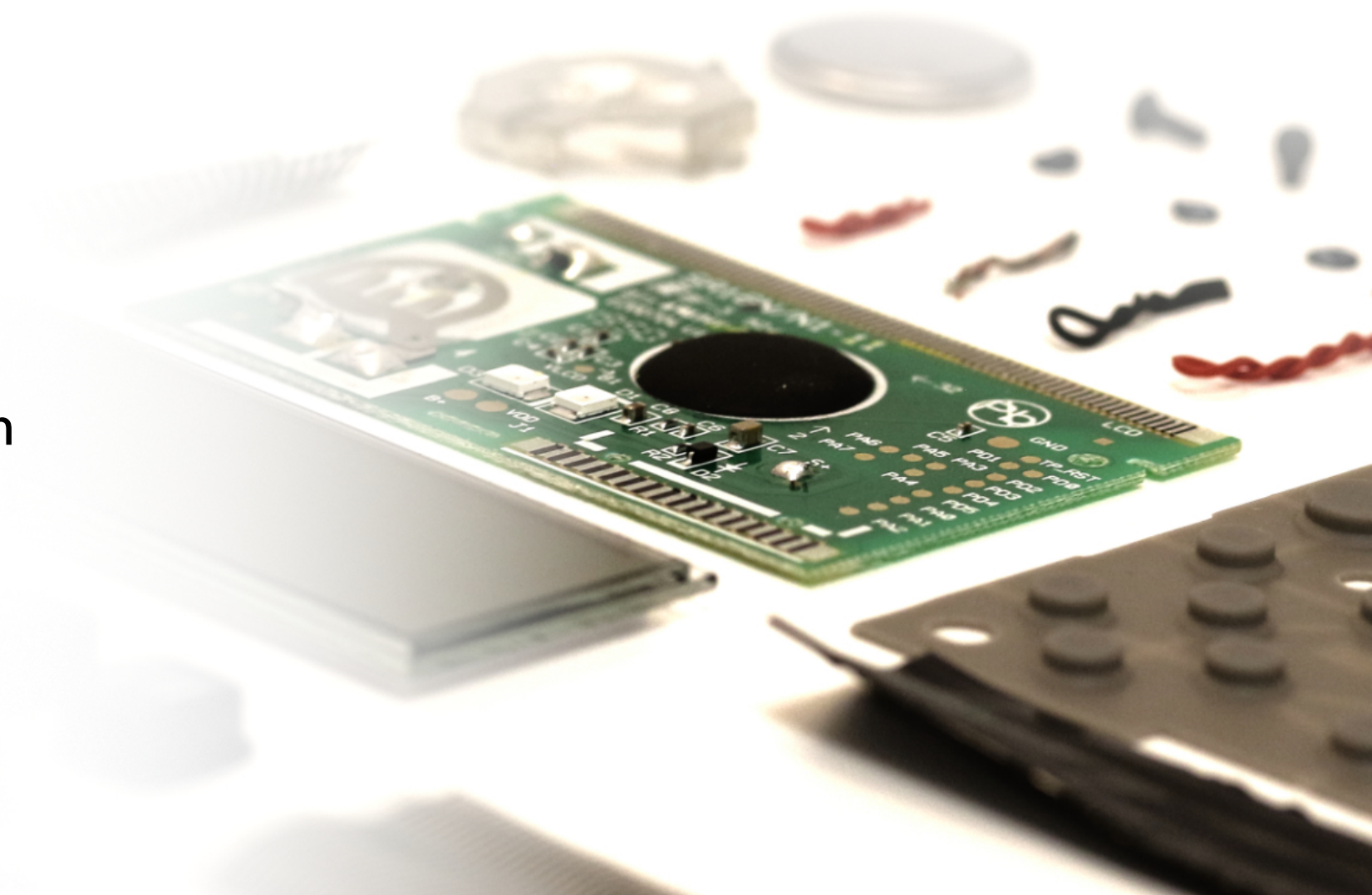


Claigan Webinar EU MDR Sensitizers

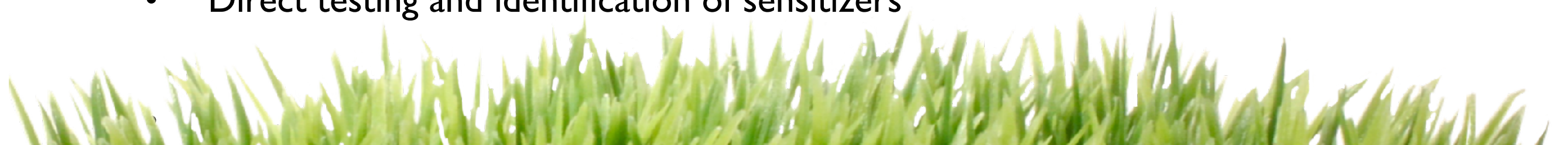
Presented by:
Bruce Calder
VP Consulting Services at Claigan

