

PQRI PODP Extractables & Leachables Workshop

Experimental Design Considerations for Ophthalmic Drug Products (ODP): Introduction and Chemistry

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Overview

- ODP scope
- Inclusion of ODP in working group scope?
- PQRI-PODP hypothesis application to ODP
 - Working group output
- Challenges and industry solutions
 - Chemistry
 - Toxicology

ODPs in Scope

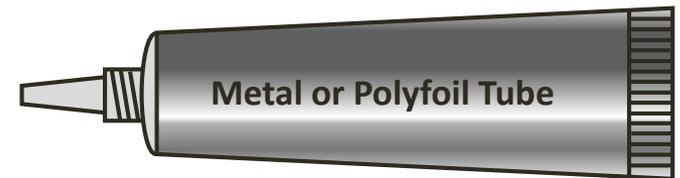
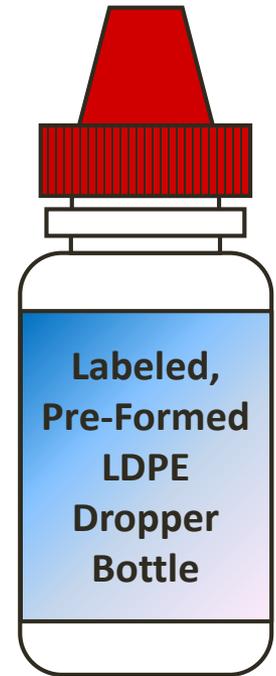
Ophthalmic dosage forms

–In scope

- Topical solutions, suspensions, gels (“eye drops”) – Most common
- Topical ointments

–Out of scope

- Solid inserts
- Implants
- Injections



Why Ophthalmics?

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component – Dosage Form Interaction		
	High	Medium	Low
Highest	Inhalation aerosols and sprays	<ul style="list-style-type: none"> • Injections and injectable suspensions • Inhalation solutions 	<ul style="list-style-type: none"> • Sterile powders and powders for injection • Inhalation powders
High	Transdermal ointments and patches	<ul style="list-style-type: none"> • Ophthalmic solutions and suspensions • Nasal aerosols and sprays 	--
Low	<ul style="list-style-type: none"> • Topical solutions and suspensions • Topical and lingual aerosols • Oral solutions and suspensions 	--	<ul style="list-style-type: none"> • Oral tablets and oral capsules (hard and soft gelatin) • Topical powders • Oral powders

Adapted from USP <1664>, items in red denote revisions from FDA 1999 packaging guideline



Why Ophthalmics?

- High risk category for safety concern
 - As classified by FDA¹ and USP <1664>
- Grouped with injectables¹
 - “These dosage forms share the common attributes that they are generally solutions, emulsions, or suspensions, and are all required to be sterile.”
 - Similar key quality attributes
 - “Although the risk factors associated with ophthalmics are generally considered to be lower than for injectables, any potential for causing harm to the eyes demands caution.”

1. FDA, Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, May 1999

Why Ophthalmics?

- Lack of official, concrete regulatory guidance
 - FDA Container Closure Guideline (1999)
 - “Case 2s: Typically provided are USP Biological Reactivity Test data and **possibly** extraction/toxicological evaluation”
 - EMEA Guideline on Plastic Immediate Packaging Materials (2005)
 - E&L required for non-Ph.Eur. ophthalmic CCS materials
 - No specific guidance on reporting, identification, or safety qualification for leachables
- History of informal practices used in the US



Informal Practices

- US-FDA - Ophthalmology
 - Unpublished, unofficial set of practices in use since ~2002
- Two-tiered approach requested from sponsors
 - Specification limits on individual, unspecified impurities: NMT 0.1%
 - Higher limits negotiable for potent APIs to avoid penalizing such products
 - Surrogate means of monitoring for unexpected leachables
 - For confirmed leachables¹

Action	Report	Identify	Qualify
Leachable Concentration	Above 1 ppm	10 ppm	20 ppm

- In practice, most sponsors ID at 1 ppm to aid control strategy
- Note that these levels are **concentration**-based, not **exposure**-based

1. Linda Ng, FDA Office of New Drug Quality Assessment. "Current Regulatory Recommendations for Leachables in Ophthalmic Products". Presented at PQRI Workshop on Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products, Bethesda, MD, 22-23 Feb 2011.

