Safety Evaluation of Food Contact Substances Containing Nanomaterials

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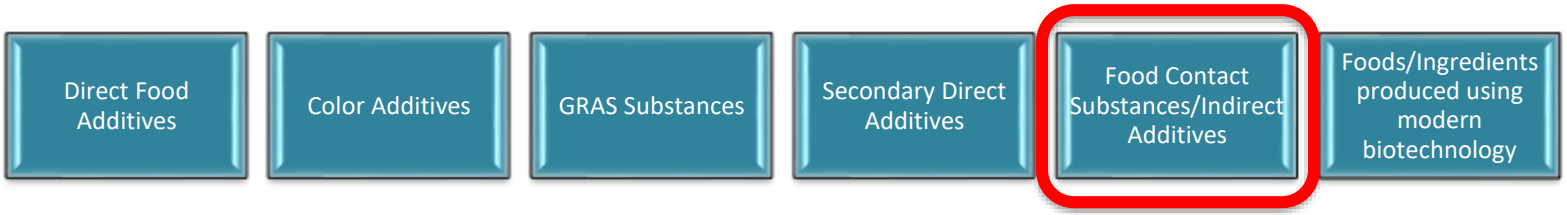
Overview

- Background about the Food Contact Notification (FCN) Program
- Evaluation of Safety: Chemistry and Toxicology
- Relevant guidance documents pertaining to FCSs containing nanomaterials
- Case study

Food Safety at U.S. FDA

- FDA Mission: Ensuring the safety of our nation's food supply
- FDA is involved in many aspects of food safety, including safety of food ingredients and food contact substances
- FDA (Office of Food Additive Safety/Center for Food Safety and Applied Nutrition) reviews the technical data and safety information for food ingredients and food contact substances



U.S. FDA Legal Authority

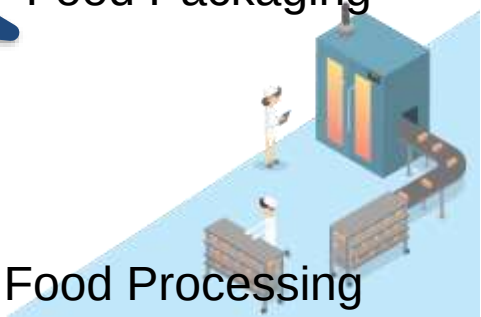
- The Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - Congress passed in 1938
- 1958 Food Additives Amendment
  - Requires pre-market approval of new uses of food additives
  - Defines a food additive
  - Established the standard of safety and the standard of review
- The Food and Drug Administration Modernization Act (FDAMA) (1997)
  - Defines a food contact substance (**FCS**)
  - Led to the food contact notification (**FCN**) program in 1999
  - Same standard of safety and standard of review as food additives

Food Contact Substance (FCS)

- "Any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food."

Antimicrobial agent	Monomer
Oxygen scavenger	Catalyst
Stabilizer	Polymer
Epoxy resin	Polymer modifier
Formulation component	Antioxidant
Colorant	Filler
Paper additive	Processing aid

Food Packaging


Food Processing

FCS Regulatory Status

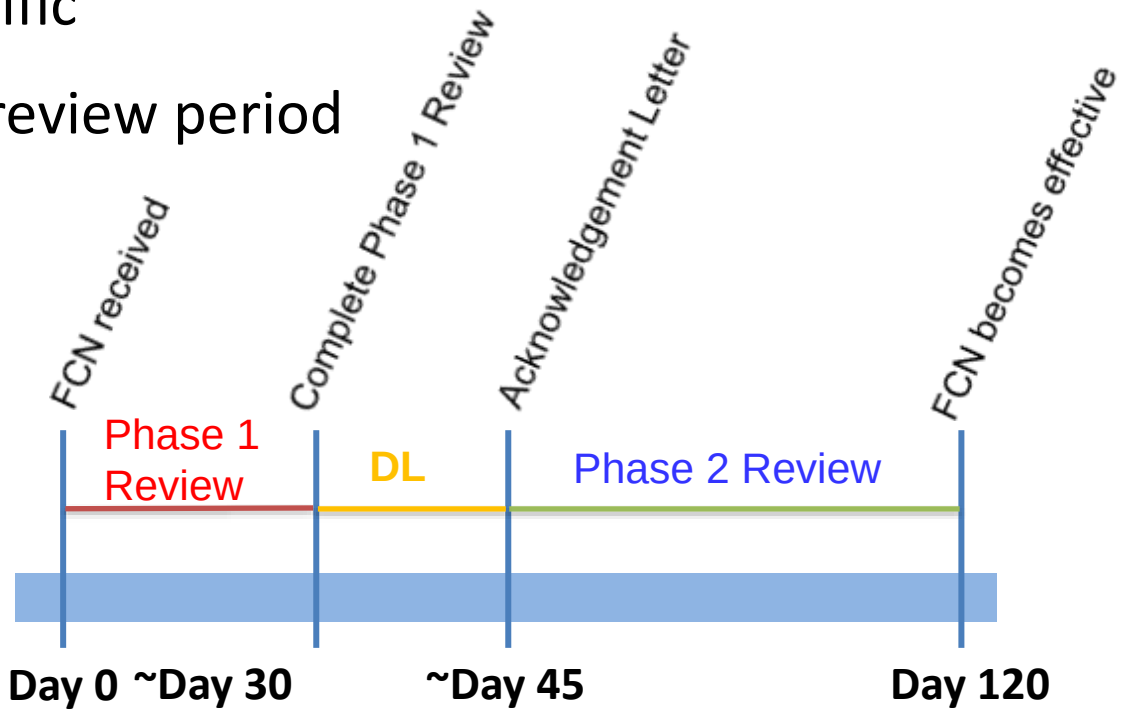
- When is an FCN needed?
  - If the FCS is not authorized for use
  - New FCS
  - Modification to an existing FCN
    - New manufacturer/supplier

