Best Practices for OINDP Pharmaceutical Development Programs Leachables and Extractables

II. OINDP Container Closure Systems

PQRI Leachables & Extractables Working Group

PQRI Training Course
April 12 - 13, 2007
Chicago

Container Closure System Components

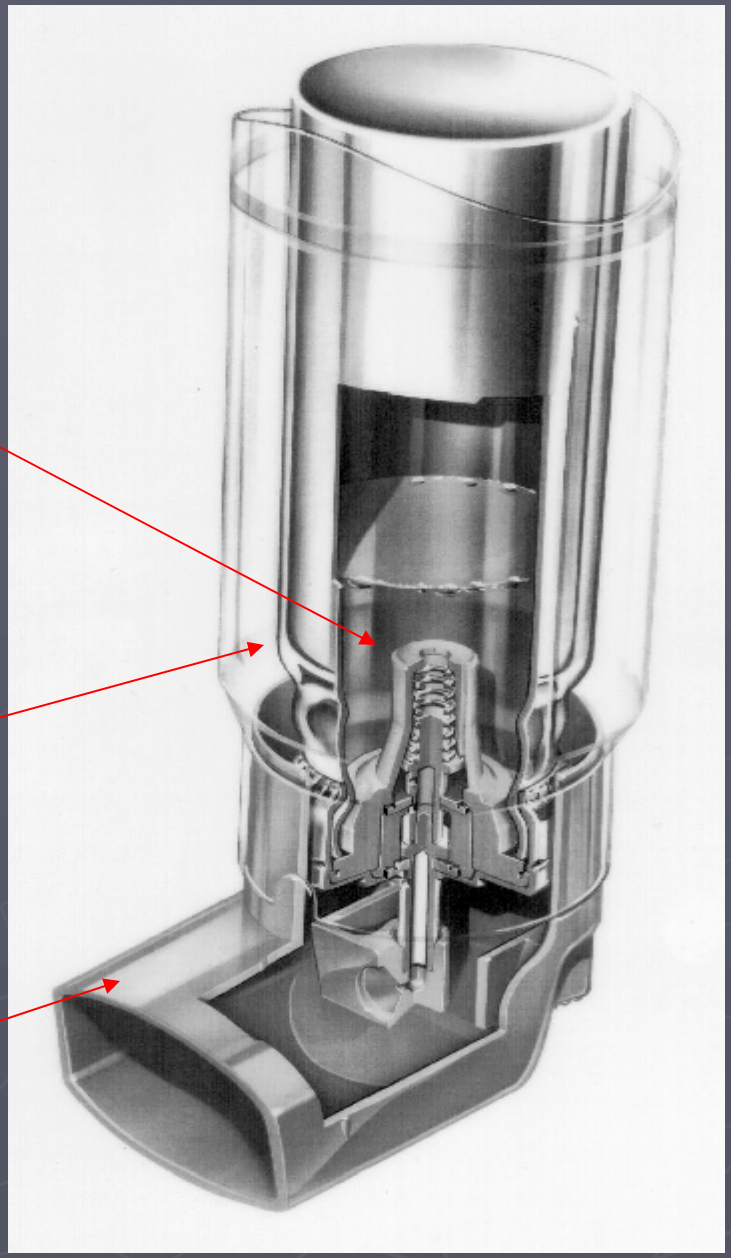
- *Primary Packaging Components*, which are or may be in direct contact with the dosage form. These include: containers (e.g., ampules, vials, bottles), container liners, closures (e.g., screw caps, stoppers, metering valves), closure liners, stopper overseals, container inner seals, administration ports, overwraps, etc.
- *Secondary Packaging Components*, which are not or will not be in direct contact with the dosage form. These include container labels, administration accessories, shipping containers, etc. Note that even though secondary packaging components are not in direct contact with the drug product, they may still contribute leachables under certain conditions.

Critical Components

"Critical components" of an OINDP container closure system are defined as those that contact either the patient or the formulation, components that affect the mechanics of the overall performance of the device, or any necessary secondary protective packaging."

MDI "Critical Components"

- Dose metering valve
  - Metering chamber
  - Stem(s)
  - Seals/gaskets
  - Sealing rings
- Canister
  - Coated?
- Mouthpiece/actuator