Questions on Informal US Practice

- ODP leachable reporting is concentration-based rather than exposure-based
 - Does not account for dose volume/frequency; should it?
 - SCT/AET for OINDP (and later, PDP) exposure-driven
 - ODP practices divergent from other therapeutic areas
- No published scientific data on 1 ppm threshold
 - Are there supportive data that we have not seen?
 - Are ODP being held to an appropriate standard?
 - Adequate patient protection? Risk / benefit?
- Global harmonization possible?



Hypothesis-Driven Process

“1. **Threshold concepts** that have been developed for safety qualification of leachables in OINDP and the existing FDA/EMA guidance documents **can be extrapolated to** the evaluation and safety qualification of packaging systems (such as container closure systems, CCS) for **PODP.**”

- Goal was to extrapolate OINDP concepts (SCT, AET) to PODP, not necessarily the thresholds themselves
- Outcome not assured
- Significant challenge



PODP Not a Uniform Class

Parenteral and ophthalmic drug products are sufficiently different that they cannot be treated in the same manner

- Dosing volumes for ODP much lower
 - μL vs mL to L for parenterals
- Different routes of administration
 - Topical ODPs designed for high local exposure and low systemic exposure versus parenterals
 - Different toxicological endpoints
 - The data used to support the PDP SCT/AET are less applicable
- Lack of **ocular safety** data at relevant concentrations

Unsatisfied Hypothesis

Can threshold concepts (SCT/AET) be extrapolated from OINDP to ODP?

- Regulatory: No consensus was reached with US-FDA Ophthalmology; currently, the US-FDA prefers for leachable assessment on a case-by-case basis for this product type
- Scientific: Currently, there is not a sufficient database developed on all relevant toxicity endpoints to allow the working group to recommend specific safety thresholds for ODP at this time

Conclusion: The team cannot support the safety-based threshold hypothesis for ODP with current data



Hypothesis #2

“2. The ‘good science’ **best demonstrated practices** that were developed for the OINDP **pharmaceutical development process** can be extrapolated to packaging systems for **PODP.**”

- Many of the parenteral drug product best demonstrated practices still apply to ODP
 - Information gathering / material selection and screening
 - Conduct of controlled extraction studies for aqueous drug products; selection of solvents, extraction conditions, analytical methods, etc.
 - Simulation studies as a valuable tool

E&L Challenges in ODP (1)

- Packaging systems for solutions, suspensions, gels
 - Bottle is often molded from a barefoot, LDPE resin
 - LDPE is semipermeable
 - Closures are often harder plastic with more additives, but make minimal product contact
 - Primary container closure rarely imparts leachables to aqueous ODPs
 - Personal experience: in 17 years of studying E&L in topical ophthalmics at two different companies:
 - Never observed a significant leachable from these primary packaging systems
 - All leachables (migrants) originated from secondary components – **these components are critical!**



