ELSIE

Extractables and Leachables
Safety Information Exchange

Presentation to ISPE, Boston Chapter

16 June 2011

Worcester, MA

Overview

- Extractables and Leachables: What Are They and Why Are They Important?
- Background on ELSIE
- ELSIE Materials Effort
- ELSIE Safety Effort
- Open Discussion

2

What are Extractables and Leachables?

- Leachables are undesired impurities in drug products
- All materials give off leachables (examples):
  - Plastics
  - Elastomers
  - Metal containers with coatings
  - Films
- Additives, oligomers, monomers, from these materials can all show up as E and/or L
- Leachables can present potential safety risk (they are non-drug related impurities, not covered by ICH Q3)
- Packaging materials are a major source of leachables

3

What are Extractables and Leachables?

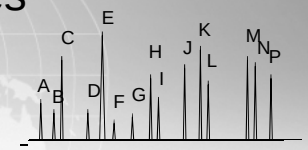
Definitions

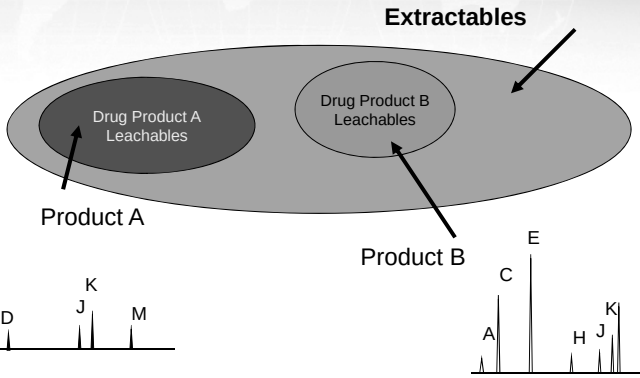
- Extractables: chemical compounds that are forcibly removed from drug product container closure systems, packaging, or from devices under rigorous laboratory conditions
- Leachables: chemical compounds that migrate from drug product container closure systems, packaging, or from devices under normal-use/stability

4

Extractables and Leachables

Different products will have unique leachables profiles from the same packaging system





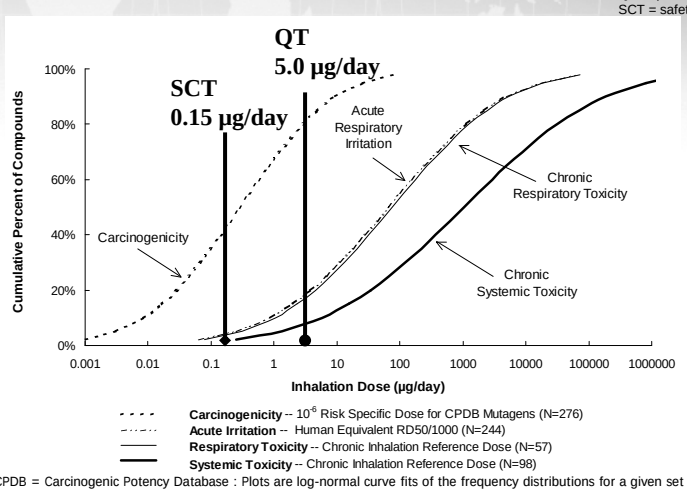
5

Low Levels of Leachables Can Lead to Safety Issues

PQRI Safe Human Inhalation Exposures for Different Toxicity Endpoints

Product Quality Research Institute - A forum for academia, industry and the FDA to work cooperatively