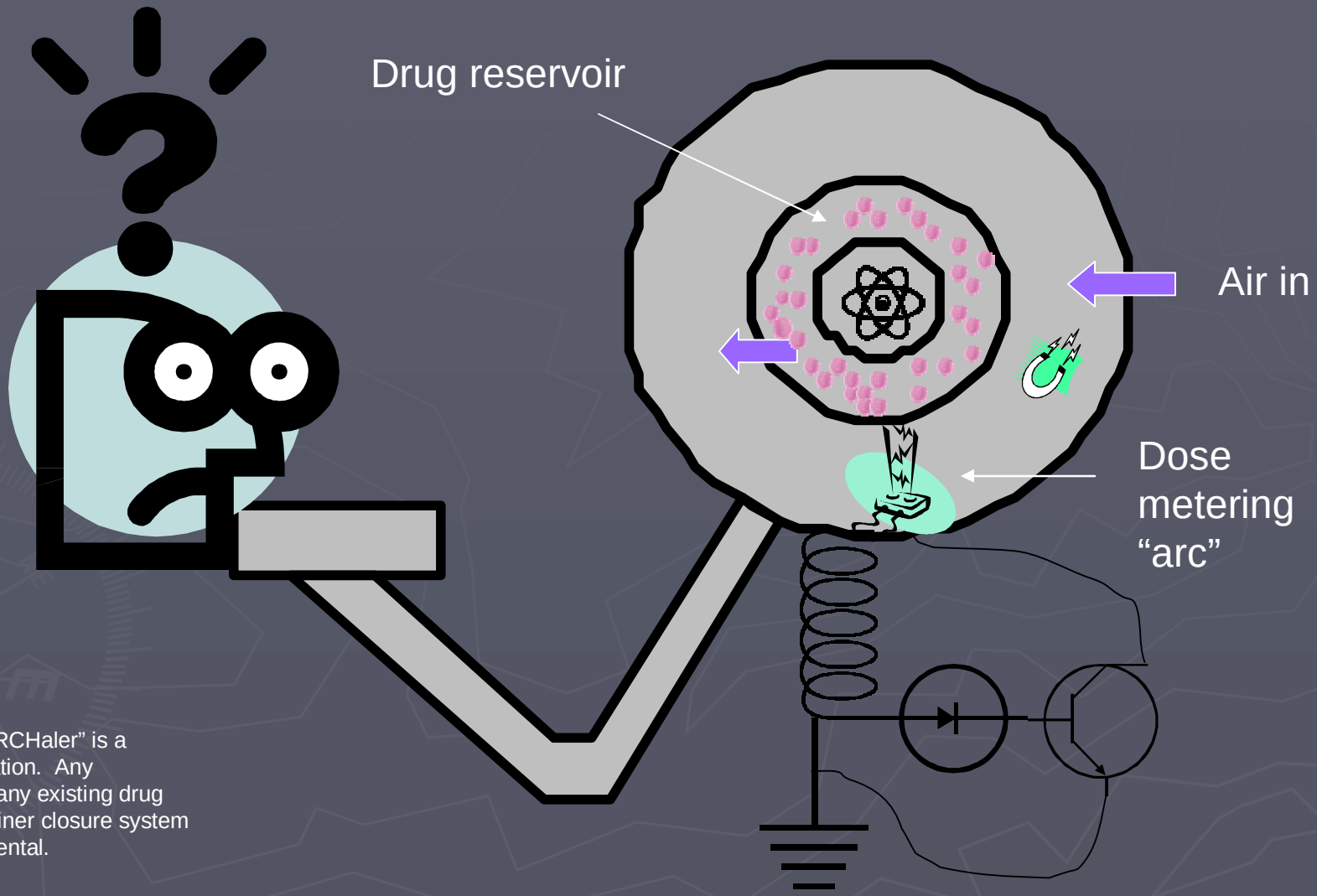
MDI Schematic Provided by Bespak Europe

OINDP Container Closure System Components

DPI

Images provided by
Bespak Europe and Pfizer

DPI Critical Components – “ARCHaler”



Note that the “ARCHaler” is a complete fabrication. Any resemblance to any existing drug product or container closure system is purely coincidental.

What are some potential sources for leachables and extractables?

- Chemical additives present in individual elastomeric/polymeric container closure system components, including contaminants in such additives (e.g. PAHs and N-nitrosamines).
- Monomers and higher molecular weight oligomers derived from incomplete polymerization reactions.
- Migrants from secondary packaging components, such as inks and label adhesives.
- Surface residues, such as heavy oils and degreasing agents on the surfaces of metal canisters and containers.
- Chemical additives on the surfaces of container closure system component fabrication machinery, such as mould release agents, antistatic and antislip agents, etc.
- Chemical entities from the storage environment (i.e., “very” secondary packaging components), such as volatiles from cardboard shipping containers or plastic storage bags.

What is an Additive????

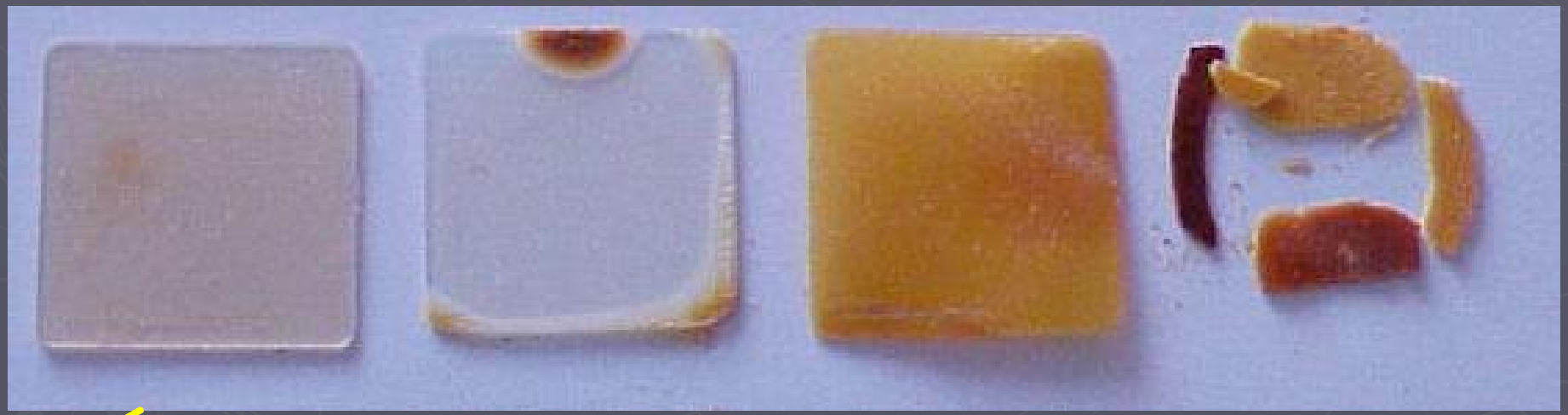
- **Additives are Ingredients Incorporated into the Polymer to Stabilize or Enhance its Performance**
  - **Stabilizers – Maintain the Polymer's Original Properties**
    - **Strength**
    - **Flexibility**
    - **Toughness**
  - **Modifiers – Change or Improve Polymers Performance**
    - **Performance Additives (Slips, Anti-Stats)**
    - **Pigments**
    - **Fillers**

Polymer Degradation

- **Physical Characterisitics**
- **Inherent Stability**
  - **Molecular Structure**
  - **Polymerization Process**
  - **Catalysts / Co-Catalysts / Residue**
  - **Finishing Steps**