October 12 2022



Overview - Agenda

- What is a sensitizer?
- EU MDR
 - Sensitizers
 - Warnings
- ISO 10993-10
 - Priority of options
- Animal testing
 - Pros and cons
- Claigan approach
 - Direct testing and identification of sensitizers



EU MDR

Sensitizers / Allergens

- **What is a sensitizer?**
 - Primarily, they are allergens that cause reactions to
 - Skin, or
 - Airway
 - However, virtually all airway sensitizers are also skin sensitizers
- Specific definition
 - (a) there is evidence in humans that the substance can lead to sensitization by skin contact in a substantial number of persons or
 - (b) there are positive results from an appropriate animal test.

EU Skin Sensitizer Classification

- In Annex VI of CLP (like CMRs)

Index No	International Chemical Identification	EC No	CAS No	Iso	Ni, Co, Be, CrO4	Has Skin sens	Risk	Comment	Classification	
004-001-00-7	beryllium	231-150-7	7440-41-7		Be	x	High	BeCu in electronics	Carc. 1B Acute Tox. 2 * Acute Tox. 3 * STOT SE 3 STOT RE 1 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1	H350i H330 H301 H335 H372 ** H315 H319 H317
004-002-00-2	beryllium compounds with the exception of aluminium beryllium silicates, and with those specified elsewhere in this Annex				Be	x	High	BeCu in electronics	Carc. 1B Acute Tox. 2 * Acute Tox. 3 * STOT SE 3 STOT RE 1 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1 Aquatic Chronic 2	H350i H330 H301 H335 H372 ** H315 H319 H317 H411
004-003-00-8	beryllium oxide	215-133-1	1304-56-0		Be	x	High	Ceramics	Carc. 1B	H350i

EU MDR

Skin Sensitizers

- **Cat I Sensitizers in the EU**
 - 1088 classified sensitizers requiring warnings in EU medical devices
 - 194 are potentially in medical devices



Isocyanate



Epoxy resin

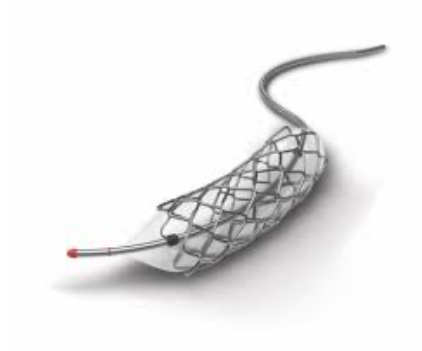
Common Allergens in Medical Devices



Monomers in
Acrylics
Polycarbonate
ABS

Allergen metals

Ni
Be
Co
Pd
Cr6+



Colourants
Textiles



Polymerization agents

Accelerators
Initiators
UV curing agents



Polymer additives

Antioxidants
Plasticizers (related to TOTM or phthalates)

Epoxies
Monomers
Hardeners

Medical Device Materials with Sensitizer Risk

- **Common medical device materials with allergens**
 - Epoxy
 - Stainless steel
 - Nitinol
 - Polycarbonate
 - Polyurethane
 - PVC
 - ABS
 - Acrylics (such as PMMA and adhesives)
 - Nitrile rubber
 - SBR rubber
 - Fabric dyes
 - Fibreglass
 - Hydrogel
 - Polyester powder coating
 - Copper beryllium alloys

Allergen of the Year - 2020

Isobornyl Acrylate

CONTACT DERMATITIS

Isobornyl Acrylate and Diabetic Devices Steal the Show for the 2020 American Contact Dermatitis Society Allergen of the Year

Cutis. 2020 June;105(06):283-285 | 10.12788/cutis.0014

By [Neel Nath, MD](#); [Margo Reeder, MD](#); [Amber Reck Atwater, MD](#)

GLUCOSE MONITORS: NOT AS SWEET AS THEY SEEM

Dermatology World Insights and Inquiries

By Christen M. Mowad, MD

Oct. 9, 2019

Vol. 1, No. 31



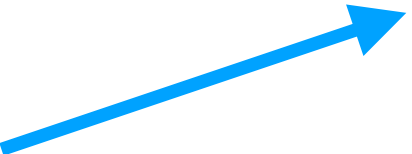
The next contact allergen of the year has been announced early by the American Contact