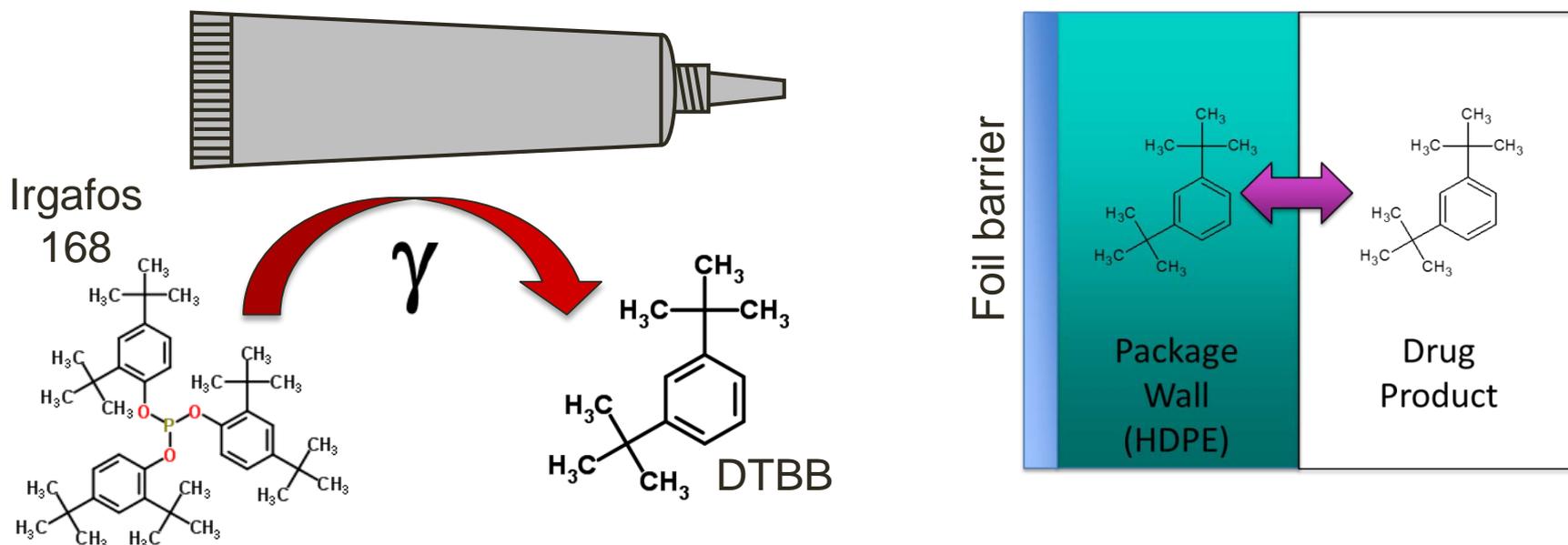
E&L Challenges in ODP (2)

- Secondary packaging
 - Includes
 - Labels, unit cartons, product information inserts
 - Inks / varnishes, adhesives, substrates (plastic, paper, cardboard)
 - Often commodity materials with poor change control or subject to frequent changes
 - Changes come with short timelines, affect multiple products
 - Insufficient time and resources to perform full shelf-life leachable studies on all impacted products
 - Migration behavior from 2° packaging can be more complex than 1° packaging (see next slides)



Migration from Primary Packaging

Ophthalmic ointment example in laminate tube

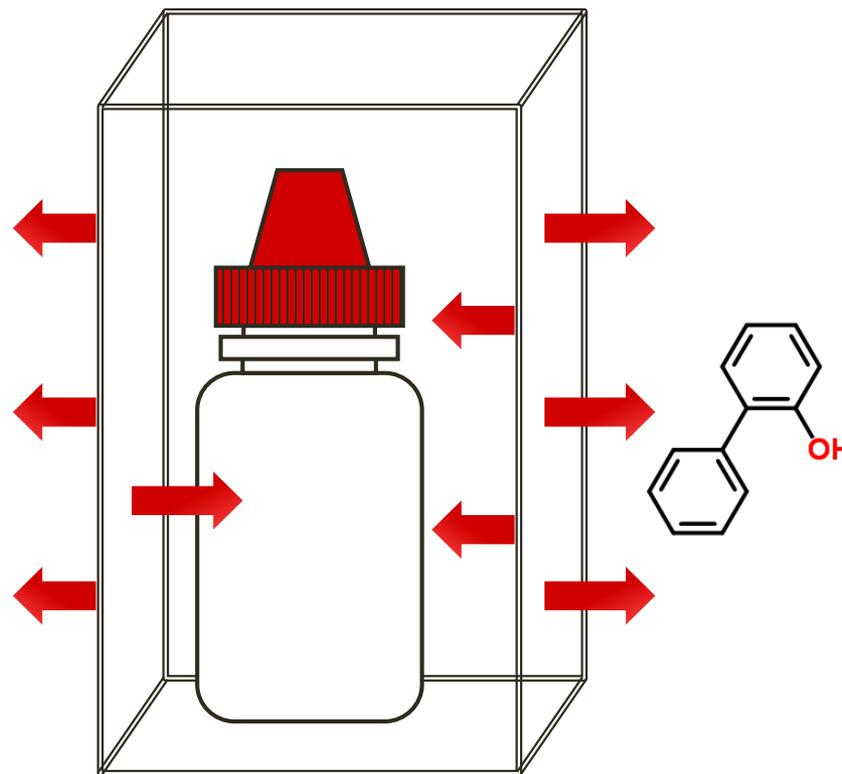


Leaching from 1° package is often simple partitioning between two phases (package and product)