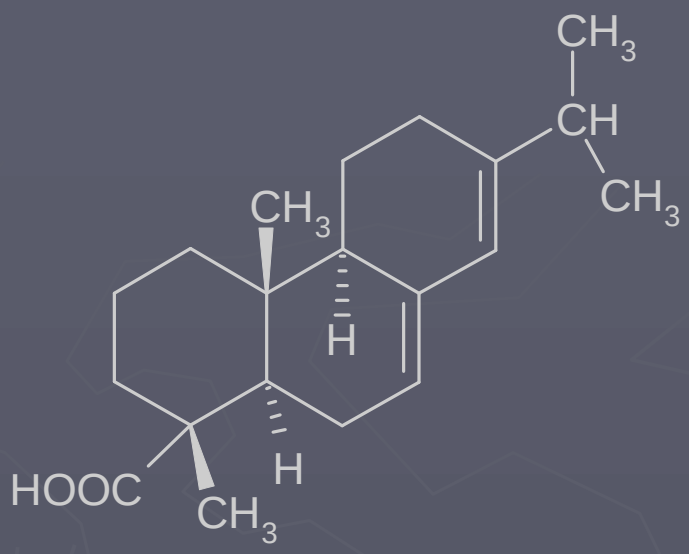
Polymer Degradation

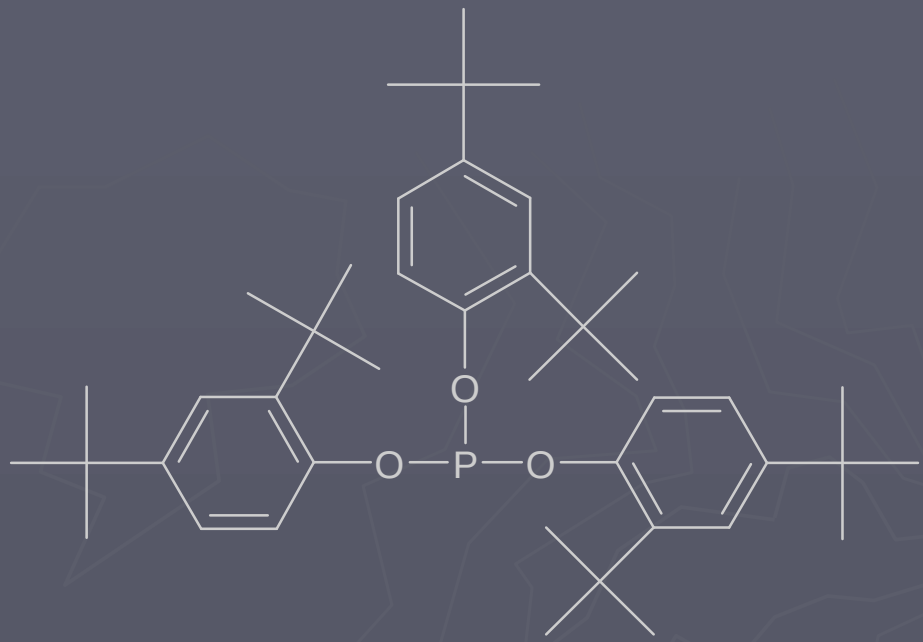
- **Processing Concerns**
  - **Temperature**
  - **Shear**
  - **Exposure Duration**
- **End Use Concerns**
  - **Intended Usage Life**
  - **Environmental Exposures**



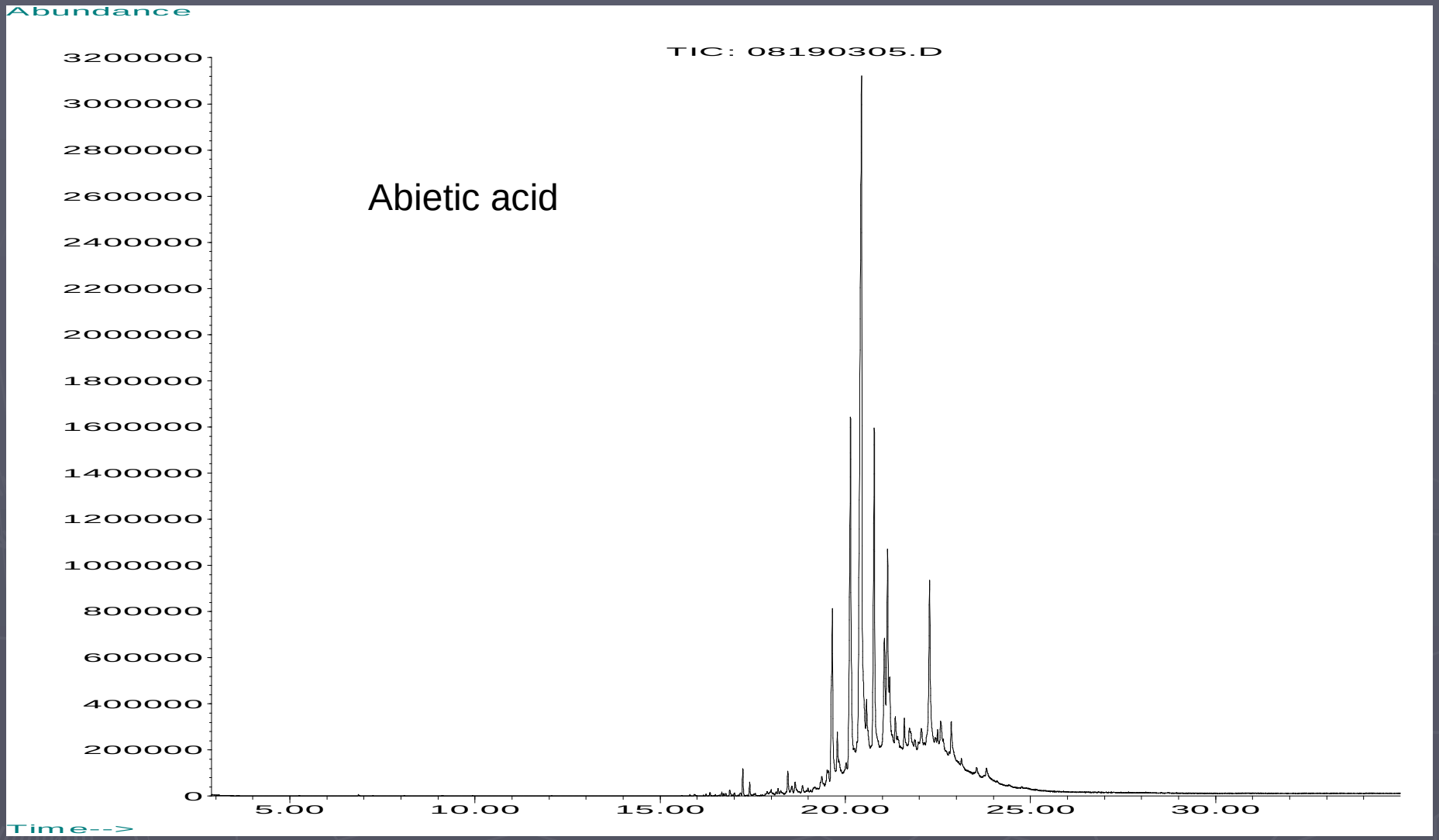
Improved High Temperature Stabilization

Examples of Chemical Additives





What's in a name?



