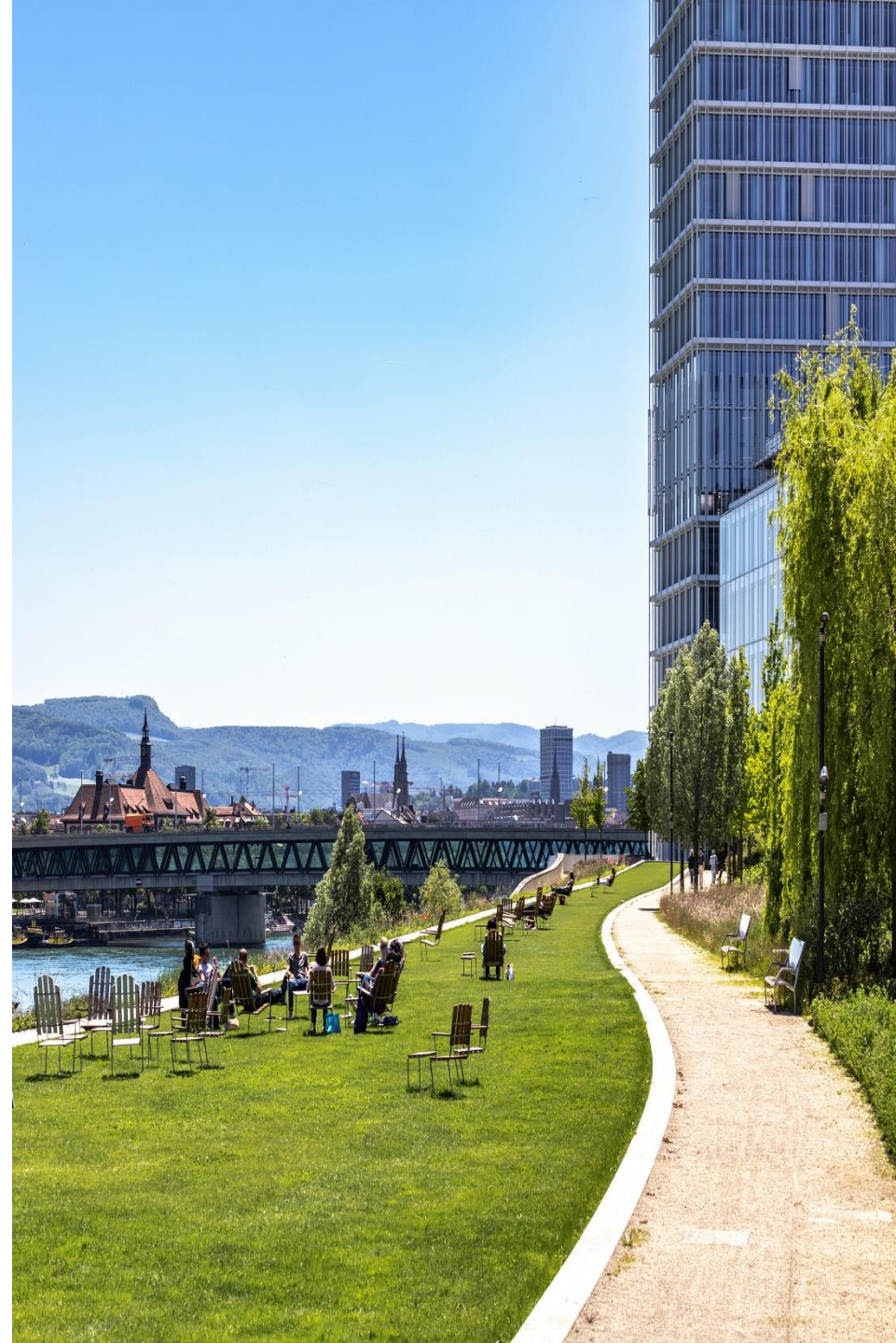
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Agenda

- 1 **Past and present of photosafety regulations**
- 2 **Stepwise photosafety testing strategies**
- 3 *The dose makes the poison?*
Quantitative endpoints in phototoxicity test systems
- 4 **Safety margins** for potentially phototoxic drugs:
Two case studies

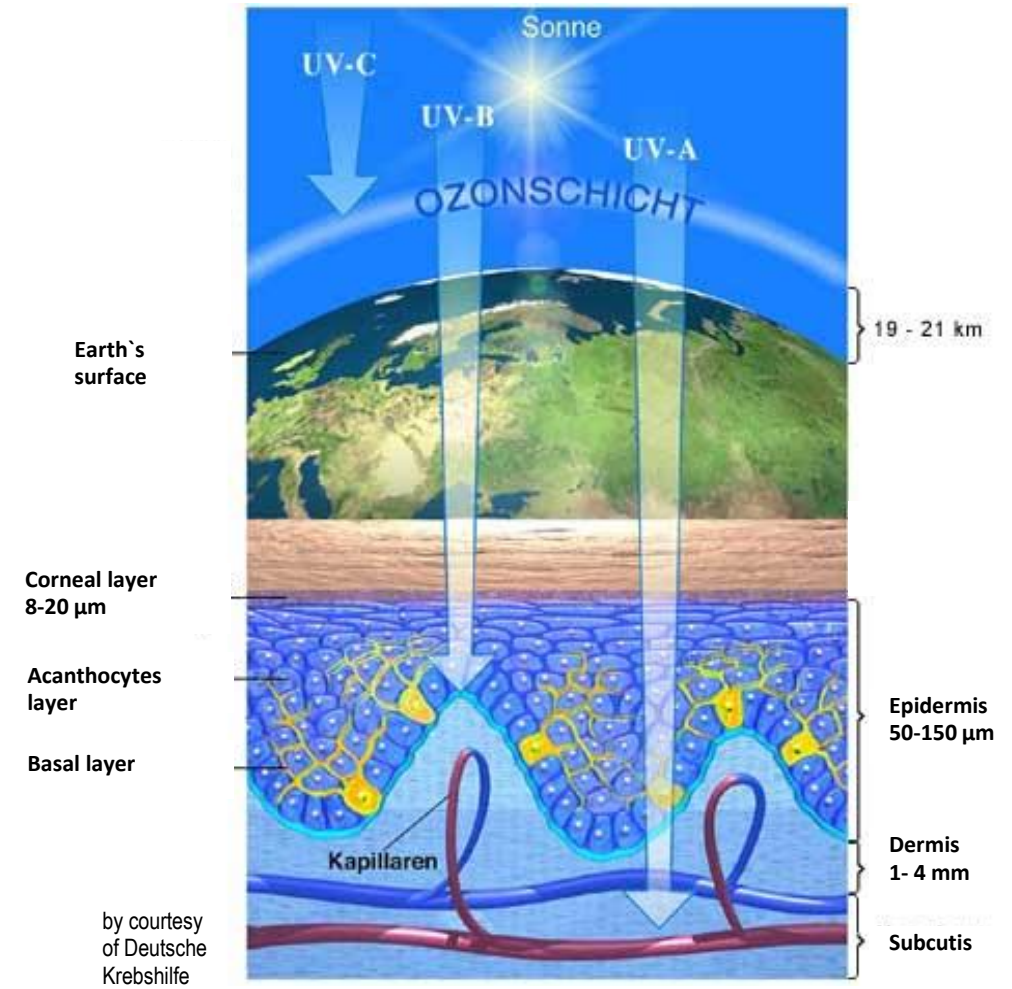
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Past and present of photosafety regulations



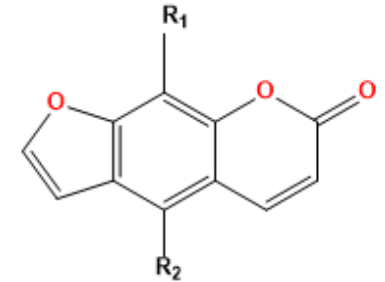
Sunlight – a driver of adverse skin reactions

- Adverse light-induced reactions are clinically often referred to as “**photosensitivity**”.
- Typically, they are related to **sunlight**, especially its short wavelength range of **blue visible** and **ultraviolet radiation**.
- **Sunburn** and **photoaging** are two well-known phenomena caused by absorption of short-wavelength (high-energy) photons by endogenous molecules in skin leading to tissue damage, inflammation, and potentially **cancer**.
- The **eye** may also be a target organ. While ultraviolet light may penetrate cornea and lens, only **visible** light is finally reaching the **retina**.



