



**Best Practices for OINDP Pharmaceutical  
Development Programs  
Leachables and Extractables**

*Early Safety Assessment of Potential Leachables*

*PQRI Leachables & Extractables Working Group*

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# Early Evaluation Process

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- Form a team
  - Pharmaceutical Sciences
  - Analytical Chemistry
  - Toxicology
  - Regulatory
  - Marketing
  - Technical Operations (Manufacturing)
  - Clinical
- Review Drug Product Specifications
  - Determine and agree what are the *Critical Components* of the DP
    - Is the actuator trigger a *Critical Component*?

# Supplier Evaluation

- ▶ Is the Supplier willing to share information?
  - § What type of data will be shared
    - ▶ Controlled extraction data
    - ▶ ISO 10993/USP <87>, <88> reports
    - ▶ MSDS
    - ▶ Other toxicology data
  - § May require confidentiality agreements
    - ▶ Allow time to get agreements in place
- ▶ Can the Supplier provide medical grade materials
  - § Has the Supplier filed DMFs for the materials?
    - ▶ Is Supplier willing to provide DMF
  - § Can non-medical grade material be used
- ▶ Can the Supplier provide information on prior use of material for approved DP?

# Example

## Drug Product with Delivery System

- ▶ An already approved DP is being revamped
  - § New/Improved delivery system
  - § Global Registration anticipated
- ▶ DP evaluation team formed
- ▶ Based on DP configuration, 5 *Critical Components* have been Identified

# Critical Components

Critical Component	Contact	Supplier Identified	Confidentiality Agreement
Ring Seal	Patient/Product	Yes	No
Plunger Insert	Product	Yes	Yes
Plunger Seal	Product	Yes	Yes
Chamber	Product	Yes	Yes
Valve Seal	Product	Yes	In Process

# Ring Seal

- ▶ Supplier has limited experience with pharmaceutical applications
- ▶ Is hesitant to provide detailed information on material
  - § Trade secret – may compromise exclusivity of material if data shared with DP manufacturer
  - § Will not disclose
    - ▶ Chemical/Physical composition
    - ▶ Safety/Risk information

# Ring Seal - Options

## ▶ Pharmaceutical Sciences

- § Material is *“optimal”* and compatible with the delivery system
- § Pharm Sci prefers to stay with this material
- § Alternatives that were evaluated were not considered *“optimal”*

## ▶ Analytical Sciences

- § Will need to conduct a controlled extraction study
- § Will have no data from supplier to compare with

## ▶ Toxicology

- § Evaluate extractable profile for potential *“red flags”*
  - ▶ PNAs, nitrosamines, MBT, etc.
- § Potential for extensive *in silico* risk assessment of extractable profile

# Ring Seal – Issues/Risks

- ▶ FTE burn by Analytical Chemistry and Toxicology
- ▶ Potential exists that an unacceptable extractable is identified
  - § May need to identify alternative material
- ▶ Potential delay in development/registration of DP

# Plunger Insert

- ▶ Material is HDPE
- ▶ Chemical information supplied
  - § Physical Properties - Yes
  - § Composition - Yes
- ▶ Toxicology information supplied
  - § Indirect Food Additive cross reference

# Plunger Insert - Composition

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Chemical Component	Range (weight %)
Ethylene-Octene-1 copolymer CAS 26221-73-8 (Sanctioned under 21 CFR 177.1520)*	99.92 – 99.97
Octadecyl 3,5-di-tert-butyl 4 hydroxyhydrocinnamate CAS 2082-79-3 (Sanctioned under 21 CFR 178.2010)**	0.025 – 0.065
Calcium Stearate CAS 1592-23-0 (Sanctioned under 21 CFR 178.2010)**	0.005 – 0.015

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\*Safe use of polyolefin articles intended for direct food contact

\*\*Safe use of antioxidants/stabilizers in polymers for indirect food contact

# Plunger Seal

- ▶ Material is PP
- ▶ Chemical information supplied
  - § Physical Properties - No
  - § Composition - Yes
- ▶ Toxicology information supplied
  - § None

# Plunger Seal - Compositon

Chemical Component	Content (Weight %)
1-propene, polymer with ethene CAS 9010-79-1	94.48
Dimethyl succinate polymer with 4-hydroxy-2,2,6,6-tetramethyl-1-piperidineethanol CAS 65447-77-0	0.2
2,2'-oxamido bis-[ethyl 3-(3,5-di-tert-butyl-4-hydroxyphenol)]propionate CAS 70331-94-1	0.07
di(stearyl) penta-erythritol diphosphate CAS 3806-34-6	0.1
synthetic hydrotalcite CAS 11097-59-9	0.05
calcium stearate CAS 1592-23-0	0.1
LLDPE CAS 25087-34-7	5

# Issues

- ▶ No Toxicology data supplied

- § Inquire on availability of toxicology data

- ▶ ISO/USP test results
    - ▶ MSDS
    - ▶ Other

- ▶ Limited Chemical Profile

- § Additional data requested

- ▶ e.g., antioxidants

# Resolution

- ▶ Analytical Chemistry

- § In-house controlled extraction studies will be conducted to obtain comprehensive profile

- ▶ Toxicology

- § Can perform initial assessment on information supplied

- § May determine *bad actors* when additional information from controlled extraction studies are evaluated

# Initial Risk Assessment (1)

- ▶ Obtain chemical structures of each extractant
- ▶ Conduct SAR Analysis
  - § DEREK - Deductive Estimation of Risk from Existing Knowledge
  - § MultiCase
  - § SAR will typically report genotoxicity, mutagenicity, carcinogenicity
    - ▶ Limited value for reprotoxicology, irritation, sensitization