Stabilizer Classes

- **Melt Processing**
  - **Phosphites**
  - **Hindered Phenols**

Process Stabilization / Base Stabilization

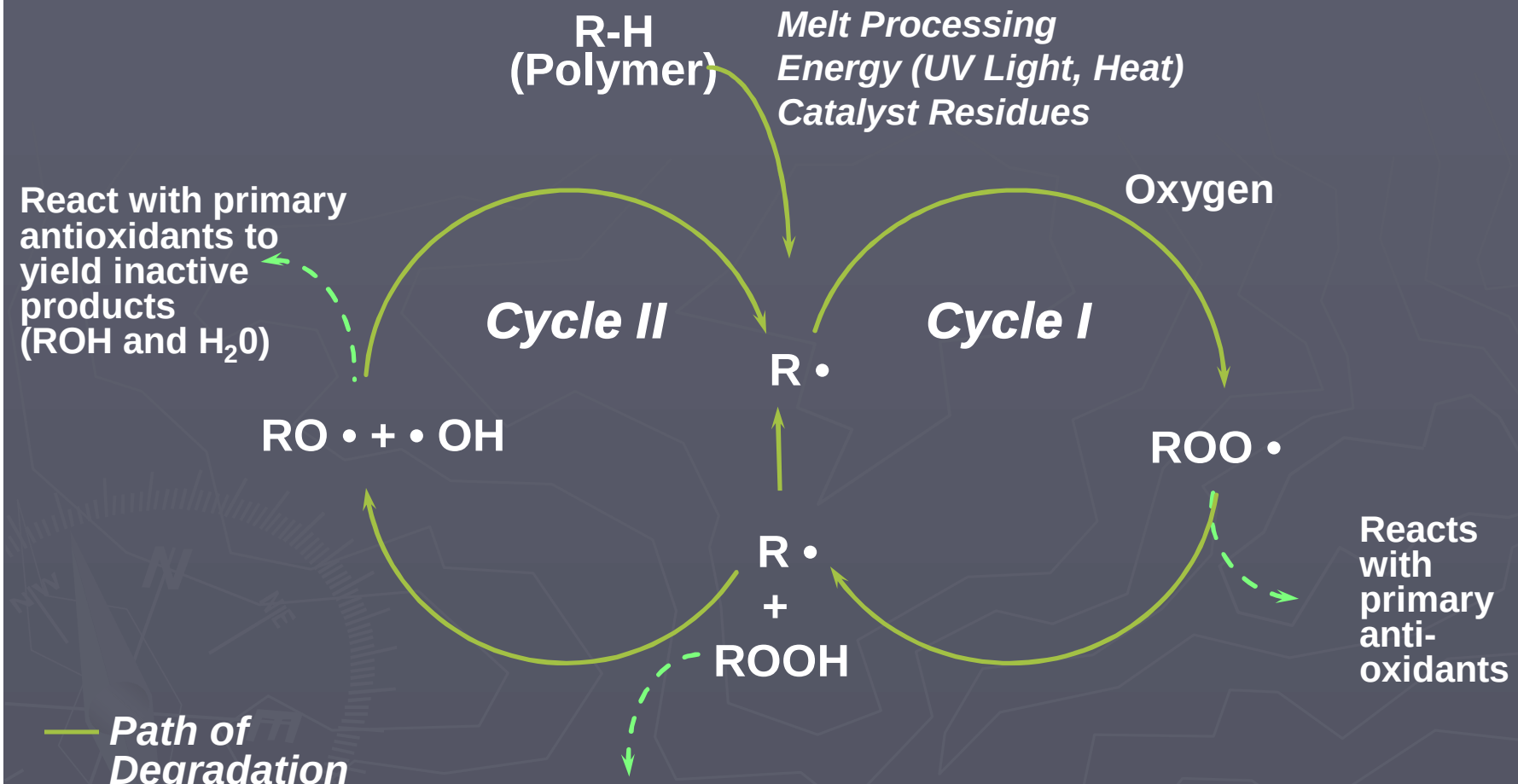
- **Long-term Thermal**
  - **Hindered Phenols**
  - **Hindered Amines**

Thermal Stabilizers

- **Light Stabilizers**
  - **Radical Traps**
  - **UV Absorbers**
  - **Excited State Quenchers**

Light Stabilization Package

Degradation and Stabilization



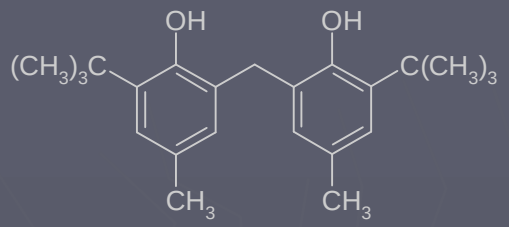
Extractables and Leachables

Challenge

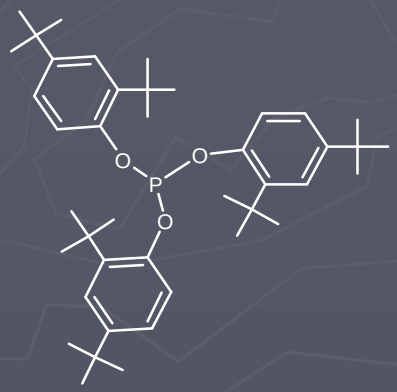
- **Stabilization is a *dynamic process***
- **Many additives will transform and/or degrade during use.**
  - **Transformation and degradation products must be considered along with the intact additives as potential *leachables and extractables.***
- ***Unexpected Additives May also be Present in the Polymer***

Stabilizers

- Auto-oxidation can be suppressed by the use of radical scavengers
- Most polyolefins contain one or more antioxidants at levels of 0.05 – 0.10 %
  - Primary antioxidants are generally radical scavengers or H-donors
    - i.e. hindered phenols such as BHT, Irganox 1010, or Irganox 1076
    - Long-term protection for the polymer
  - Secondary antioxidants are typically hydroperoxide decomposers
    - i.e. trivalent phosphorus compounds such as Irgafos 168
    - Process stabilization (protects the primary AO against decomposition during processing)