Sunlight – a driver of adverse skin reactions

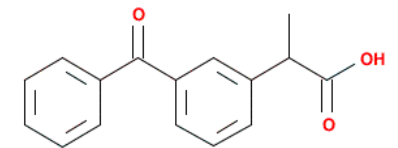
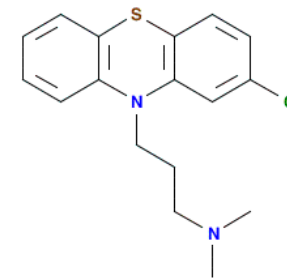
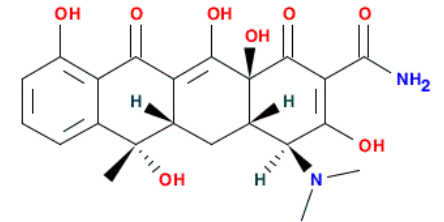
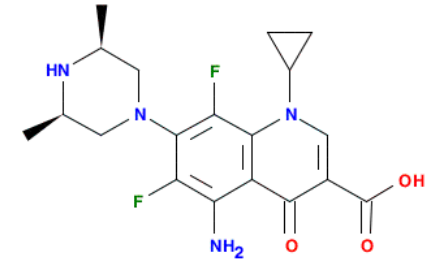
- **Exogenous molecules** which can **absorb** within **sunlight** range may contribute to **light-induced adverse reactions**
- **Acute** reactions are generally called **phototoxicity**. They are often similar to sunburn (erythema, edema, blisters) but may also show more distinct patterns.
- **Delayed** reactions, called **photoallergy**, are much less frequent, but are relevant for local skin exposure (contact-photoallergy).
- **Local** skin reactions might be caused by contact to certain **plants** (like **Giant Hogweed**), to finished products like **cosmetics** (containing, e.g., **bergamot oil**) or to **agrochemicals**.



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Photosafety evaluation of pharmaceuticals

- Many **active pharmaceutical ingredients** also can mediate light-induced adverse reactions limiting its clinical use significantly.
- Both, distribution via **systemic circulation** to light-exposed tissues (such as skin and eye) or **local application** to the surface of light-exposed tissues are relevant routes of administration.
- **Accumulation** or **retention** in skin (e.g., via melanin-binding) is **not** essential.
- The **main endpoint** is **acute phototoxicity**.
- In addition, for evaluation of **topical** drug products, **contact-photoallergy** is important.
- The areas of **photogenotoxicity**, **photocarcinogenicity** and **systemic photoallergy** are of less relevance due to the absence of suitable test systems. However, these aspects are also addressed indirectly by avoiding photoreactive molecules.



How photosafety regulations have evolved

Before ICH S10 (until 2009)

- **OECD Test Guideline 432 “in vitro 3T3 NRU Phototoxicity Test”** was developed during the **1990s** (Spielmann et al.) and published as final version in **2004**
- **Regional guidance** documents for pharmaceuticals were published but contained, in part, inconsistent and conflicting requirements (e.g. for photogenotoxicity)
- **ICH M3, Revision 2 (2009)**, added a section “**14. Photosafety**” emphasizing general expectations

Since implementation of ICH S10 (developed from 2010 to 2013)

- Revision of **OECD TG 432 “in vitro 3T3 NRU Phototoxicity Test”** in **2019**
- New **OECD TG 495 “Reactive Oxygen Species (ROS) Assay for Phototoxicity”** in **2019**
- New **OECD TG 498 “in vitro Phototoxicity - Reconstructed Human Epidermis Phototoxicity Test Method”** in **2021**

Status of ICH S10 according to www.ich.org

S10 Photosafety Evaluation

✓ S10 Photosafety Evaluation of Pharmaceuticals

The ICH Harmonised Guideline was finalised under *Step 4* in November 2013. This Guideline provides international standards for photosafety assessment and harmonises such assessments supporting human clinical trials and marketing authorizations for pharmaceuticals. It includes factors for initiation of and triggers for additional photosafety assessment and should be read in conjunction with ICH M3(R2), Section 14 on Photosafety Testing.


Date of *Step 4*: 13 November 2013


Status: *Step 5*

Guideline


 S10 Guideline

Endorsed Documents

 S10 Concept Paper

 S10 Business Plan

WG Presentations / Trainings

 S10 Training Material

Implementation status:

ANMAT, Argentina - Not yet implemented;

ANVISA, Brazil - In the process of implementation; Date: 1 November 2029;

COFEPRIS, Mexico - In the process of implementation; Date: 10 October 2024; Reference: Photosafety Evaluation of Pharmaceuticals

EC, Europe - Implemented; Date: 1 June 2014; Reference: CHMP/ICH/752211/2012

EDA, Egypt - Implemented; Date: 1 January 2013; Reference: Regulatory Guide for mechanisms, procedures and rules of implementing the Decree of Egyptian Drug Authority No.343 of 2021

FDA, United States - Implemented; Date: 1 March 2015; Reference: Vol. 80, No. 17, Docket No. FDA, US/2013/D/0068, p. 4282-3

HSA, Singapore - Implemented; Date: 1 November 2013; Reference: HSA, Singapore webpage: Guidance documents for clinical trials

Health Canada, Canada - Implemented; Date: 22 January 2016; Reference: File #: 15-114073-949

JFDA, Jordan - Not yet implemented;

MFDS, Republic of Korea - Implemented; Date: 24 October 2014; Reference: Guideline on the Photosafety Evaluation of Drug [Guideline-042-01]

MHLW/PMDA, Japan - Implemented; Date: 1 May 2014; Reference: PFSB/ELD Notification No. 0521-1

MHRA, UK - Implemented; Date: 12 December 1995;

NMPA, China - Implemented; Date: 1 May 2020; Reference: NMPA, China Announcement No. 89 (2019)

SFDA, Saudi Arabia - Not yet implemented;

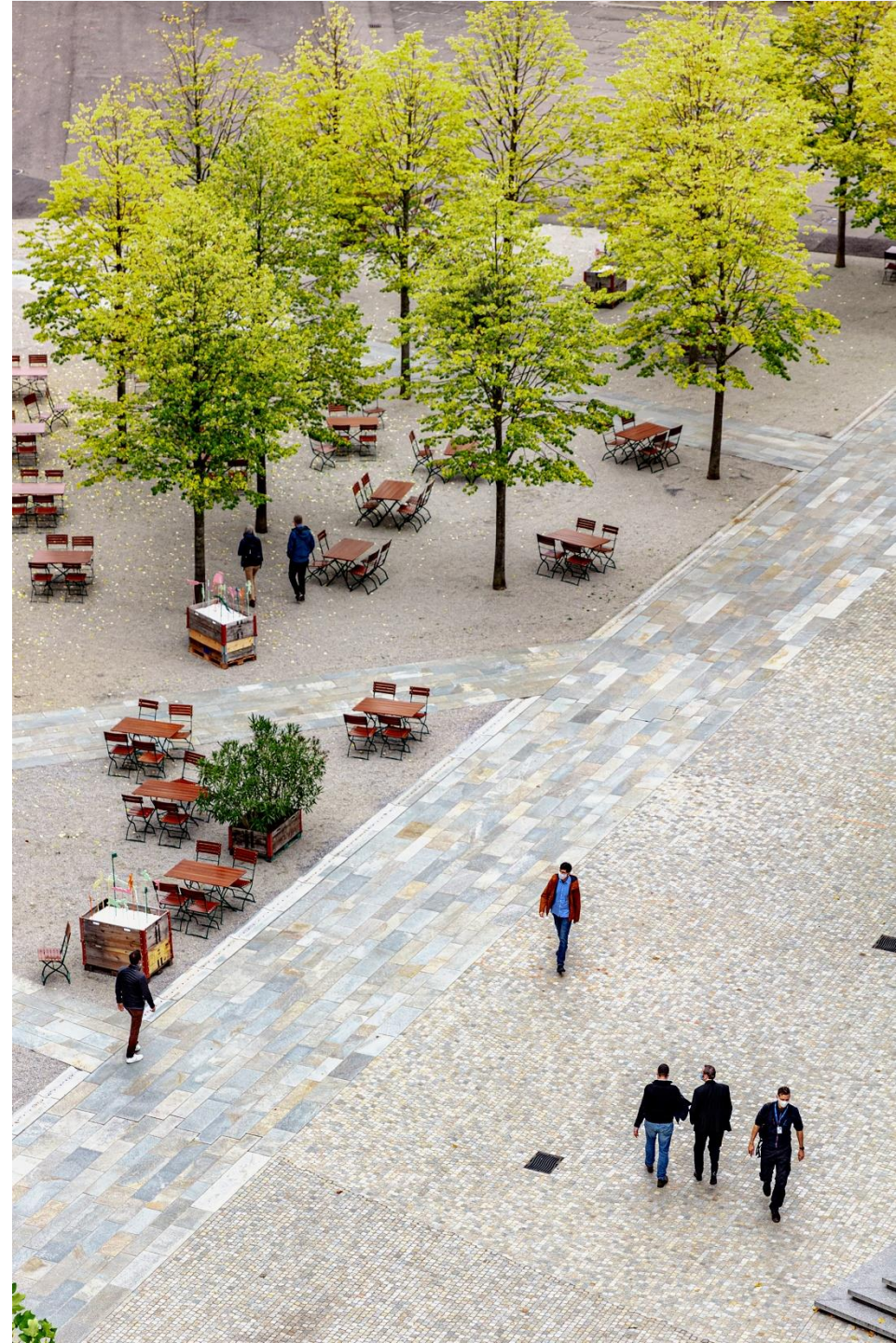
Swissmedic, Switzerland - Implemented; Date: 13 November 2013; Reference: Swissmedic, Switzerland press release