QT = qualification threshold
SCT = safety evaluation threshold



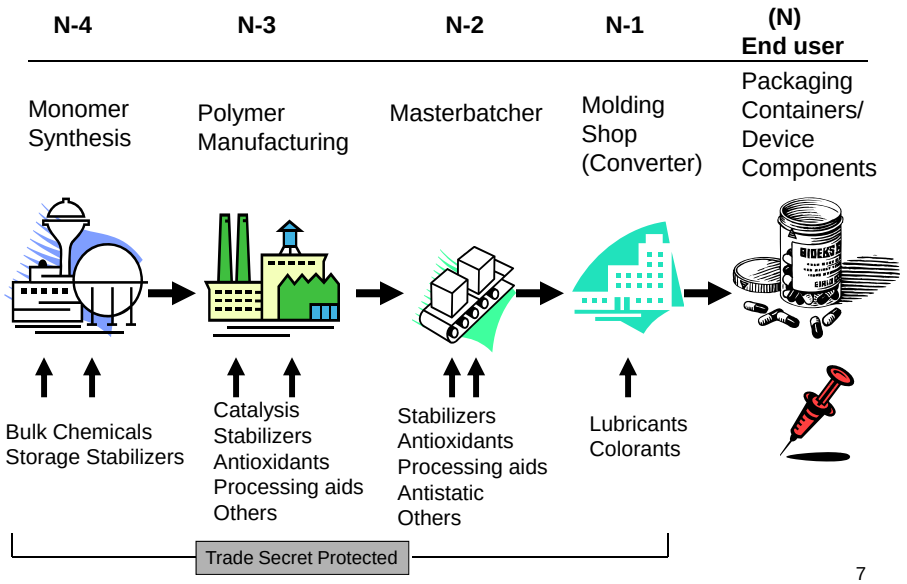
Carcinogenicity -- 10^{-6} Risk Specific Dose for CPDB Mutagens (N=276)
Acute Irritation -- Human Equivalent RD50/1000 (N=244)
Respiratory Toxicity -- Chronic Inhalation Reference Dose (N=57)
Systemic Toxicity -- Chronic Inhalation Reference Dose (N=98)

CPDB = Carcinogenic Potency Database : Plots are log-normal curve fits of the frequency distributions for a given set of data

Reference: PQRI OINDP L&E Working Group – Aug 2006

6

Plastics – A Complex & Competitive Industry



7

E&L in Regulatory Guidelines

- EMA Guideline on Plastic Immediate Packaging Materials
- EMA and Health Canada Guidance: Pharmaceutical Quality of Inhalation and Nasal Products
- FDA Guidance: Container Closure Systems for Packaging Human Drugs and Biologics
- FDA Draft Guidance: Metered Dose Inhaler and Dry Powder Inhaler Drug Products
- FDA Guidance: Nasal Spray, Inhalation Solution, Suspension, and Spray Drug Products

8

ELSIE History

- Initial discussions in February 2007
- Companies wanted to:
  - Reduce duplicative safety evaluation associated with leachables and extractables
  - Encourage accessibility and use of extractables safety information early in the development process, e.g., during materials selection
- ELSIE formally established in May 2007

9

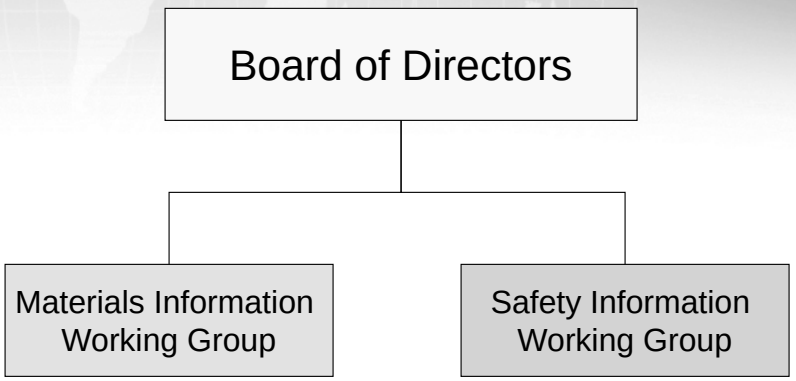
Membership

Abbott
AstraZeneca
Baxter
Boehringer Ingelheim
Eli Lilly
GSK
Merck Serono
Novartis
Pfizer
sanofi-aventis

All pharmaceutical, biotechnology, and medical device companies are invited to join ELSIE. Several additional companies are actively considering membership.

10

ELSIE Structure



11

Core Objective

ELSIE's core objective is to establish a comprehensive database that will provide a jointly-developed and credible source of

- Safety information on extractables and leachables and
- Extraction profiles and standardized study protocols for a range of materials commonly used in pharmaceutical, biological and device applications and processes (e.g., container closure systems, devices, manufacturing/processing)

12

ELSIE Outreach to Regulators

- FDA (CDER and CDRH) have expressed interest in the ELSIE effort
  - CDER indicated interest in a future meeting once further data and progress has been made
  - CDRH indicated interest in continuing dialogue with ELSIE
- MHRA have expressed interest in the effort and in regular updates