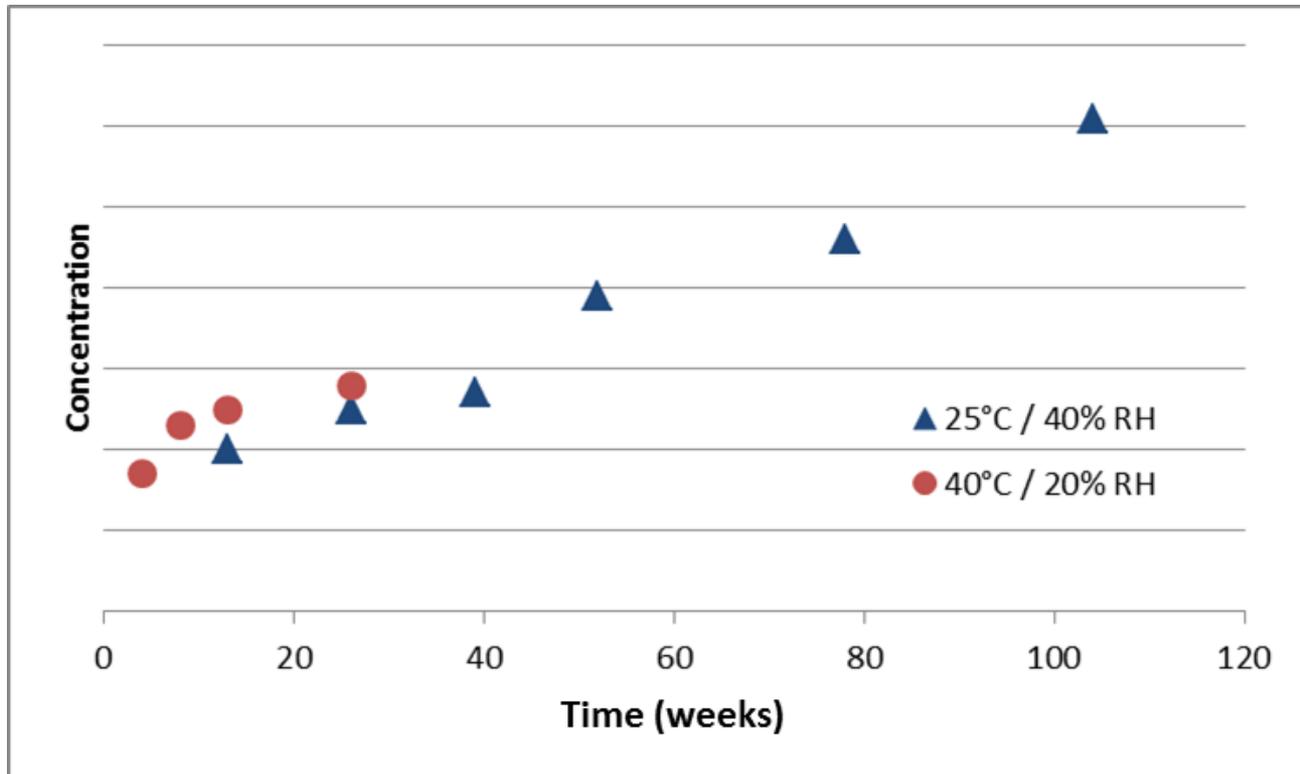


Migration from 2° Packaging

- 2° packaging migrants will not necessarily diffuse into product
 - Some vapor pressure is required
 - Environment strongly influences partitioning
 - Challenges at elevated temperature
- Is there a driving force for a 2° packaging substance to partition into drug product?



To Accelerate or Not To Accelerate?