TFDA, Chinese Taipei - Implemented; Date: 7 July 2014; Reference: Guidance on Pharmaceutical Non-clinical Safety V5

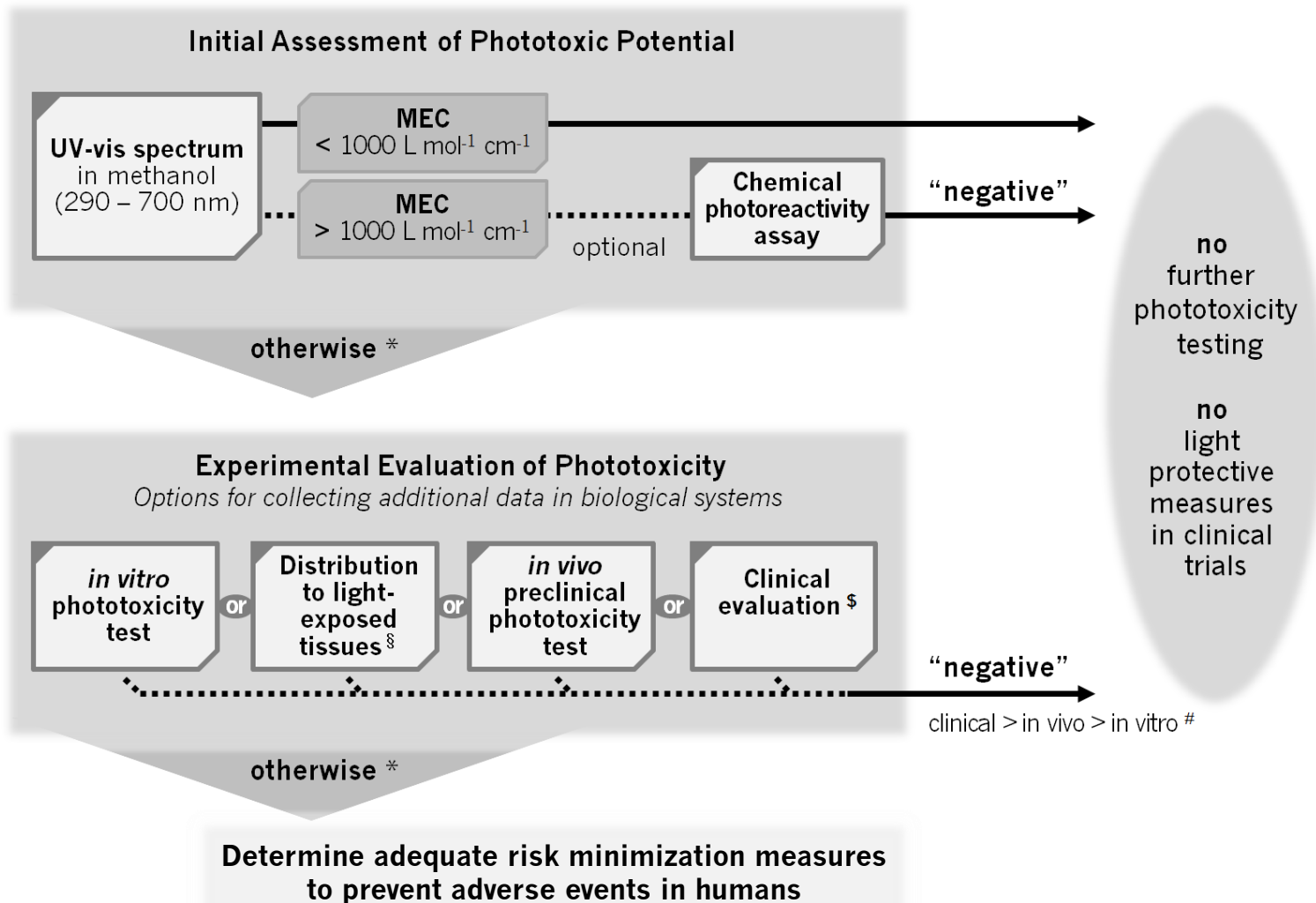
TITCK, Türkiye - Not yet implemented;

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Stepwise photosafety testing strategies



ICH S10 – a stepwise, tiered approach



- * “otherwise”: data do not support a low potential for phototoxicity or have not been generated (assay/test/evaluation not conducted)
- # A “negative” result in an appropriately conducted *in vivo* phototoxicity study supersedes a positive *in vitro* result. A robust clinical phototoxicity assessment indicating no concern supersedes any positive nonclinical results. A positive result in an *in vitro* phototoxicity test could also, on a case-by-case basis, be negated by tissue distribution data (see text). In the United States, for products applied dermally, a dedicated clinical trial for phototoxicity on the to-be-marketed formulation can be warranted in support of product approval.
- § Clinical evaluation could range from standard reporting of adverse events in clinical studies to a dedicated clinical photosafety trial.
- § Tissue distribution is not a consideration for the phototoxicity of dermal products.

What agencies expect from companies today

Before entering late-stage clinical trials, i.e., first-in-human up to phase 2:

- Photosafety evaluation based on appropriate data (physicochemical, in vitro, in vivo, clinical)
- Protective measures in early clinical trial protocols if photosafety evaluation has not been completed already (or if a relevant risk remains)

In support of late-stage clinical trials (phase 3) & marketing authorization:

- Completed photosafety evaluation

If remaining risk cannot be neglected

- **Risk/benefit** assessment
- Instructions on how to avoid adverse reactions
- **Informed consent** to communicate the risk (for clinical trials) or **label** to limit the use of the drug if necessary (for marketed drugs)

5.7 Photosensitivity [Label information in the U.S.]

Mild to severe photosensitivity can occur in patients treated with **ZELBORAF**. Advise patients to avoid sun exposure, wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors.

Institute dose modifications for intolerable Grade 2 or greater photosensitivity.

as listed in the current, FDA-approved label

Impact on Development and Marketing

Learning late about phototoxic properties might be painful

- Protective measures remain necessary
- Years and \$\$\$ and ~~WWW~~ invested already
- No quick change to another drug candidate