Dermatitis Society and it is an acrylate, isobornyl acrylate. (1) This chemical is a photopolymerizable monomer that has been used in industrial products such as UV-cured ink or adhesives. As a group, acrylates are well-

EU MDR

Section 23.4 (Allergens)

- **23.4. Information in the instructions for use**
 - The instructions for use shall contain all of the following particulars:
 -
 - (s) information that allows the user and/or patient to be informed of any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device. That information shall, where relevant, allow the user to brief the patient about any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device. The information shall cover, where appropriate:
 - ...
 - precautions related to materials incorporated into the device that contain or consist of CMR substances or endocrine-disrupting substances, or that could result in sensitisation or an allergic reaction by the patient or user;



Allergens
Claigan Testing

Example Warning

- **Warning:**
 - This device contains nickel. Persons with allergic reactions to nickel may suffer allergic reaction to this implant.
- **Warning:**
 - This device contains rubber vulcanization accelerators. Persons with sensitivity to this substance may suffer allergic reaction.
- **Warning:**
 - This device contains acrylates and UV curing agents. Persons with sensitivity to these substances may suffer allergic reaction.

EU MDR

Skin Sensitives

- **Cat I Sensitizers in the EU**
 - 1088 classified sensitizers requiring warnings in EU medical devices
 - 194 are potentially in medical devices



Isocyanate



Epoxy resin

Sensitizer Approaches

- **Order of priority for ISO 10993-10**
- **Step-wise order of options for sensitizer compliance**
 1. Literature and supplier information review.
 - Risk assessment if further testing is necessary
 2. Materials testing
 - Are allergens present?
 3. In vitro tests
 - Simulated human or animal testing
 4. Animal testing
 - Testing on animals
- **Animal testing is the last option**
 - But is commonly done....

Limitations of Data Gathering

Supplier Error

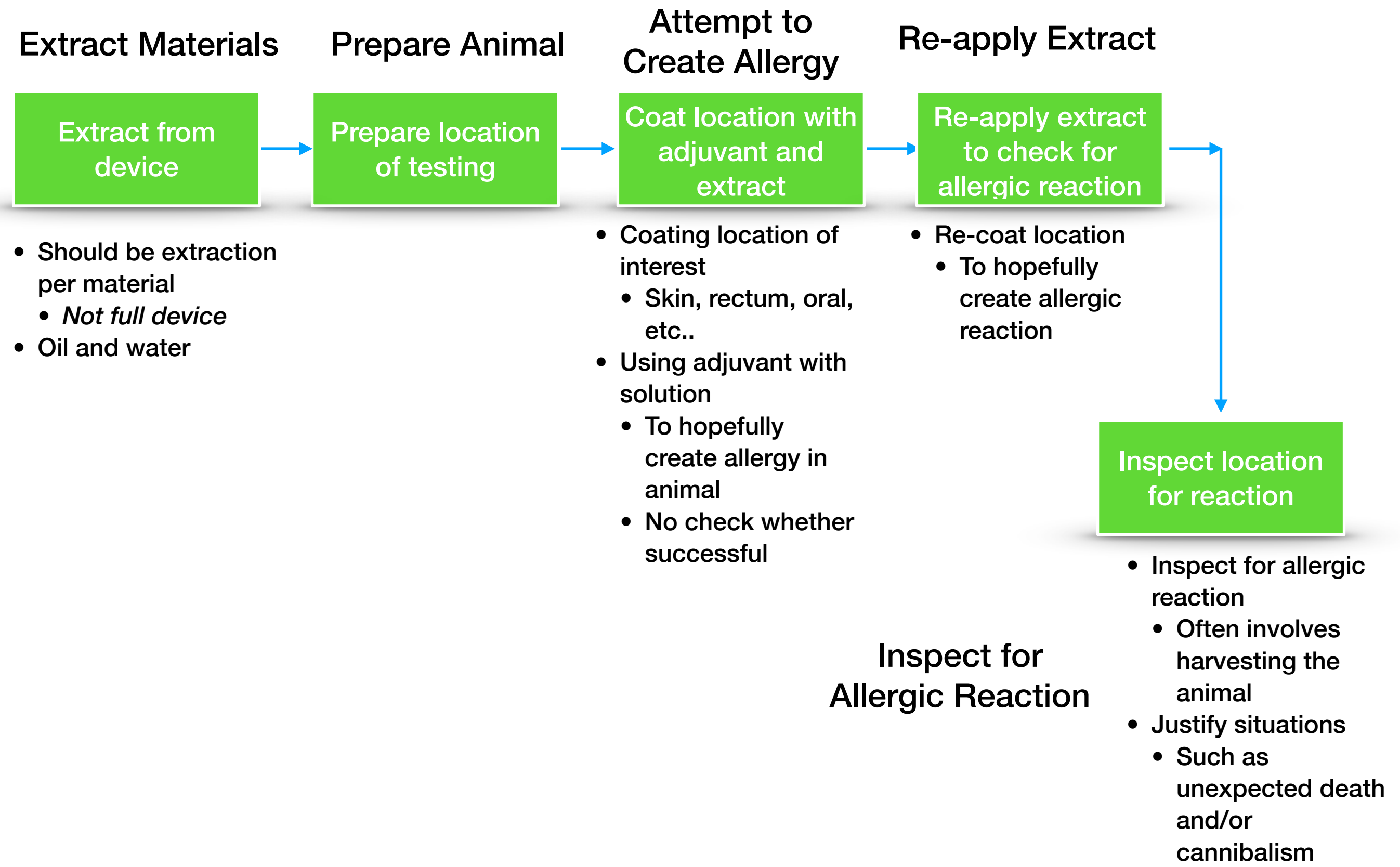
- **Supplier error / limitations**
 - **90%+** of the products we test have different results than what was reported by suppliers
 - Main reasons
 - Human error (ex. Wrong material. Wrong information. Old information)
 - Additives and monomers (ex. acrylates)
 - Contaminants (ex. Phthalates)
 - Lack of chemical knowledge, and
 - Chemical modification in the end product
- **Remember**
 - The brand owner is ultimately responsible