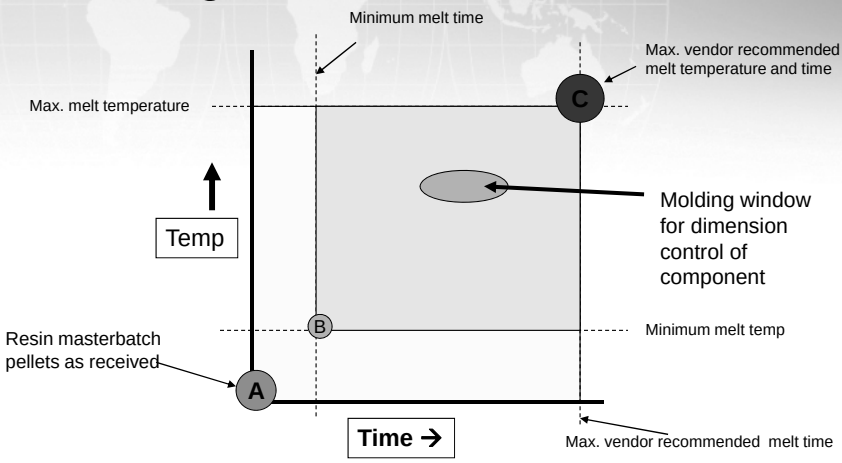
13

Materials Information Working Group Core Goal

- Define the extractables knowledge space for container closure systems and devices that could:
  - Provide a basis to reduce the risk of selecting “unacceptable” materials; and
  - Expedite further product-specific extraction and/or leachable studies

14

Extractables Design Space-Molding



Extractables information on plastic at point A and point C plus knowledge of potential degradation pathways is used to build the molding "knowledge space"

15

Safety Information Working Group: Core Goal

- Develop database of safety information on extractables and leachables

16

Safety Information Working Group: Summary of Activities

- Developed safety information template
  - Chemical Summary
  - Safety Summary
  - Key government assessments
  - Details on types of studies
- Flow and structure of the database follows the Common Technical Document (CTD)
- Developed detailed “user requirements” for safety database, including search capability and other tools

17

Safety Information Working Group: Summary of Activities (II)

- Compiled initial list of leachables and extractables for inclusion in safety database
  - Approximately 210 compounds
    - Will grow over time and based on member company needs
  - Facilitates priority-setting
  - Continuously updated with new compounds of interest
- Created prototype database meeting user requirements
- Developed protocols for data entry, updating and quality control under development

18

Populating the Safety Database
1st Phase: Publicly Available Information

For example:

- Peer-reviewed journal studies
- Government reports
- Industry reports (where available)
- MSDS (where available, and relevant)

19

Populating the Safety Database
2nd Phase: Proprietary Information

- Promote sharing of member company safety study information when:
  - There are specific gaps in publicly available information
  - Members agree on need for that specific information
- Possibility for joint prospective safety studies to be conducted
- Issues of confidentiality will be carefully managed

20

Update on Recent Progress

- Members identified priority compounds (from the list of ~210)
- Consortium engaged: (i) dedicated toxicologists to compile safety information and (ii) developer to transition prototype database into secure, web-based system meeting identified user requirements
- Operational Safety Information Database will be launched soon with approximately 40 compounds
- Goal is 100-150 compounds in database by end 2011 and by 2012 fully populated with initial 200+

21

Example Compounds in Database

Irgafos 168 phosphate
Tinuvin 326
Erucamide
Oleamide
Irganox 1310
Tinuvin 320
Irgafos PEPQ
Dibenzylamine
Millad 3905
2,2'-Methylene-bis(6-*tert*-butyl-4 methylphenol)
Irgafos 168
Stearic Acid
2-ethyl-1hexanol
2-4-di-t-butyl phenol
Irganox 1010
Irganox 245
Irganox 1076

Calcium Stearate
Irganox 1330
Dioctyl sodium sulfosuccinate
MBT
o-toluenesulfonamide
Dehydroabietic acid
Diisodecylphthalate
Butanal
Butylated hydroxytoluene
DEHP
Bis-phenol A
Palmitic acid
Benzophenone
Oleic acid
Caprolactam
T-butanol
Dibutyl phthalate

22

Demonstration of ELSIE Safety Information Database

23

Next Steps

- Continue to populate the database (both safety and materials information)
- Publish key outcomes and information
- Provide progress updates to international regulatory bodies

24

Questions?