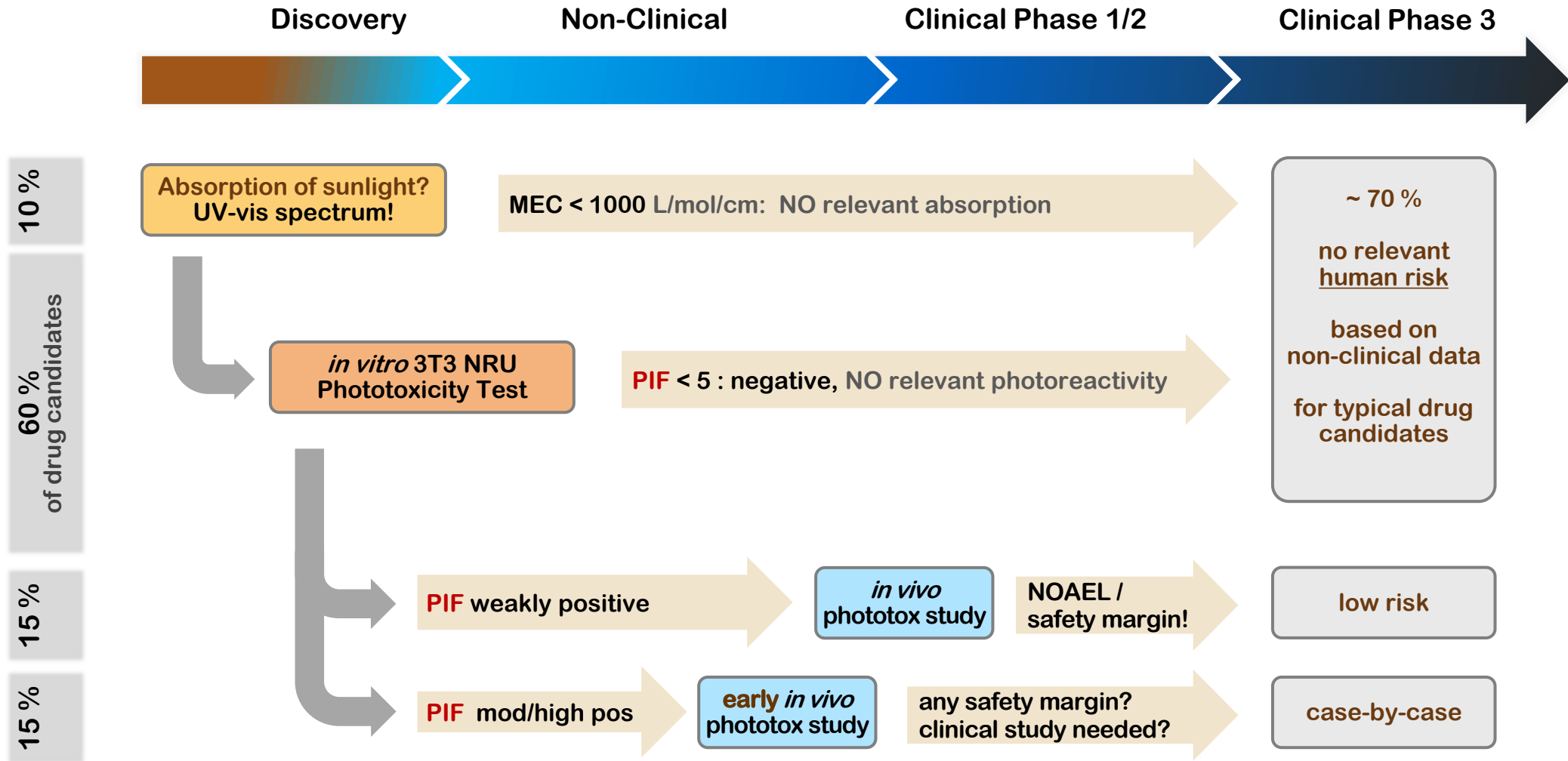
Marketing will be difficult

- Protective measures and risk/benefit will affect label
- Competitor drugs without a phototoxicity risk will have a commercial advantage

Selecting the “right” drug candidate upfront is key

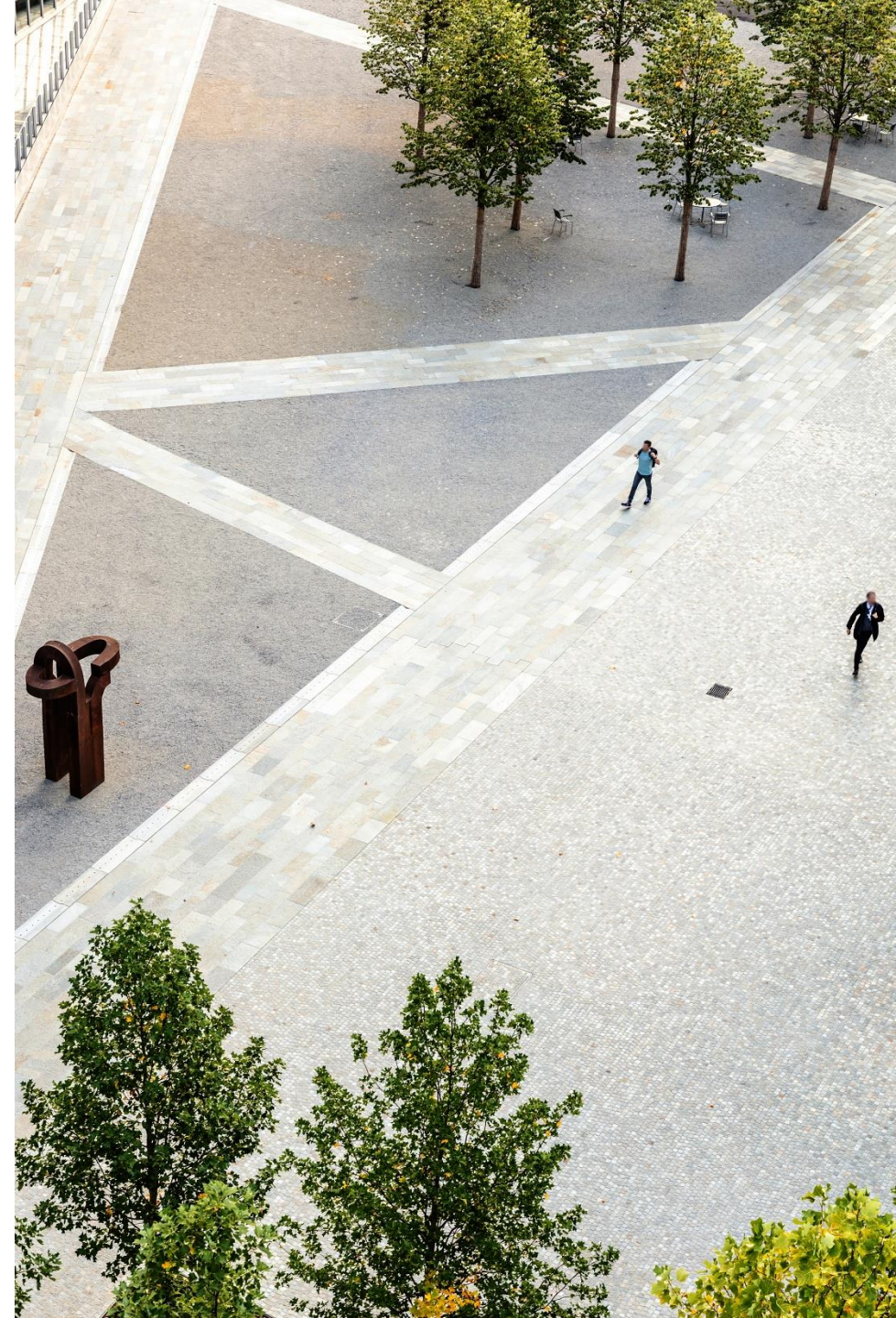
- Pharmaceutical companies are typically using phototoxicity screening assays early
- Definitive in vitro and/or in vivo phototoxicity studies (under GLP) are often conducted before first-into-human studies (instead of waiting until before phase 3)

How companies typically implement ICH S10



3

*The dose makes the
poison?*
**Quantitative endpoints
in phototoxicity test
systems**

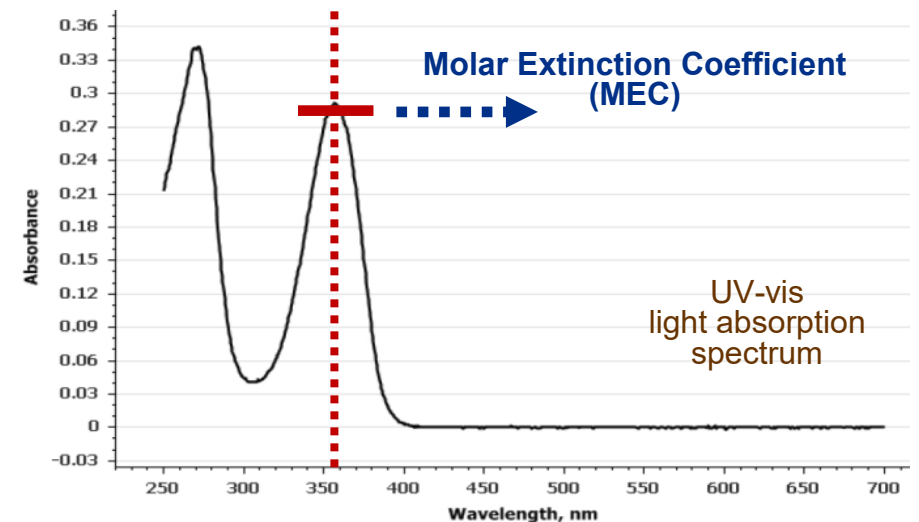
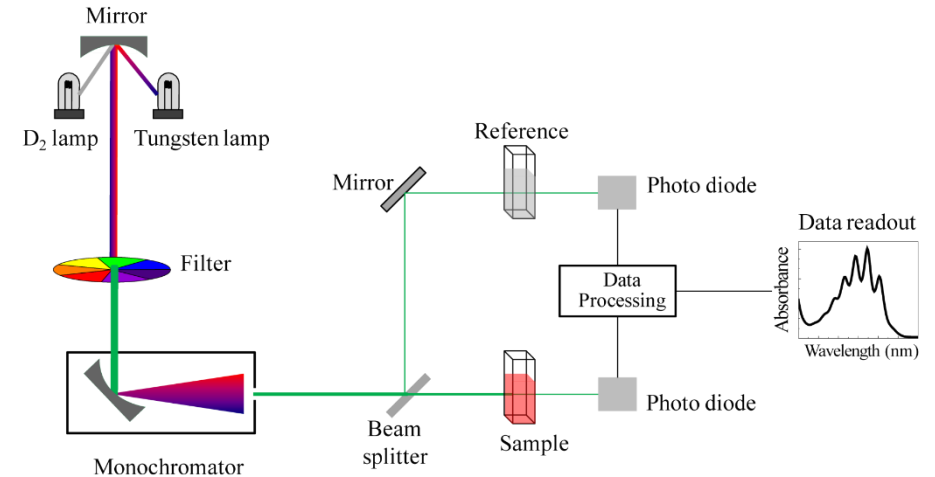