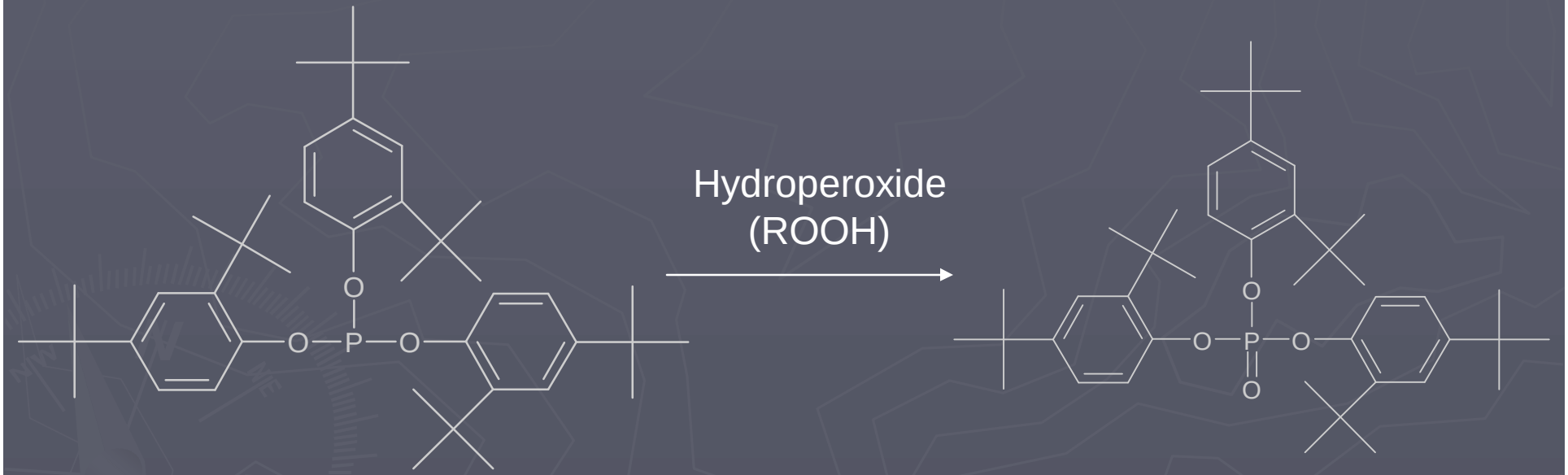


Irganox 2246



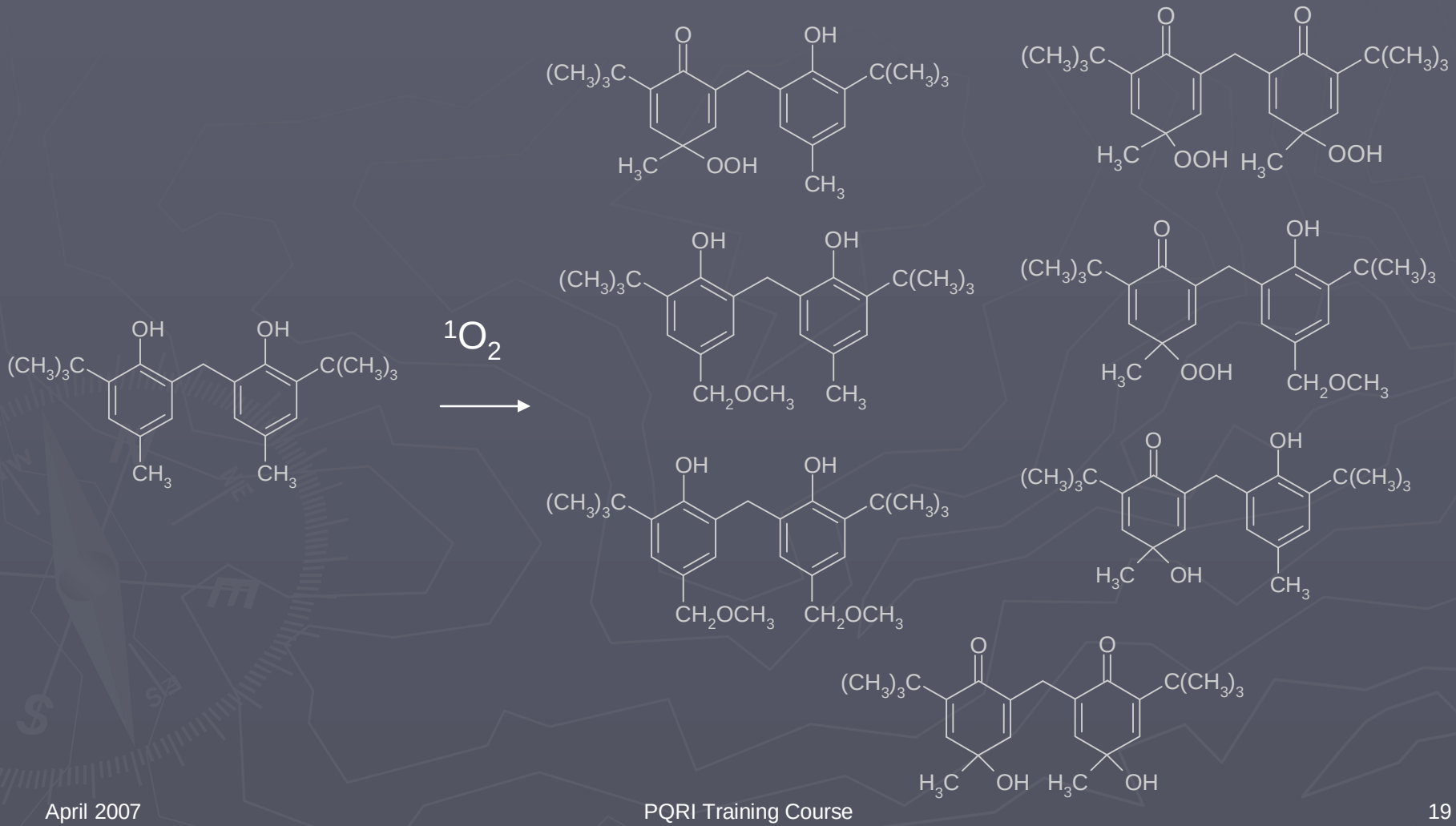
Irgafos 168

Additive Chemistry

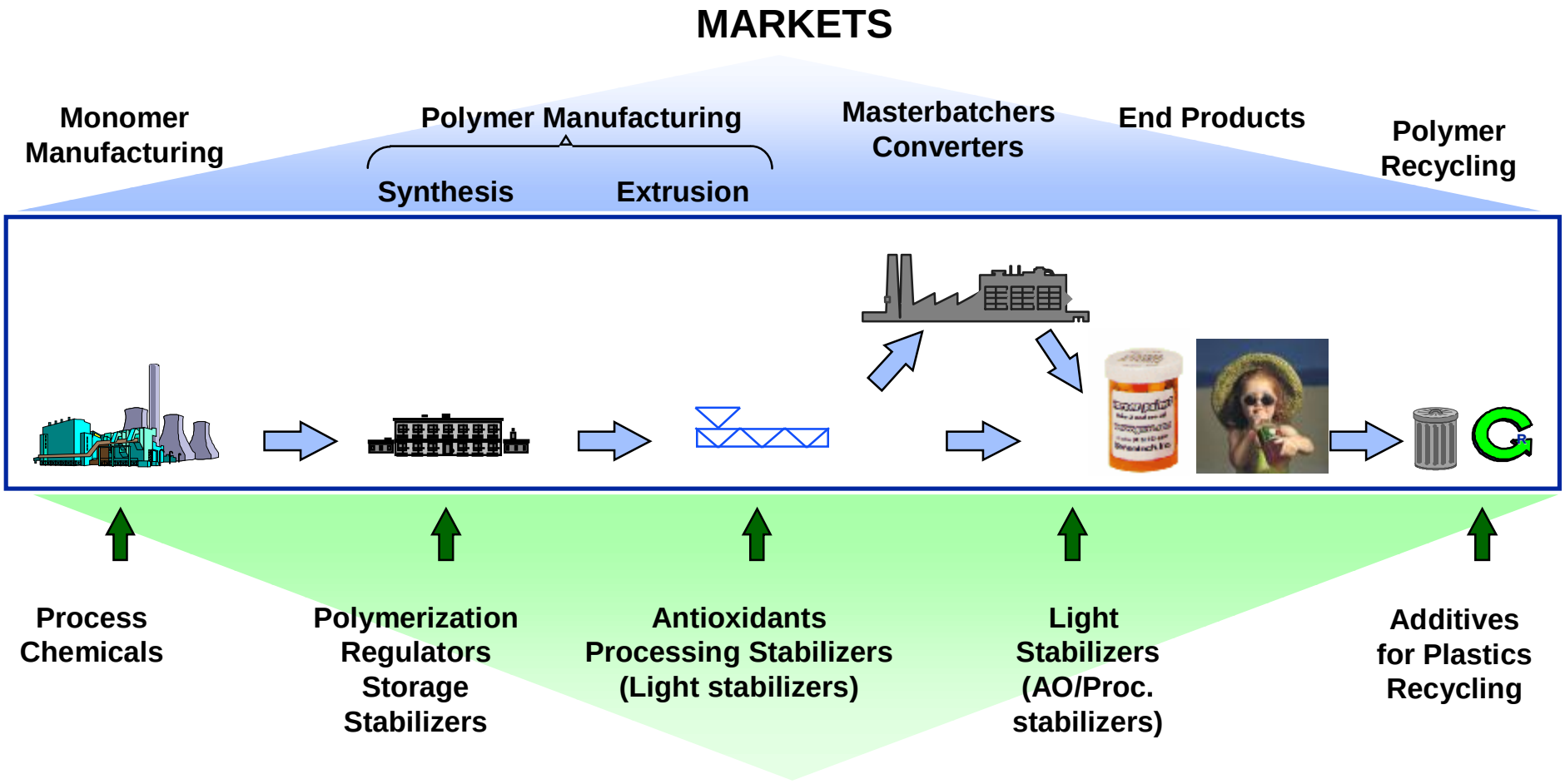


Irgafos 168

Reaction of Hindered Phenol with Singlet Oxygen

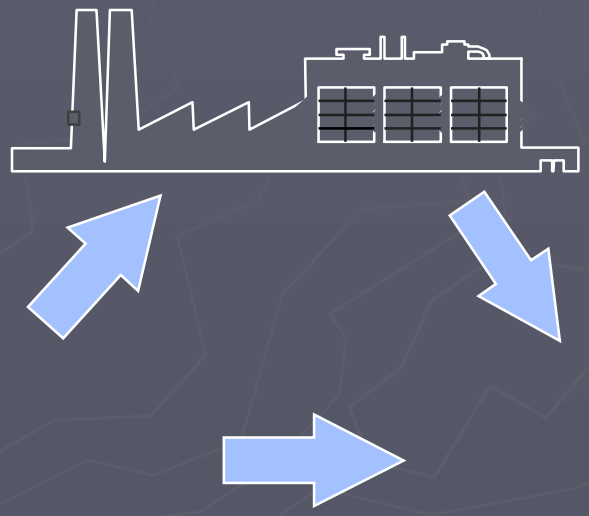


Stabilization Systems Along The Value Chain



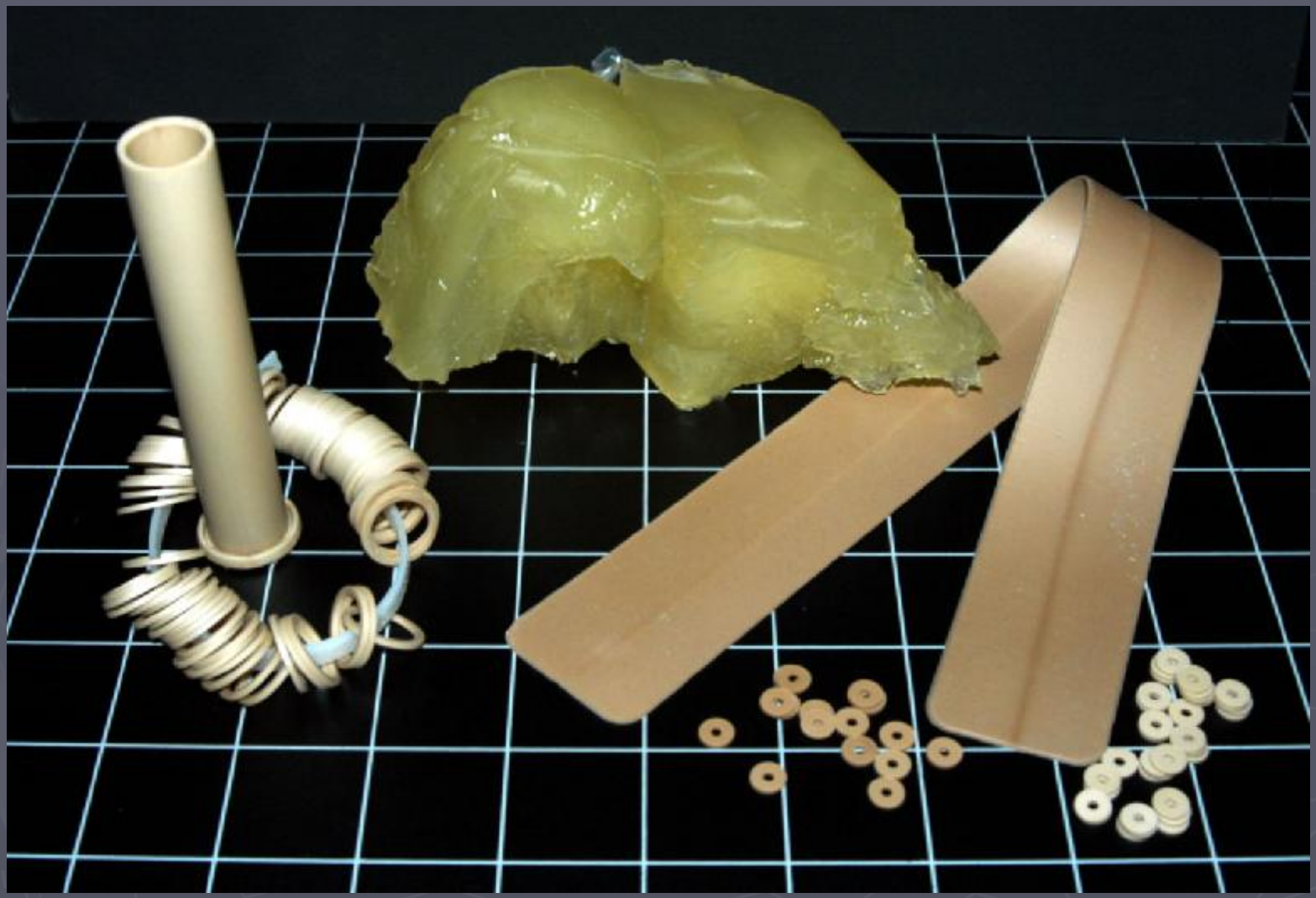
Masterbatchers and Converters

Polymer Concentrate
-Stabilizers
-Pigments
-Antistats



Polymer Often Contains a Base Stabilization Package

Raw Materials – Supply Chain



Raw Materials - Supply Chain

Component Fabrication

Extruder

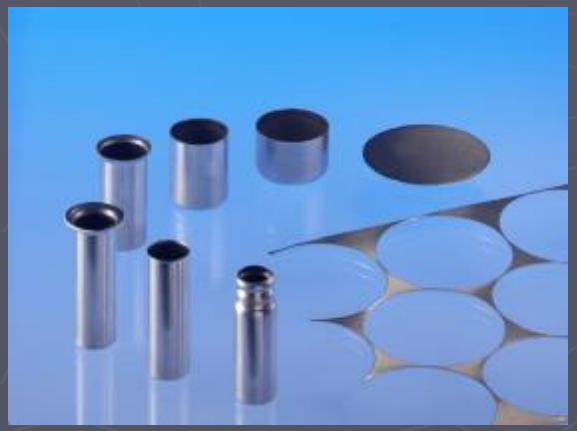
Image Provided by Ciba

Moulding machine

Image provided by Bespak Europe