ELSIE
Extractables and Leachables Safety Information Exchange

25

For More Information, please contact ELSIE SECRETARIAT

Maureen Donahue Hardwick
- Maureen.hardwick@dbr.com

Lee Nagao
- Lee.nagao@dbr.com

26

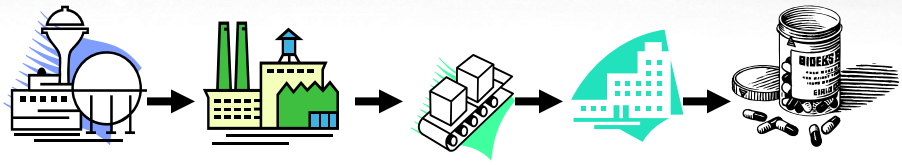
BACK UP RESOURCE SLIDES

27

Figure 2

Plastics – A Complex & Competitive Industry

N-4	N-3	N-2	N-1	(N) End user
Monomer Synthesis	Polymer Manufacturing	Masterbatcher	Molding Shop (Converter)	Packaging Containers/ Device Components



Bulk Chemicals
Storage Stabilizers

Catalysis
Stabilizers
Antioxidants
Processing aids
Others

Stabilizers
Antioxidants
Processing aids
Antistatic
Others

Lubricants
Colorants

Trade Secret Protected

28

Benefits – Safety Information

- Safety information needed for toxicology assessment for a given chemical compound is located in one place—
  - Eliminates hours/days of searching, reviewing and assessing toxicological data
  - Based on knowledge and experience of Consortium members ("peer-reviewed")
- ELSIE is now considering creation of an appropriate forum for sharing more proprietary tox data and possible joint tox testing by the Consortium
  - Could significantly further reduce costs and minimize unnecessary safety studies

29

Benefits – Materials Information

Materials information is readily available

- Significantly reduces cost and time for performing controlled extraction studies
- Allows streamlined and knowledge-based selection of materials for a specific application

30

Additional Benefits

- Reduces duplicative testing across companies
- Minimizes delays in product development due to late-stage "surprises"
- Implements approach to building quality into products
- Provides forum for exchange of experience and perspectives among experts—an opportunity to be on the front edge of new developments in the industry
  - Allows individual members to "play bigger than their size"
- Promotes opportunities for positive and constructive interactions with regulators and suppliers

31

The Database is Not…

- A replacement for risk assessments or safety qualification
  - Users must perform their own risk assessments and safety qualifications based on their product (information in database will be a valuable tool for assessment)
- A replacement for conducting leachables testing
- An "approvable" entity
  - Information from the database can be incorporated into a submission, which would then be reviewed/approved
- Specific for any one type of product

32

Materials Information Working Group Database and Pilot Program

- Materials information database will include
  - Extractables profiles generated from raw materials and materials processed/molded at extremes of recommended time/temperature
  - Protocol(s) used to generate profiles
- Materials information database is linked to the safety information database
- Conducting Pilot Program with 11 CROs
  - Determine feasibility of generating useful data
  - Develop controlled extraction study protocol to serve as basis for a standard protocol that could be used on a variety of materials to generate data for database

33

Materials Information Working Group: Protocol for Pilot Program

- *Controlled Extraction Studies on Materials for ELSIE Database – Qualitative and Semi-Quantitative Studies*
  - Conducted molding studies on 2 materials for pilot program: PVC and polyethylene
  - Studies to be conducted on the molded and unmolded forms
  - Covers studies for all common product types (e.g., parenterals, inhalation products, ophthalmics), therefore includes wide variety of solvents, and extraction and analytical techniques
  - Follows principals set forth in PQRI L&E Recommendations for OINDP
  - General principals and findings from the Pilot will be used to create a more focused protocol

34

Protocol: Solvents

- Range of solvents to address a wide variety of end uses (organic solvents of varying polarity, water of varying pH)
  - Water at pH 2.5
  - Water at pH 9.5
  - Water
  - IPA:water (1:1)
  - IPA
  - Dichloromethane
  - Iso-hexane

35

Protocol: Extraction Methods

Sonication
Reflux
Soxhlet
Sealed container
Microwave
ASE
Headspace

Results from pilot program will be used to select appropriate extraction methods for final protocol

36

Protocol: Analytical Methods

Headspace GC/MS (volatiles)

GC/FID/MS (semi-volatiles)

LC/DAD/MS (non-volatiles)

ICP/MS (metal ions)

37

Materials Information Working Group:
Current Priority Activities

- Working with CROs to complete controlled extraction studies (pilot program)
- Engaging suppliers to determine interest and develop relationships

38