A threshold for absorbing sunlight: the MEC

UV-vis light absorption spectrum, a prerequisite for each test item

Why it matters:

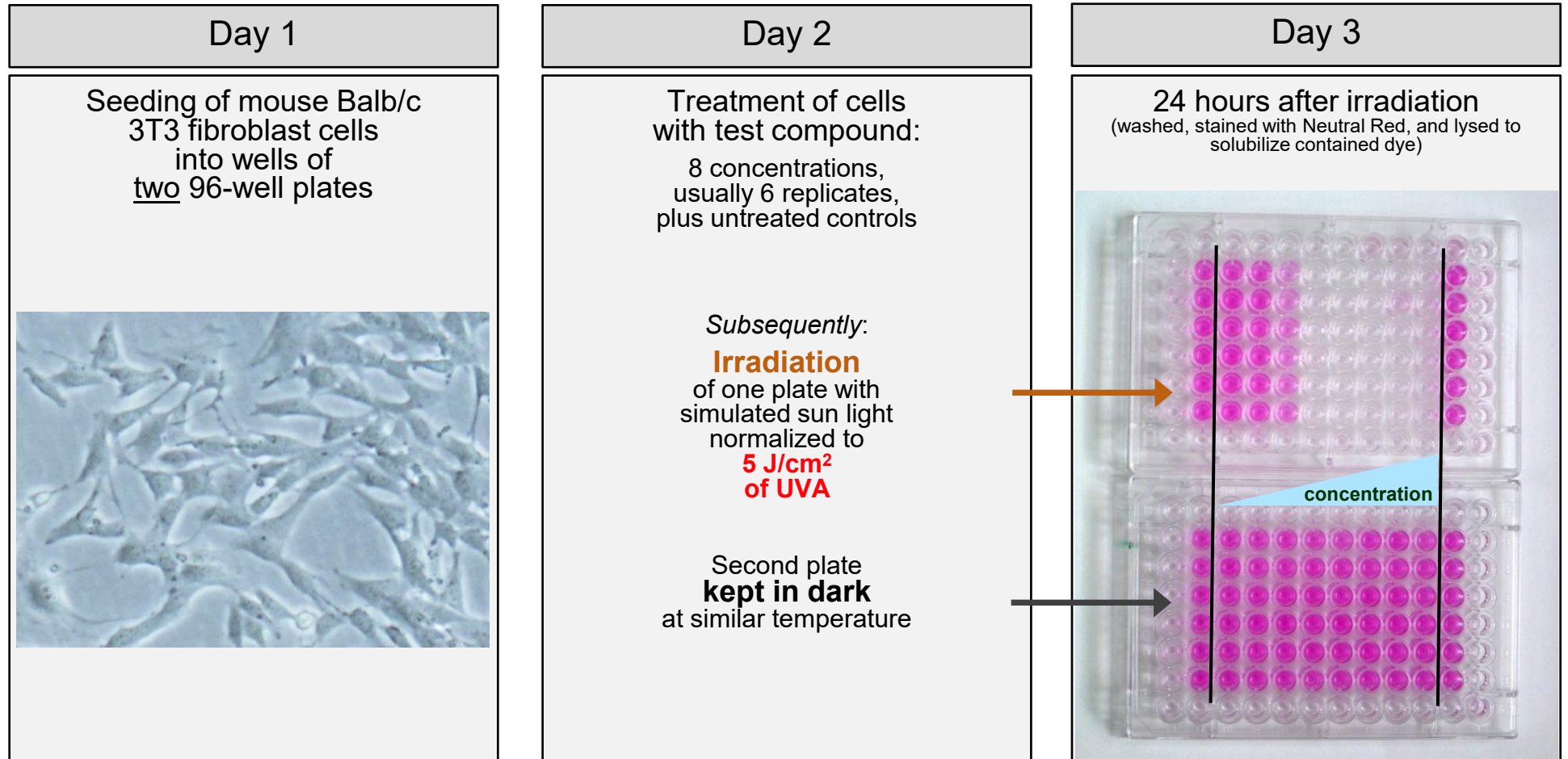
- Test items that do not significantly absorb light within the range of sunlight (290 to 700 nm) may not need any further photosafety evaluation.
- For pharmaceuticals, a **molar extinction coefficient (MEC, also molar absorptivity) of less than 1000 L/mol/cm** (across 290 to 700 nm) has been defined as threshold.
- Standardized measurement conditions (**methanol as solvent**) are required to support this claim.



A threshold for phototoxicity *in vitro*: the PIF

in vitro 3T3 NRU Phototoxicity Test

OECD TG 432



A threshold for phototoxicity *in vitro*: the PIF

in vitro 3T3 NRU Phototoxicity Test

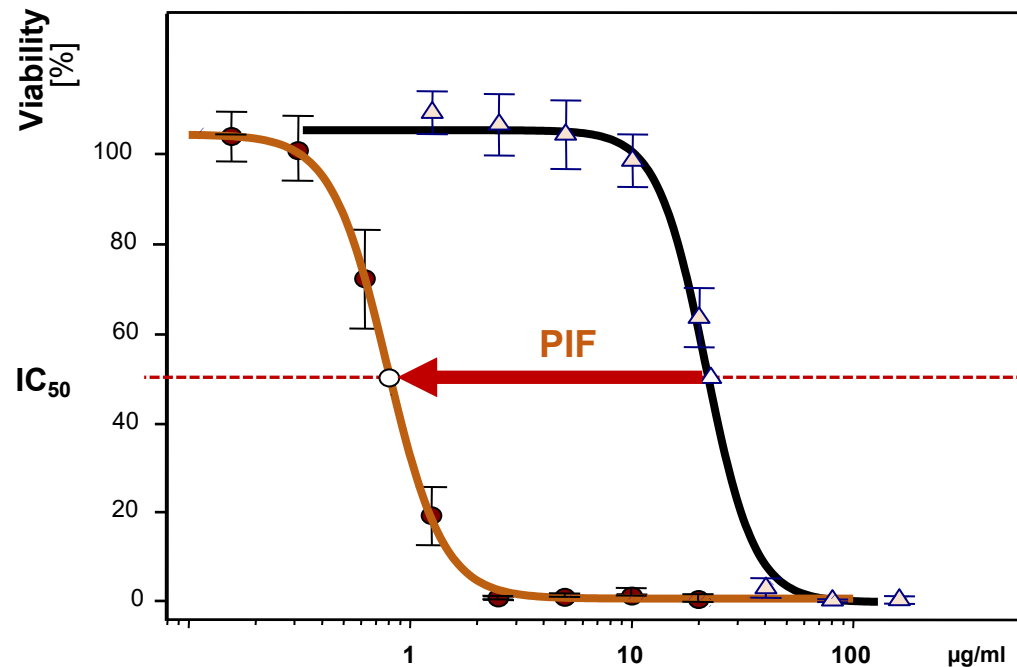


Photo Irritation Factor (PIF)

$$\text{PIF} = \frac{\text{IC}_{50} (-\text{irr})}{\text{IC}_{50} (+\text{irr})}$$

PIF < 5

considered “negative”

“PIF of 5”
threshold based on
OECD TG 432
and ICH S10

PIF = 5 – 25

weakly *

PIF =

25 – 100 moderately * **positive**

PIF >

100 highly *

* positivity categories
based on Novartis-
internal comparison
to in vivo outcomes
(Schümann 2014)

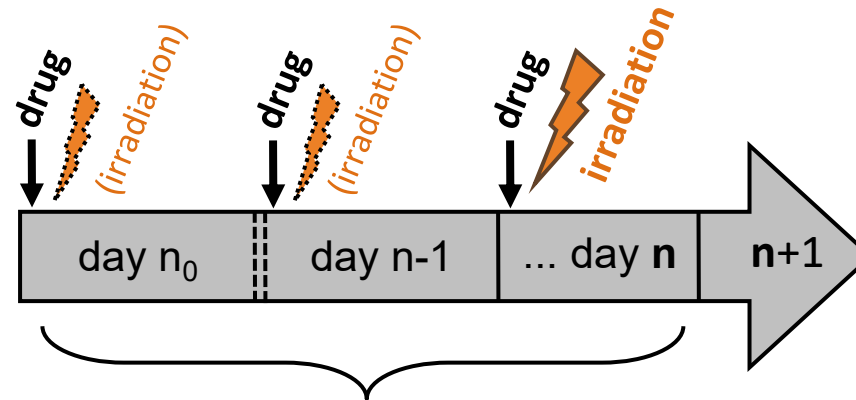
A threshold for phototoxicity *in vivo*: NOAEL

Considerations for

- primary endpoints
- examinations
- sampling
- optional endpoints

Ocular assessments

Only needed for compounds absorbing light within the visible range (i.e., above 400 nm)



Clinical signs (e.g.)