Limitations of Data Gathering

Supplier Error

- **Chemical modification**
 - All of the following activities change the chemical properties of your product
 - Curing
 - Coating
 - Hardening
 - Painting
 - Applying
 - Molding
 - Polymerizing or
 - Plating
 - The chemicals, allergens in particular, change during all the above
- **Remember**
 - The brand owner is ultimately responsible

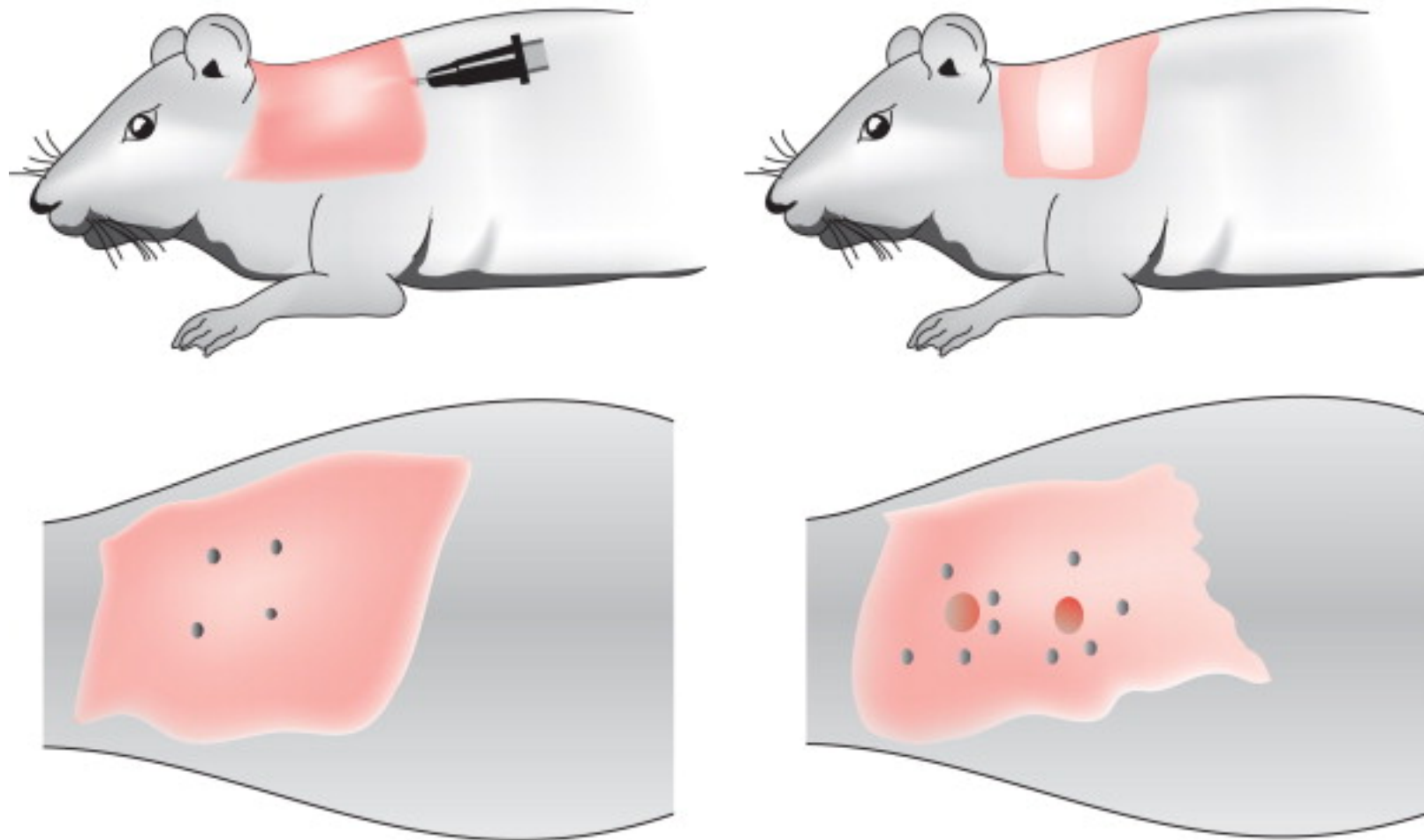
Animal Testing



Example Animal Testing

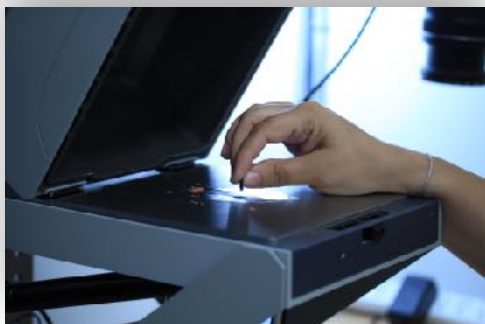
M&K maximization test

- Week 1 – Injection induction with Freund's complete adjuvant at the highest mild to moderately irritating concentration
- Week 2 – Topical induction by 48 h-occluded patch at the highest mild to moderately irritating concentration
- Week 4 – 24 h-Occluded patch challenge at the highest nonirritating test concentration
- Week 6 – Cross challenge