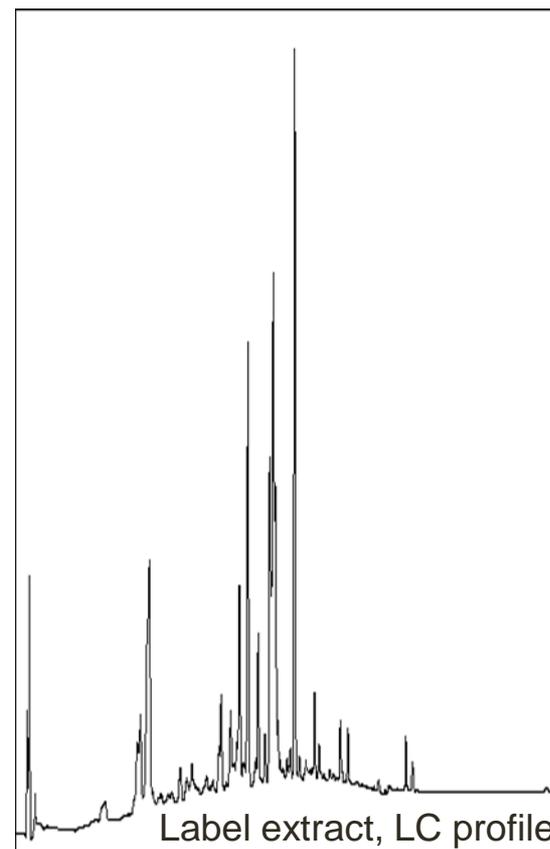


- Consistently low quantitative estimates or false negatives associated 2° package migrants at 40°C storage

Bringing Relevance to Extractions

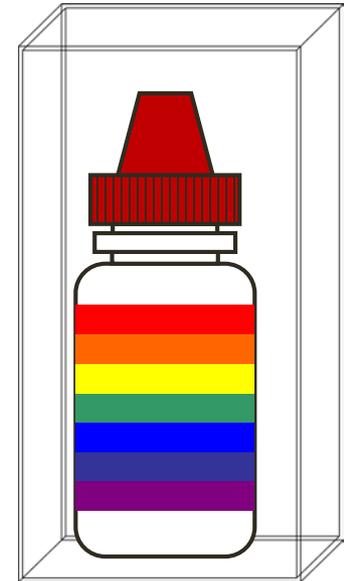
Consider an extraction study on a label for an ODP in a semi-permeable container

- Direct solvent extraction is an unrealistic contact condition for a label
- Label represents a variety of components with different extractables
 - Substrate (often, polyolefin)
 - Adhesive
 - Inks and coatings
- Yields a large number of extractables for ID in order to conduct a targeted leachable study



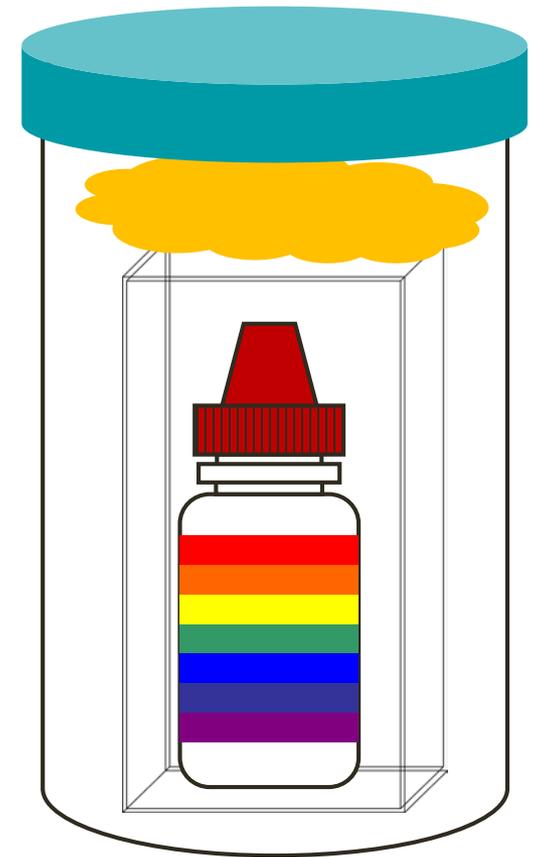
Value of ODP Simulation Studies

- To observe a migrant from secondary packaging, it must...
 - Migrate from the original component
 - Permeate the bottle
 - Dissolve in the formulation
- Secondary packaging profiled by simulation
 - Simulating solvent placed inside the bottle
 - Label affixed to bottle exterior and/or
 - Bottle placed inside unit carton
- Creates a realistic contact condition where the selectivity of the packaging system and properties of the extractables reveal probable leachables/migrants