- Erythema
- Edema (swelling)
- Behavior
- Ocular exam

Pharmacokinetics *

- Blood/plasma sampling
- Daily PK profile
- t_{max} and c_{max} for NOAEL

* integrated or subsequent or stand-alone, but needed to establish margins

Necropsy

- Eye histopathology
- Body weight

Photo-LLNA (only mice)

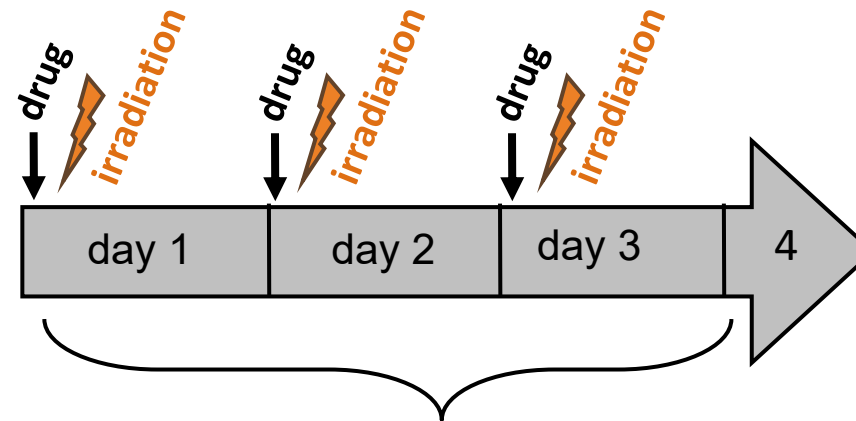
- Edema (ear weight)
- Auricular lymph node weight
- Auricular lymph node cell count

Bioanalytics at necropsy

- Blood/plasma
- Skin
- Eye

A threshold for phototoxicity *in vivo*: NOAEL

Photo-Local Lymph Node Assay (photo-LLNA, Schümann 2014)



- BALB/c mice**
(albino)
groups of 6 females
- vehicle (no irradiation)
 - positive control (+/- irradiation)
 - low/mid/high dose (each +/- irradiation)

Daily treatment

systemic: p.o. / i.v.
or topical: ears

Daily irradiation

simulated sunlight normalized to **10 J/cm² of UVA** for 30 to 45 minutes covering t_{max} applied to conscious and unrestraint mice

Clinical signs (e.g.)

- Reddened skin
- Behavior

PK sampling

- Daily kinetics in satellite animals
- c_{max} at t_{max} for NOAEL

@ Necropsy

- Body weight
- Edema (ear weight)
- Auricular lymph node weight
- Auricular lymph node cell count
- Eye histopathology

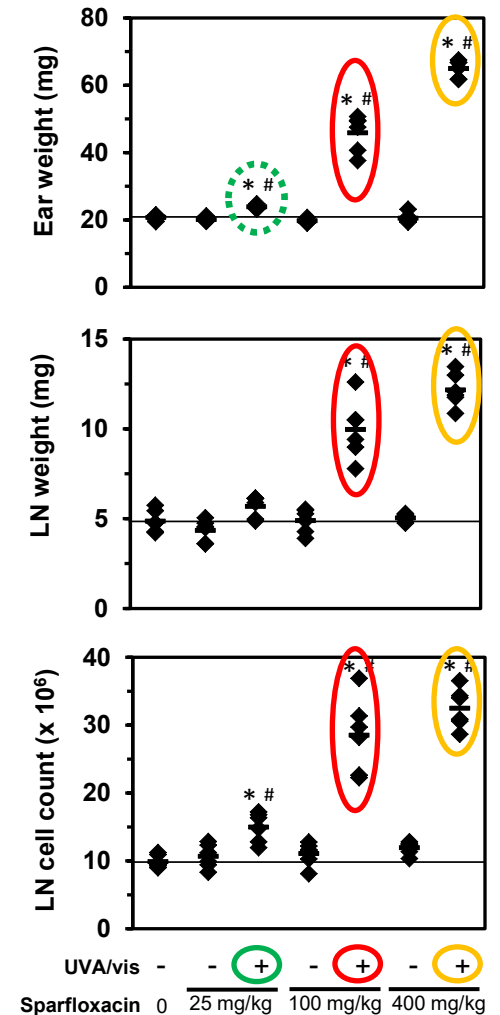
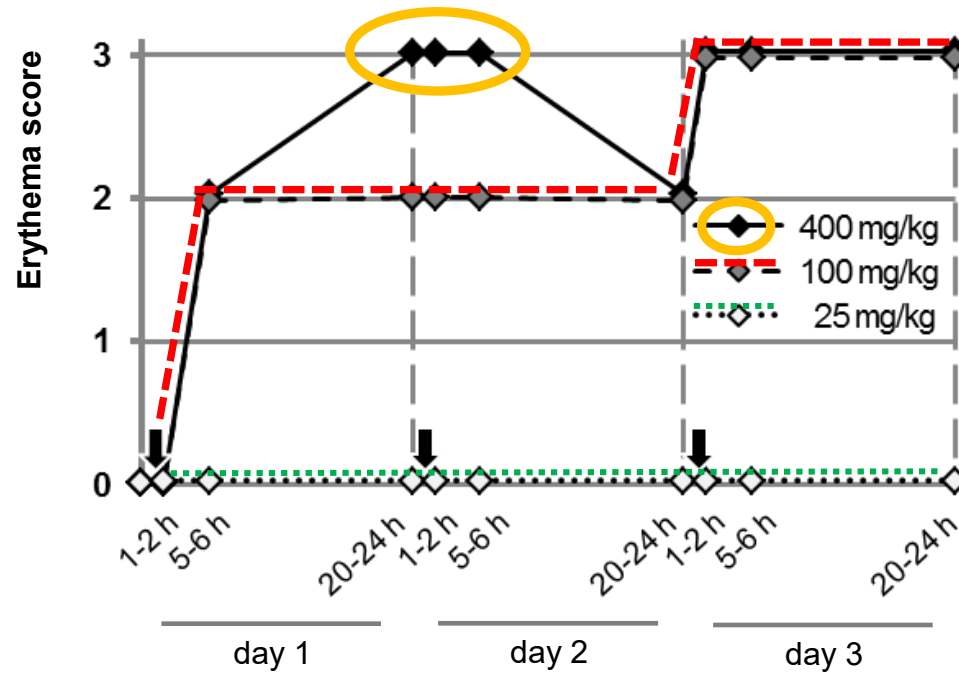
TK bioanalytics

- Blood/plasma
- Skin
- Eye

A threshold for phototoxicity *in vivo*: NOAEL

Dose- and time-dependent endpoint changes (photo-LLNA)

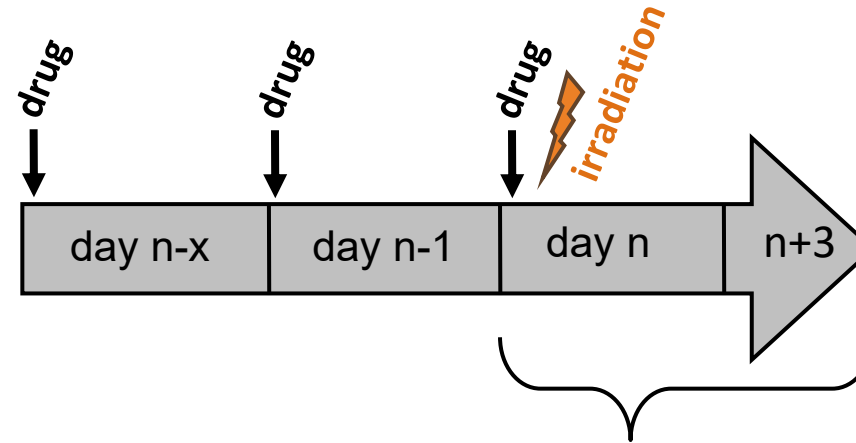
- Sparfloxacin
- 25, 100, 400 mg/kg
- **Erythema**: scoring three times each day
- **Edema**: ear weight by punch-out biopsy
- **Local Lymph Nodes**: weight and cell count as additional markers, but **key endpoints** for **topical studies** indicating **contact-photoallergy**



A threshold for phototoxicity *in vivo*: NOAEL

Long-Evans rat model

(example of a typical design, see, e.g., **Learn 2016**)



CrI:LE “Long-Evans”
(pigmented, mosaic)
groups of 5 females

- vehicle (with irradiation)
- ~~positive control~~
- low/mid/high dose (with irradiation)
- high dose only (no irradiation)

Daily treatment

systemic: p.o. / i.v.