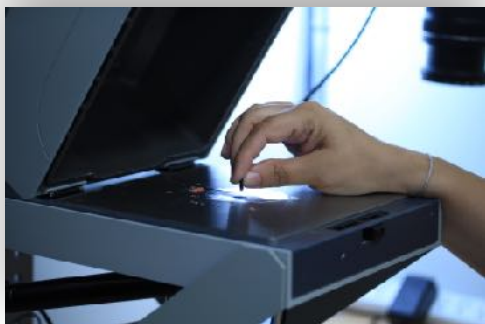
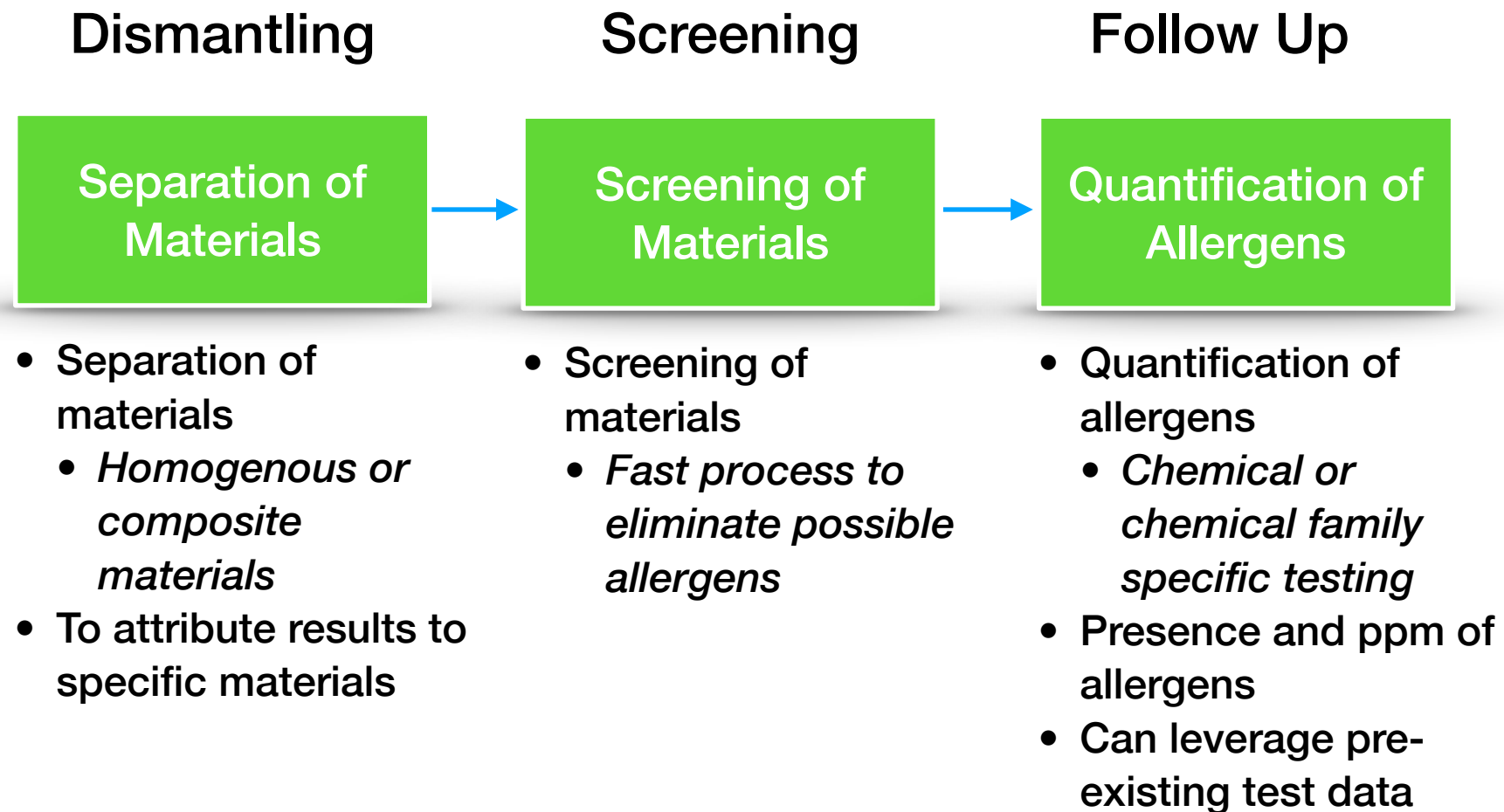


Claigan Testing

- **Extension of Claigan EU MDR CMR testing**
 - Direct testing of allergens
 - Allergen concentrations, and
 - Identification of specific materials containing allergens



Testing Options



EU MDR

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Epoxy resin

Common Allergens in Medical Devices

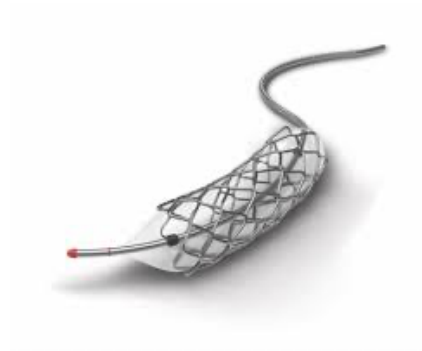


Monomers in

Acrylics
Polycarbonate
ABS

Allergen metals

Ni
Be
Co
Pd
Cr6+



Epoxies

Monomers
Hardeners



Colourants

Textiles



Polymerization agents

Accelerators
Initiators
UV curing agents



Polymer additives

Antioxidants
Plasticizers (related to TOTM or phthalates)

Claigan Sensitizer Testing Advantages

- **Advantages**

- Reduced animal testing



- Material specific data



- Re-usable data

- If allergens are present but similar levels, re-use previous animal testing

- More accurate

- Presence of allergen - not hoping the animal developed an appropriate allergy and shows a response appropriate to all patients
- Mice, rats, and rabbits are not allergic to some major human allergens (example - nickel)

Claigan Sensitizer Testing Additional Advantages

- **Additional advantages**

- Less expensive

- Leverages CMR testing

- Very significant overlap between CMRs and allergens
 - In substances and testing process



Animal Testing

- Replaces most animal testing**



B

	Edema			Erythema		
	Control	PGS	PGS/HAp	Control	PGS	PGS/HAp
day 1	0;0;0	0;0;0	0;0;0	0;0;0	0;0;0	0;0;0
day 2	0;0;0	0;0;0	0;0;0	0;0;0	0;0;0	0;0;0
day 3	0;0;0	0;0;0	0;0;0	0;0;0	0;0;0	0;0;0