ODP Simulation Study Setup

- Enclosure of system in a sealed vessel drives equilibrium toward simulant in bottle
 - Allows for elevated temperature (40°C) storage w/out false negatives; shortens study
 - Increases risk of false positives
- Parameters
 - Run to equilibrium
 - Account for worst case mass:volume ratio
 - Solvent choice
 - Moderately better sink than formulation(s)
 - “Reasonable worst case” – balanced risk



ODP Simulations

- In the ODP recommendations, simulation is identified as essential for efficiently generating knowledge in cases where 2° packaging is critical
- Simulation:
 - Characterizes important and/or relevant extractables from 2° packaging components
 - Useful because 2° components are often chemically complex, but not all extractables will become leachables/migrants
 - Manage complex partitioning behavior of migrants
 - For change control situation, simulation allows
 - Rapid assessment of impact (often < 1 month)
 - May provide insight across multiple products in the same packaging system if designed appropriately

Chemistry Conclusions

- There is no consensus SCT/AET concept for ODP
 - Start with historical precedent (1 ppm) and adjust as necessary
- E&L assessments of drug products in semipermeable container closure systems (e.g., ODP in LDPE) must include packaging components that do not make direct drug product contact (e.g., labels, product information inserts, unit cartons)
- Simulation studies on these components are recommended to bring focus to the most relevant extractables (i.e., probable leachables) and expedite assessments for packaging changes

PQRI PODP Extractables & Leachables Workshop

Experimental Design Considerations for Ophthalmic Drug Products (ODP): Toxicology

Presented by: Mary Richardson, PhD, DABT
CSO and EVP iuvo BioScience



Current thinking and strategy for ODP

- Parenteral and ophthalmic drug products have unique attributes which drives the need to be treated different
- At previously discussed, there is not a sufficient database developed on all the relevant toxicity endpoints to allow the working group to recommend specific safety thresholds
- However, science-based best practices and key considerations for the Toxicology assessment of ODP can be offered



FDA Practices for E&L in ODP

- FDA practices for E&L have been in place for more than 10 years
- Thresholds are concentration-based, rather than total daily intake-based
- Leachables should be identified when possible and toxicology assessment evaluated as necessary
- Typically, leachables are:
 - Reported at above 1 ppm
 - Identified at 10 ppm
 - **Qualified at 20 ppm**
- *Adapted from Linda Ng (US-FDA), PQRI PODP Workshop, Bethesda, MD, Feb 2011*

ODP Considerations: Toxicology Assessment

Types or Nature of Leachable may be influenced by:

- Typically liquid-based

- More likely to interact and possibly extract leachables from packaging

- Formulation

- Leaching can be strongly dependent on drug product formulation
 - Excipients may impact/increase the extraction of chemicals from container
 - Leaching may require a significant amount of time to occur



ODP Considerations: Toxicology Assessment

•Small Dose Volume

–Small volumes generally administered (<100 uL)

–low dose volume can result in high concentration (ppm) in drug product

Concentration Values vs. Total Daily Intake: Relationship to Dosing Frequency

Concentration (ppm)*	Number of Eyes treated	Daily Dosing Frequency	Total Daily Intake (µg/day)
20	1	2	2
20	2	2	4
20	2	4	8

*Assumes 50 uL dose volume



ODP Considerations: Toxicology Assessment

- Primary Packaging:
 - The semi-permeable nature of ophthalmic primary packaging is a major factor for E&L
- Secondary Packaging:
 - Major contributor of leachables to ophthalmic products and definitely influences a drug product leachable profile



Toxicological Endpoints

- Ocular drugs are designed to achieve a “high” local exposure and corresponding low systemic exposure
 - low ng/mL range
 - typically 50–80% of the topically administered drug is absorbed systemically
- Systemic effects including general and developmental and reproductive toxicity are less relevant to ODP relative to other product types
- Primary toxicological endpoints of consideration for qualifying leachables for topical ophthalmic products include:
 - Ocular irritation (toxicity)
 - Sensitization
 - Genotoxicity