Single irradiation

simulated sunlight normalized to **10 J/cm² of UVA** for 40 to 45 minutes covering t_{max} applied to anesthetized, shaved (backside) restraint and aluminum foil mask-covered rats with open eye-lids

@ Necropsy

- Eye histopathology
- Body weight

Clinical signs (e.g.)

- Reddened skin (defined areas on the back, pigmented and non-pigmented parts)

PK sampling

- Single timepoint at time of irradiation (day n) in satellite animals
- c_{max} (assumed) for NOAEL

Thresholds for phototoxicity *clinically*: MED & PI

A *clinical* phototoxicity study

The ultimate answer

see, e.g., **Bauer 2016**

Study design

- ~50 healthy adults, randomized to a two-part, partially-blinded, parallel-group, placebo- and ciprofloxacin-controlled, single-center study
- Initial treatment phase until steady state exposure is reached
- **Primary endpoint:**
Minimum Erythematol Dose (MED) assessed at baseline and at steady-state, and the derived **Photosensitivity Index**

$$PI = \frac{MED_{\text{baseline}}}{MED_{\text{on-drug}}}$$

- **Secondary endpoints:**
percent change from baseline in MED, scoring of skin reactions



- Irradiation setup
Xenon-arc sunlight simulator with two filters (UVB/UVA, UVA-only) and 6 fiber optic channels

Thresholds for phototoxicity *clinically*: MED & PI

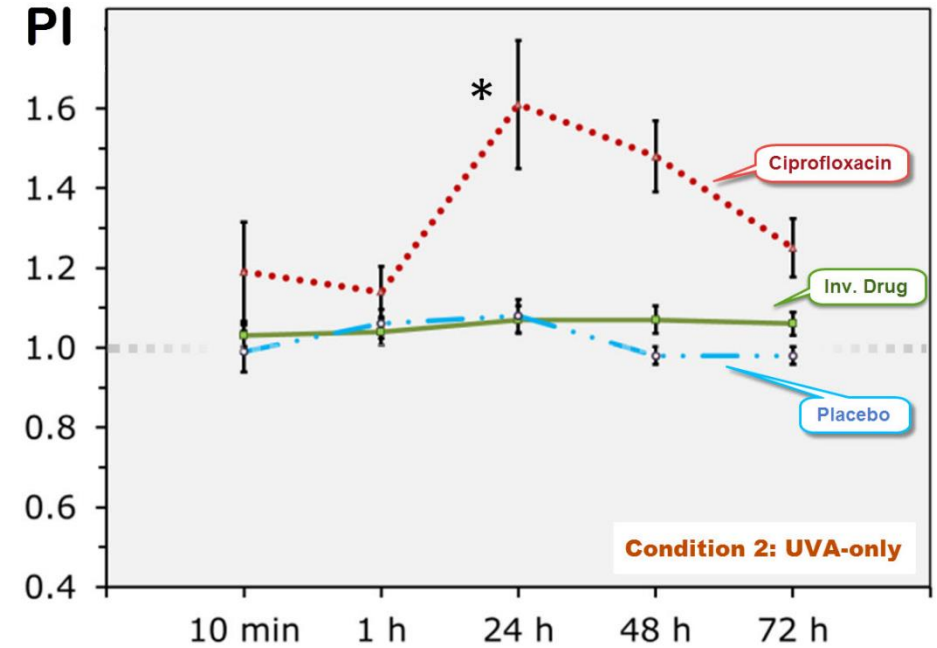
A *clinical* phototoxicity study

The ultimate answer

Irradiation scenarios

Three scenarios to simulate different environments

- 1.) **full range UVB/UVA**
simulating outdoor exposure at midday summer
- 2.) **UVA only**
simulating indoor exposure behind window glass
- 3.) **½ MED from UVB/UVA + 16 J/cm² UVA**
accounting for skin types, individual sensitivity, behavior

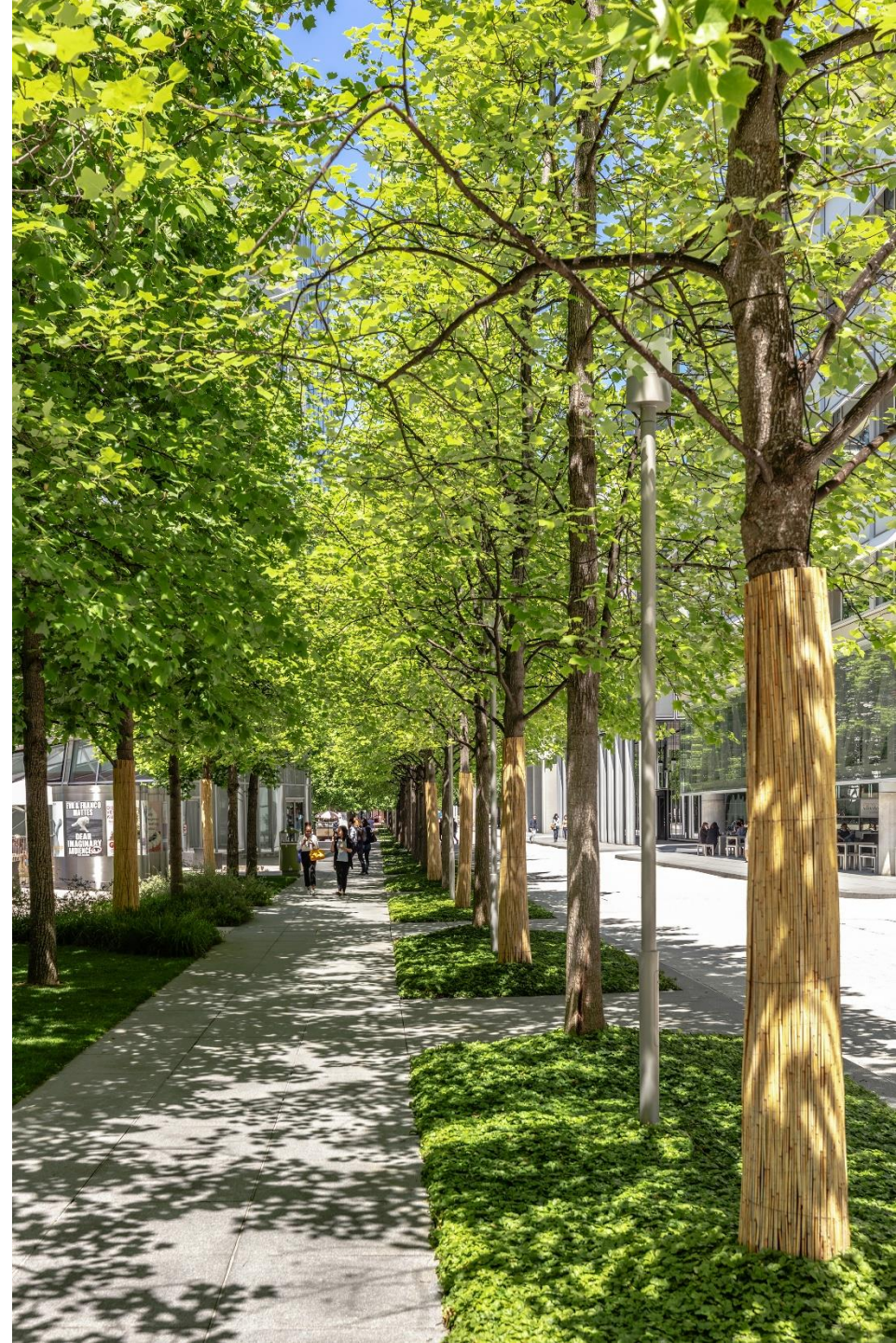


Conclusion from example shown

- The study design works well, Ciprofloxacin was positive following conditions 2 and 3
- The investigational drug did not induce photosensitivity at clinical efficacious dose levels