    (An effective FCN is specific to a manufacturer)
    - New intended use of FCS
    - Change in manufacture
    - Change in impurity profile
    - Change in exposure estimate

Features of FCN

- Manufacturer specific
- 120-day statutory review period

FDA Review:
Typical Timeline



Standard of Safety

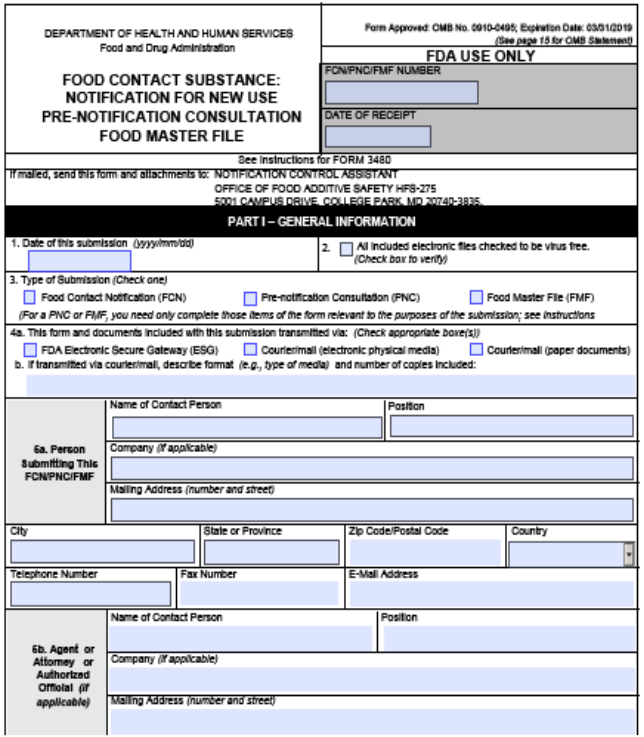
- Requires “Reasonable Certainty of No Harm”

“ a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use” (21 CFR 170.3)

- Based on Safety only (no risk/benefit analysis)
- Information necessary to demonstrate safety is dependent on exposure, determined by intended use

FCN Submission

- Form 3480 (FCN Application)
- Administrative
- Chemistry
- Toxicology
- Environmental
- Microbiology*



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FOOD CONTACT SUBSTANCE:
NOTIFICATION FOR NEW USE
PRE-NOTIFICATION CONSULTATION
FOOD MASTER FILE

Form Approved: OMB No. 0910-0495; Expiration Date: 03/31/2019
(See page 15 for OMB Statement)

FDA USE ONLY

FCN/PNC/FMF NUMBER

DATE OF RECEIPT

See instructions for FORM 3480

If mailed, send this form and attachments to: NOTIFICATION CONTROL ASSISTANT
OFFICE OF FOOD ADDITIVE SAFETY HFS-275
5001 CAMPUS DRIVE, COLLEGE PARK, MD 20740-3835

PART I – GENERAL INFORMATION

1. Date of this submission (yyyy/mm/dd)

2. ☐ All included electronic files checked to be virus free. (Check box to verify)

3. Type of Submission (Check one)
☐ Food Contact Notification (FCN) ☐ Pre-notification Consultation (PNC) ☐ Food Master File (FMF)
(For a PNC or FMF, you need only complete those items of the form relevant to the purposes of the submission; see instructions

4a. This form and documents included with this submission transmitted via: (Check appropriate box(s))
☐ FDA Electronic Secure Gateway (ESG) ☐ Courier/mail (electronic physical media) ☐ Courier/mail (paper documents)
b. If transmitted via courier/mail, describe format (e.g., type of media) and number of copies included:

6a. Person Submitting This FCN/PNC/FMF
Name of Contact Person | Position
Company (if applicable)
Mailing Address (number and street)
City | State or Province | Zip Code/Postal Code | Country
Telephone Number | Fax Number | E-Mail Address

6b. Agent or Attorney or Authorized Official (if applicable)
Name of Contact Person | Position
Company (if applicable)
Mailing Address (number and street)

FCN Chemistry Information

- Identity
- Physical/chemical specification
- Manufacturing Information
- Impurities
- Conditions of Use
- Technical Effect
- Stability
- Migration Levels in Food
- Exposure Estimates

What is the FCS?