Deep Drawing Process

metal rolls



deep-drawing tool

Images provided by Presspart

Deep Drawing Process

degreasing process

Images provided by Presspart

Information Required

- The elastomeric/polymeric or other material constituting the principal structure of the component (e.g., High Density Polyethylene, Ethylene-Propylene-Diene rubber, stainless steel, etc.)
- The polymerization/cross-linking/curing process, or processes, for the component base polymer, including any chemical additives employed.
- The compounding/fabrication process, or processes, including any additives designed to assist in compounding/fabrication.
- All individual chemical additives/ingredients in the component, including the composition and chemistry of each individual additive.
- Any cleaning/washing processes for finished components, including knowledge of cleaning, washing, or other agents.
- The storage/shipping environment for both components and drug product, if the potential for environmental leaching exists.

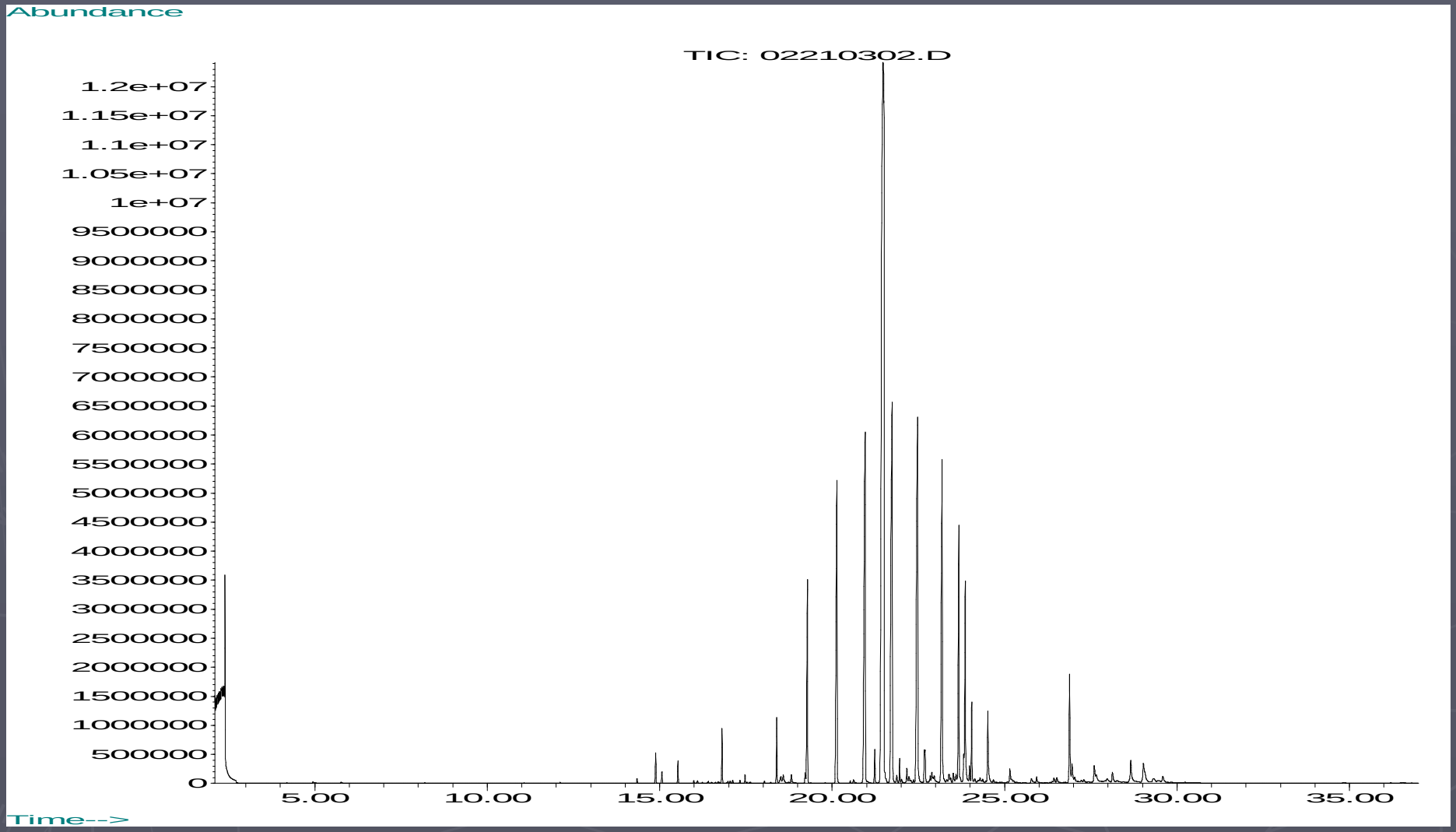
Rubber Formulation A (Sulfur Cured)

Ingredient	%
CALCINED CLAY	8.96
BLANC FIXE (barium sulfate)	25.80
CREPE	38.22
BROWN SUB MB	16.84
1722 MB	2.11
ZINC OXIDE	4.04
2, 2’ METHYLENE-BIS (6-TERTIARY BUTYL-4-ETHYL PHENOL)	0.56
COUMARONE-INDENE RESIN	1.12
PARAFFIN	1.12
TETRAMETHYLTHIURAM MONOSULFIDE	0.11
ZINC 2-MERCAPTOBENZOTHIAZOLE	0.29
SULFUR	0.84

What do we know?