D

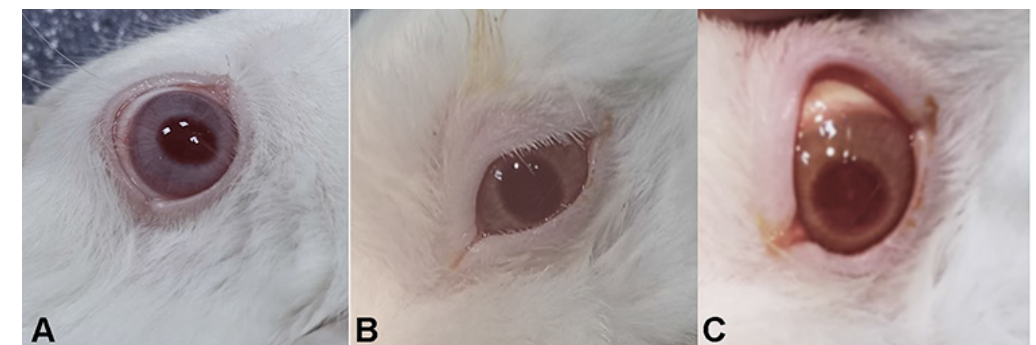
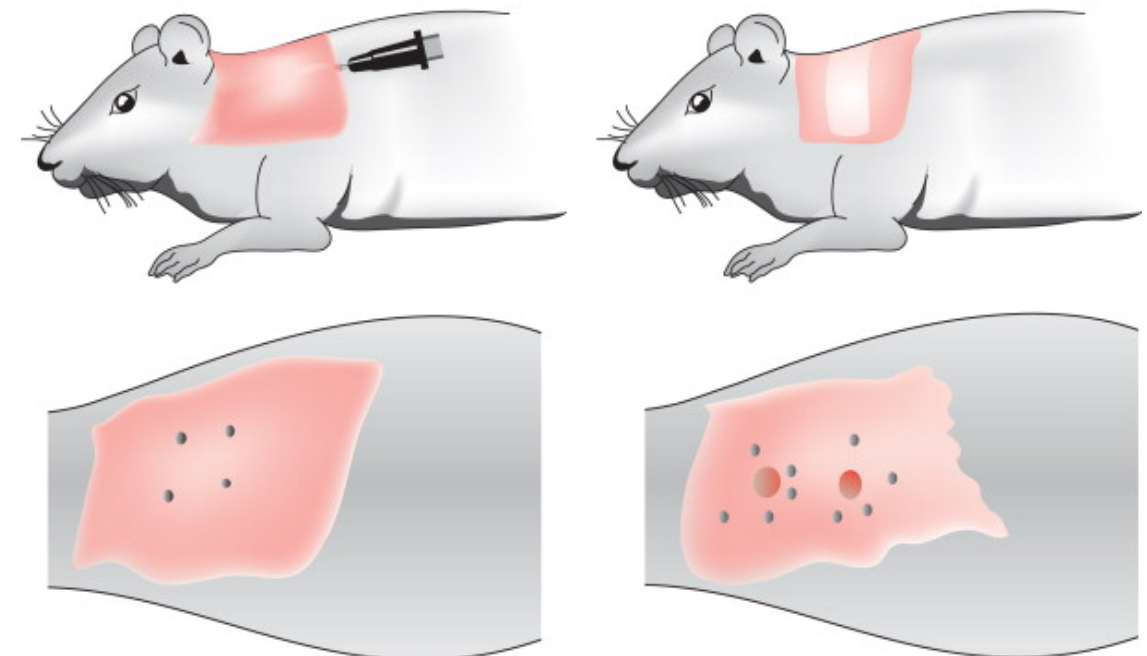
5×10^5

4×10^5

T

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Spleen

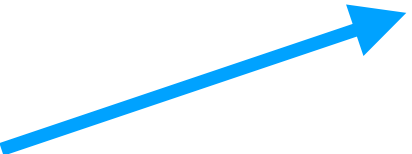
Ocular irritation

EU MDR

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Allergens
Claigan Testing



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Claigan Sensitizer Testing Advantages