4

Safety margins for potentially phototoxic drugs: *Two case studies*



Case study: Vemurafenib

Margins!

in vitro
to *in vivo*
to *human*

Example:
Boudon 2014

BRAF kinase inhibitor (Zelboraf[®], Roche) approved 2011 (FDA) and 2012 (EMA) for first-line treatment of metastatic and unresectable melanomas

- Caused **significant photosensitivity reactions during clinical trials** although an initially conducted *in vivo* phototox study (Roche) was **negative**
- Showed, however, relevant **phototoxicity in vitro (PIF above 29)** and triggered structural alerts, thus, questioning the reliability of the negative *in vivo* results

Root cause analyses using the **oral photo-LLNA** (in-house)

- Vemurafenib proved to be a challenging compound (e.g., PK differences between crystalline/amorphous material), but was **identified as a clinically relevant photosensitizer at dose levels above 350 mg/kg (C_{max} , comparable to human)**
- The initially used light source was inappropriate: a **sunlight simulator worked finally!**

Case study: Pradigastat

Margins!

in vitro
to *in vivo*
to *human*

Example:
Bauer 2016

DGAT1, diacylglycerol acyltransferase, inhibitor (investigational drug)
evaluated for treatment of familial chylomicronemia syndrome and related diseases

- Initial preclinical evaluations identified a **potential phototoxicity risk *in vitro*** based on UV-vis light absorption spectrum and subsequent *in vitro* testing (**PIF above 56**)
- Follow-up *in vivo* testing using the **oral photo-LLNA did not reveal any signs of phototoxicity up to 500 mg/kg (top dose)**, later, an **additional photo-LLNA** was conducted at 500, 1000, 2000 mg/kg on request of regulatory agencies, which **revealed signs of phototoxicity starting at 1000 mg/kg**
- Finally, a **clinical photosensitivity study** was conducted to evaluate phototoxicity at therapeutic exposure levels which was found negative
- Apparently, a **safety margin of 15-fold** is separating the NOAEL C_{\max} in mice from therapeutic exposure levels at steady-state in humans

Case studies

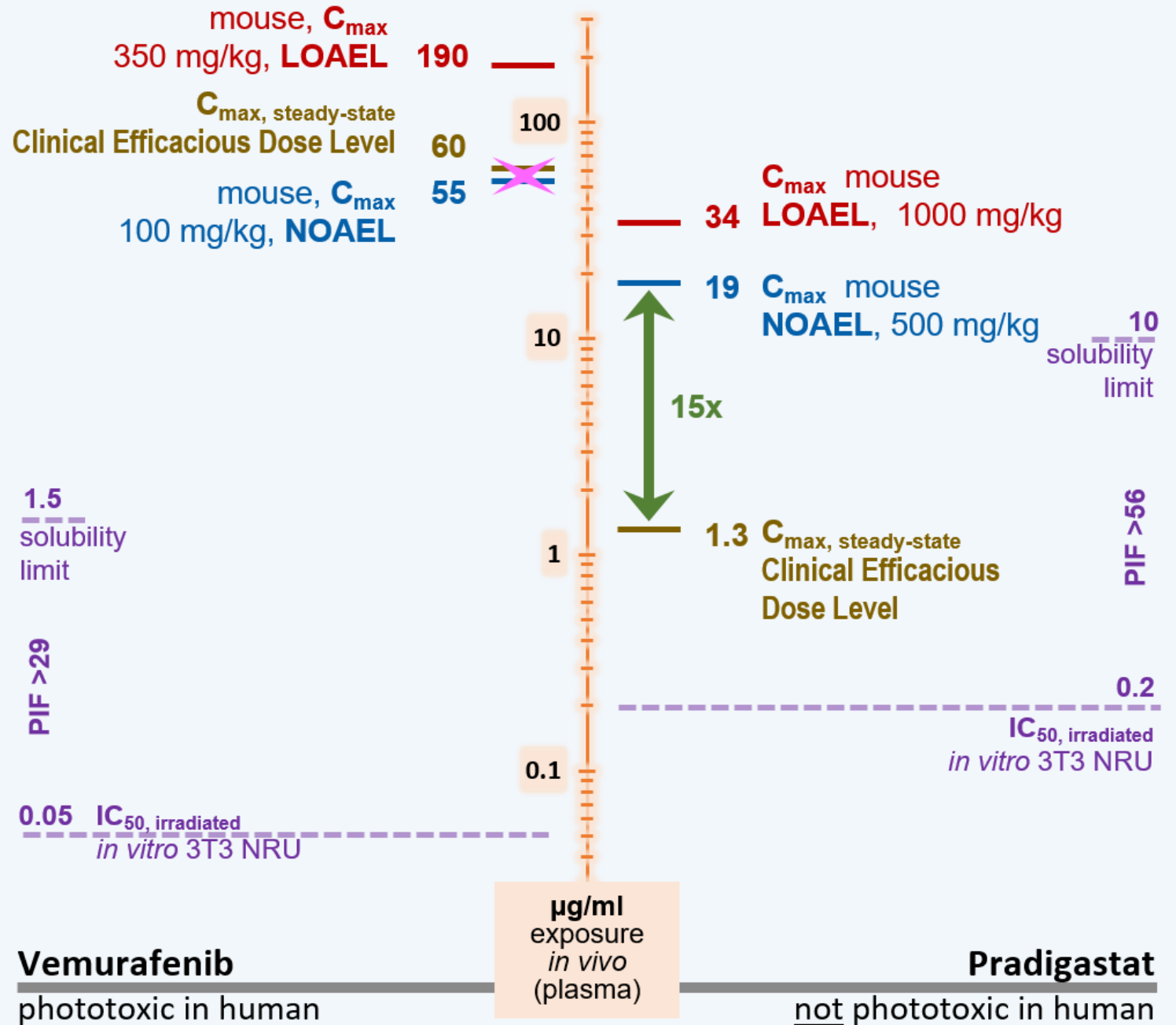
Visualized exposure margins

based on

C_{max}
@ NOAEL
of photo-LLNA

versus

C_{max}
@ steady-state
of clinical efficacious
dose level



Industry experience

Regulatory Toxicology and Pharmacology 125 (2021) 105017



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Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



A cross-industry survey on photosafety evaluation of pharmaceuticals after implementation of ICH S10

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^k Translational Research, SeaGen Inc., Bothell, WA, USA

Industry experience

EFPIA / IQ DruSafe Photosafety Survey with input from 27 companies

- Most participating companies indicated **successful adoption of ICH S10**, no relevant regional differences observed
- **In vitro 3T3 NRU Phototoxicity Test** (following OECD TG 432) **most frequently used** routinely, ROS Assay for Phototoxicity (OECD TG 495) rarely used due to high positivity rate
- Most widely used **in vivo** approach involves dosing **rodents** (often pigmented Long-Evans rats, also Balb/c mice) with **at least 3 dose levels up to MTD**, exposing skin and eyes to simulated **sunlight** (most frequently **normalized to 10 J/cm² UVA**), evaluating the skin for changes in **erythema** or **edema** (and **eye** when warranted due to absorption of visible light)
- Limited information obtained about dedicated clinical phototoxicity studies, likely attributed to effective de-risking approaches employed based on ICH S10 and early screening strategies
- **Margin of safety approach** successfully applied to support clinical development, based on **C_{max} at NOAEL** for phototoxicity versus **C_{max} value in the clinic**, most frequently reported **margin** was **10 to 50x** (although in one case a margin of 5-10x was successful).

Summary

- **Phototoxic properties of systemically applied pharmaceuticals** may be the cause of serious adverse drug reactions. Despite being clinically manageable in principle, they can limit the use of a drug depending on the indication.
- **Protective measures** against sunlight can be applied very reasonably during a few days but may not be practicable for chronic treatments. Thus, both patients and health authorities are unlikely to accept a relevant phototoxicity risk in such situations.
- **ICH S10** provides guidance how a potential phototoxicity risk should be addressed during drug development in a tiered approach.
- **“Phototoxic” is *not like* “genotoxic” or “contact allergen”**. Rather, **safety margins** can be used to support human risk assessment based on **C_{max}** (**NOAEL** in animals vs. clinically efficacious exposure at steady state).
- Industry experience more than ten years after ICH S10 implementation indicate **successful adoption by sponsors and regulators globally**.

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Hans-Jörg Martus, Rachel Soon

Guideline development

Phil Wilcox (GSK/EFPIA), the ICH S10 Expert Working Group

Industry associations

EFPIA Photosafety Working Group, EFPIA PDEG, IQ DruSafe