- Carbon black is a known source of PAHs and has also been shown to be involved in N-nitrosamine formation in rubber (“special cases”).
- Thiurams are known precursors of N-nitrosamines.
- 2-Mercaptobenzothiazole is a known “special case”.
- Paraffin and Coumarone-indene resin are natural product materials and are likely complex mixtures of related structures.
- Individual additives are likely GC-able.

Sulfur Cured Rubber – Extractables Profile by GC/MS



Polypropylene Formulation

Ingredient	wt %
Primary Stabilizers	
Tetrakis (methylene(3,5-di-t-butyl-4-hydroxyhydrocinnamate)) methane	
Irganox 1010 (Ciba) Anox 20 (Great Lakes)	0.08 wt%
Secondary Stabilizers	
Bis(2,4-di-t-butylphenyl)pentaerythritol diphosphite	
Ultranox 626 (GE)	0.05 wt%

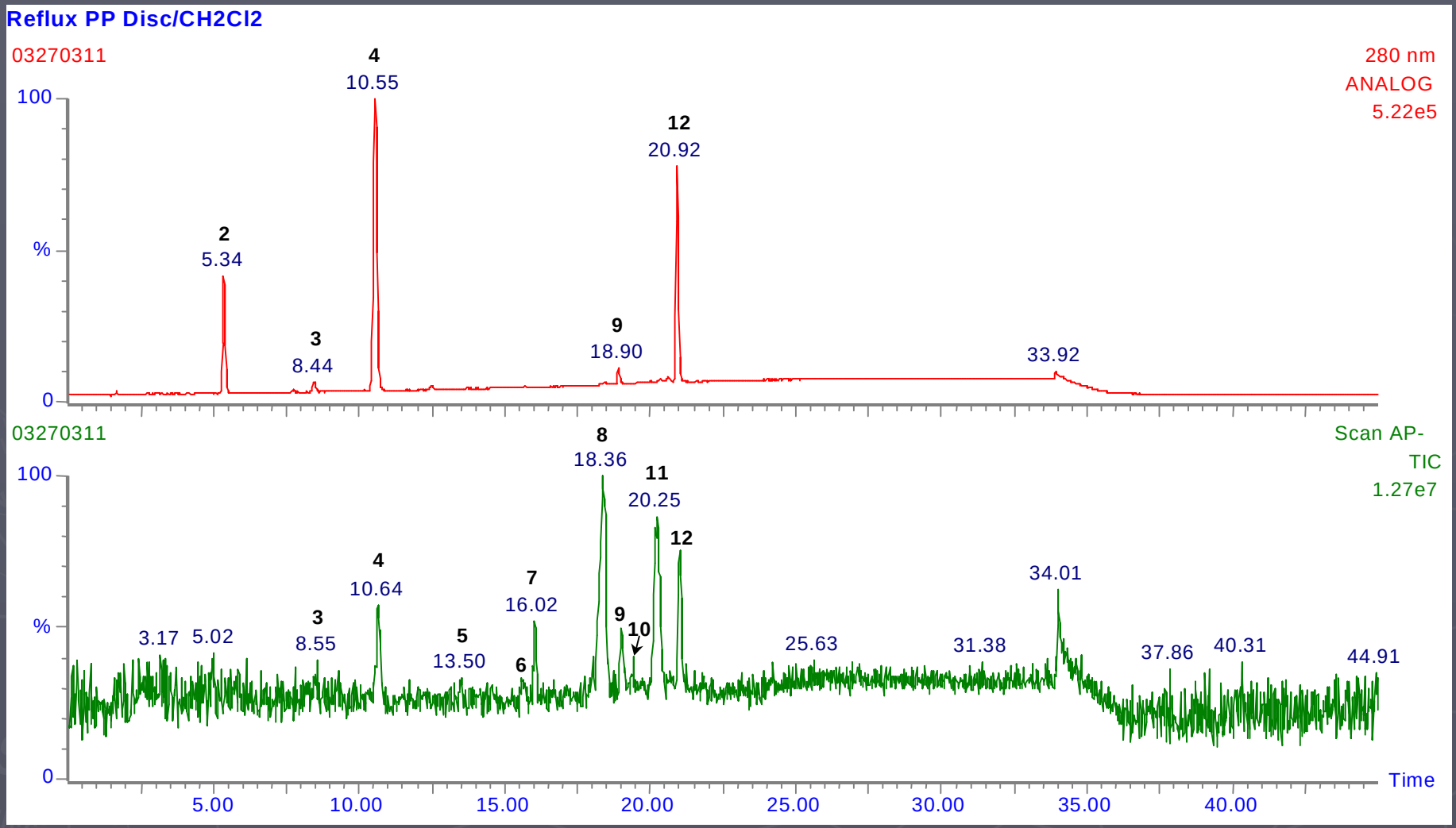
Polypropylene Formulation

Ingredient	%
Corrosion Inhibitors	
Calcium Stearate 114-50 (Ferro)	0.03 - 0.4 wt%
Antistatic	
Vegetable oil derived 90% alpha monoglycerides (soybean) Pationic 901 (Patco) Dimodan HS-KA (Danisco)	0.3 wt%
Nucleating Agents	
3,4 -dimethyl dibenzylidene sorbitol Millad 3988 (Milliken)	0.2 wt%

What do we know?

- Polypropylene is known to contain many soluble oligomers.
- Individual additives will likely require analysis by HPLC based methods.
- Individual additives could be both chemically complex and have complex degradation chemistries.
- No reason to suspect the presence of “special cases”

Polypropylene – Extractables Profile by LC/UV/MS



Summary of PQRI Recommendations

- *The pharmaceutical development team should obtain all available information on the composition and manufacturing/fabrication processes for each component type to the extent possible, and determine which components are "critical," before beginning extractables and leachables studies on a given OINDP and its associated container/closure system components.*
- *Component formulation should inform component selection.*
- *Risk Assessment should be performed during the selection of components and materials.*
- *Extractables testing, including Controlled Extraction Studies and the development and validation of Routine extractables testing methods, should be accomplished for all critical OINDP components.*