Ocular Irritation/Toxicity

- For topical ODP leachables that are not genotoxicants or carcinogens, due to the local concentrated delivery of the drug, ocular irritation/toxicity is a key toxicity endpoint
- 20 ppm may provide a solid starting point when attempting to establish a rationale-based threshold for ocular endpoints through literature and/or experimentally derived data
- Data from a preliminary study* conducted to evaluate the potential of establishing a threshold for ocular irritation/toxicity support that 20 ppm is a sound starting point
 - Eleven chemicals from nine different classes
 - Tested compounds include acids, acrylates, acyl halides, alcohols, alkalis, amines, and surfactants

**SOT poster, 2013. Evaluation of the potential for establishing a threshold for chemical ocular irritation using a model of repeated topical ocular administration in albino rabbits. Eckles K, Amin J, Krenzer K, Richardson M. Bausch and Lomb.*



Sensitization Potential

- A primary concern for this endpoint is skin sensitization
- Eyelid contact allergic dermatitis as a result of ophthalmic drug administration is well established indicating that surrounding ocular tissues are susceptible to the delayed hypersensitivity response
- A guinea pig maximization test or murine local lymph node assay (LLNA) although not directly relevant to the eye, may provide sufficient weight of evidence to evaluate whether the compound would have a high likelihood of stimulating an immune response leading to sensitization
- A similar approach to what has been proposed for skin sensitizers and good scientific judgment is appropriate when assessing the potential for ocular drug-induced sensitization

Genetic Toxicity

- Although systemic exposure following ocular drug administration is typically very low, alignment with established genotoxic impurity guidance when assessing extractables and leachables is considered warranted
- Leachables provide no therapeutic benefit to the patient and genotoxic risk would be unacceptable
- As with other product types, evaluation using in silico structure-activity relationship (SAR) evaluation could be acceptable
 - follow-up in vivo and in vitro genetic toxicity assays may need to be conducted



Safety Assessment

- Qualification of leachables for ODP is similar to other drug types
 - toxicological endpoints of concern would be more focused on local toxicity
- Limits and/or qualification are usually established on a case-by-case basis using safety assessments in conjunction with quality manufacturing considerations
- If an extractable study is conducted, may do SAR evaluation or literature review
 - Identify extractables that need monitoring in leachable study
 - Support material selection

Qualification of an Ophthalmic Leachable

- Literature evaluation should be conducted focusing on the local effects including ocular toxicity, potential for carcinogenicity/genotoxicity, and sensitization
 - systemic data may be used to support the qualification
- A safety assessment should be performed
 - data on the irritancy potential in relevant ranges may be limited
- Evaluate whether the literature provides adequate information to qualify the leachable or if additional testing is required
- The safety assessment should evaluate local effects on the eye (i.e., ocular irritation) on a concentration basis (ppm)
 - For evaluation of genotoxicity potential, it may be useful to also calculate the TDI to aid in the assessment of systemic risk
- Any potential additional testing would be focused on areas where there were data gaps for the primary endpoints of concern

Possible Future Direction

Establishment of an acceptable Qualification Threshold for ocular irritation endpoint is possible

- The small volume of administration with ophthalmic products will need to be accounted for - large differences in concentration based on dosing regimen
- Is irritancy acceptable with safety margin- need for other endpoints?
- The Qualification Threshold for ocular irritation:
 - could be based on available literature
 - consider the levels previously justified for respiratory irritants
 - will need to be verified



Summary of Toxicological Assessment

- Literature data on the ocular irritancy potential in the relevant ranges is limited therefore defining an SCT has proven difficult
- Ophthalmic products have unique characteristics which may impact the approach/rationale applied to qualify leachables
 - small dose volume/dose
 - impact of primary and secondary packaging
 - importance of local effects vs. systemic effects
- Primary toxicological endpoints of consideration for ODP
 - Ocular irritation
 - Sensitization
 - Genotoxicity
- Consistent with other product types, final limits in product set based on many considerations including safety



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