- **Advantages**

- Reduced animal testing



- Material specific data

- Most animal testing is just dump the device in sesame oil

- Re-usable data

- If allergens are present but similar levels, re-use previous animal testing

- More accurate

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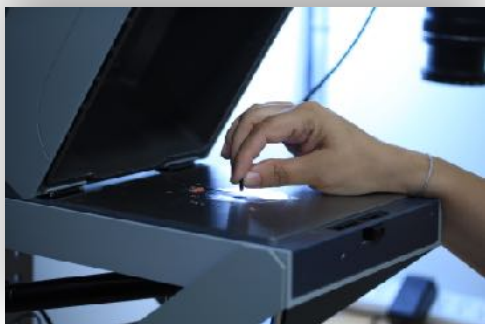
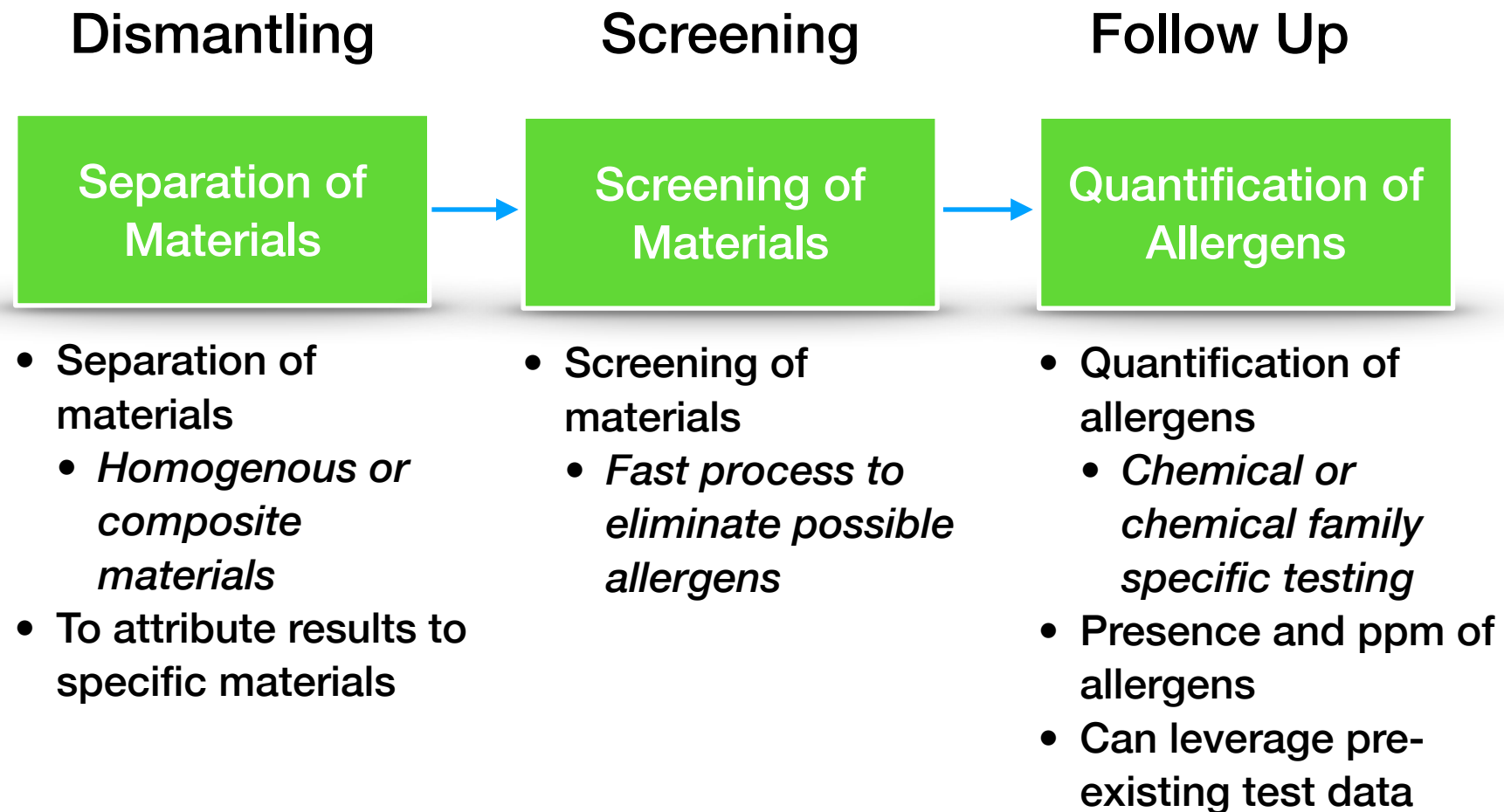
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Testing Options



Q&A