# Risk Assessment (2)

## ► Perform Literature Search

- § Agency for Toxic Substances and Disease Registry
- § Chemical Hazards Response Information System
- § Material Safety Datasheet Database
- § New Jersey Hazardous Substance Fact Sheet
- § Micromedex
- § National Toxicology Program Testing Information
- § National Institute of Occupational Safety and Health Registry of Toxic effects of Chemical Substances
- § Occupational Safety and Health Technical Links to Safety and Health Topics
- § Toxnet (National Library of Medicine Specialized Information Services)
- § Registry of Toxic Effects of Chemical Substances
- § Center for Drug Evaluation and Research and the Integrated Risk Information System
- § National Institute of Environmental Health Sciences
- § Environmental Protection Agency Integrated Risk Information System
- § Technical Information Exchange System

# Risk Assessment (3)

- ▶ Evaluate available information
  - § Assume worst case scenario – all extract leaches into DP
- ▶ Provide initial risk assessment to team
  - § Identify any/all potential issues
  - § Make recommendations on further use of material based on risk assessment profile

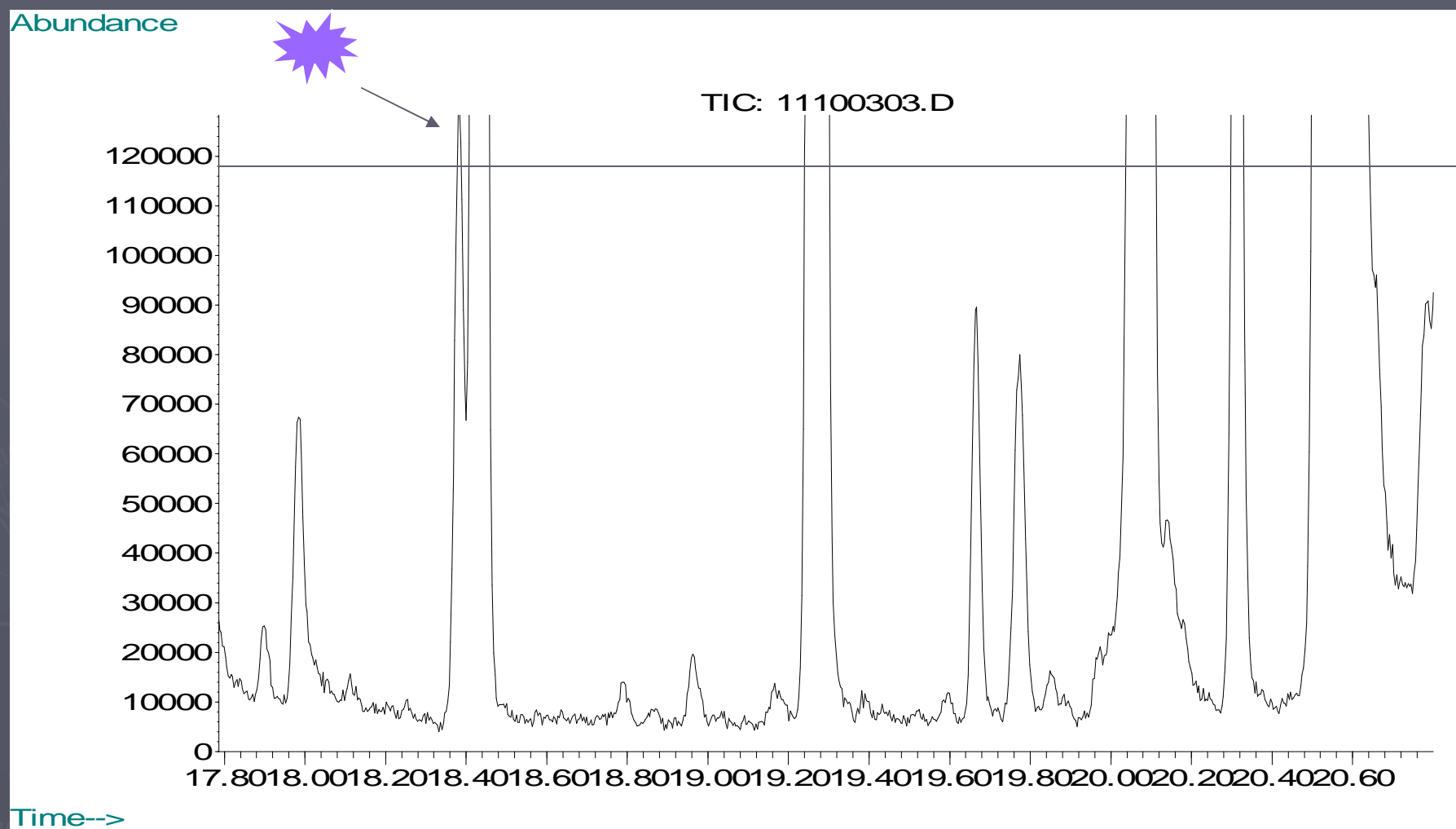
# Analytical Evaluation Threshold

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The *Analytical Evaluation Threshold* concept converts the SCT (0.15 µg/day for an individual leachable) into a threshold which can be applied to an individual drug product leachables profile, and by extension to a critical component extractables profile. It attempts to address the question:

*How low do we go?*

# Leachables Profile – 1 Week Timepoint Expanded Section



# Conclusions

- ▶ Data from suppliers may be limited in scope
  - § May not provide a total extract profile
  - § May not provide significant toxicity information
- ▶ May require a controlled extraction study to assist in component selection
  - § Obtain more comprehensive profile of the material
- ▶ Risk Assessment is only as good as the data that is available