What has the potential to migrate?

How much is migrating?

How much are we consuming?

Migration of FCS & Its Impurities

- Focused on migration into the food based on the intended use
- Report **µg FCS/ in^2 packaging**
- Calculate migration values as concentrations of the FCS in the food

  (µg FCS/ kg food)

Migration Levels in Food

- Migration levels in food may be estimated by:
  - **Migration Testing**
    - Evaluation in food
    - Evaluation in food simulant
  - **Calculation**
    - 100% Migration Assumption
    - Migration modeling

Migration Testing

- Food simulants: mimic the migration expected to a food type

Aqueous
Acidic
Low-alcohol → 10% Ethanol

- Conditions: consistent with the intended conditions of use with respect to **use level, food types, contact time, and temperatures; accelerated time temperature conditions**

Intended Use Conditions:
6 months at room temperature

Migration Test Conditions:
40°C for 10 days

Exposure Assessment

- Estimate potential **consumer exposure** to a substance including all impurities and breakdown products

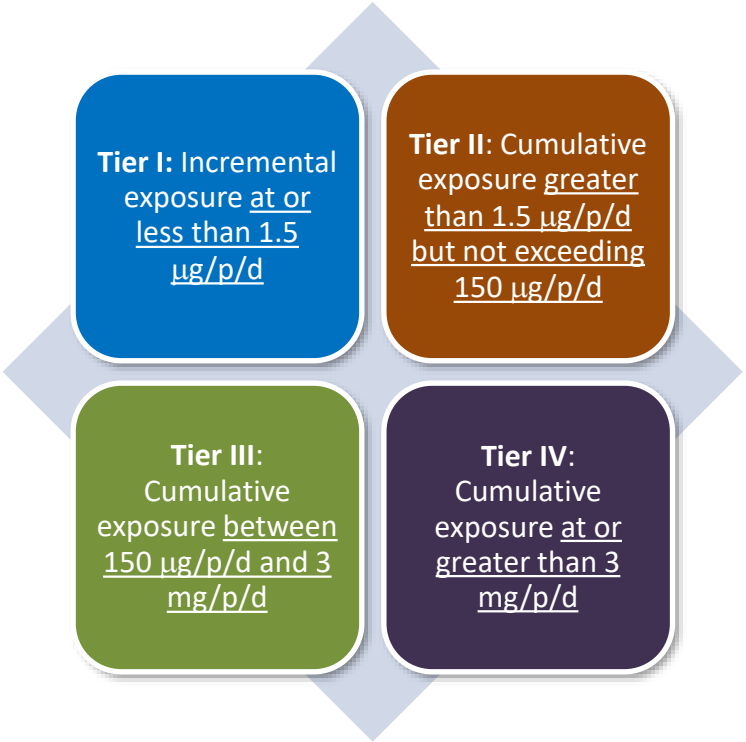
FCN Toxicology Information

Toxicology data needed for **establishing a safe level** of consumer exposure to an FCS and its constituents

- Safety Narrative (SN)
  - Describes the scientific basis of the notifier's safety determination
- Comprehensive Toxicology Profile (CTP)
  - All unpublished and published safety studies and related information relevant to the safety assessment

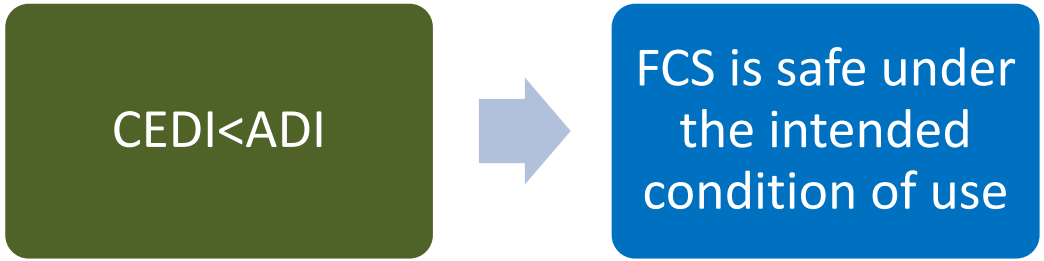
FCN Toxicology Information

- FDA has an **exposure-driven tiered** approach for safety testing

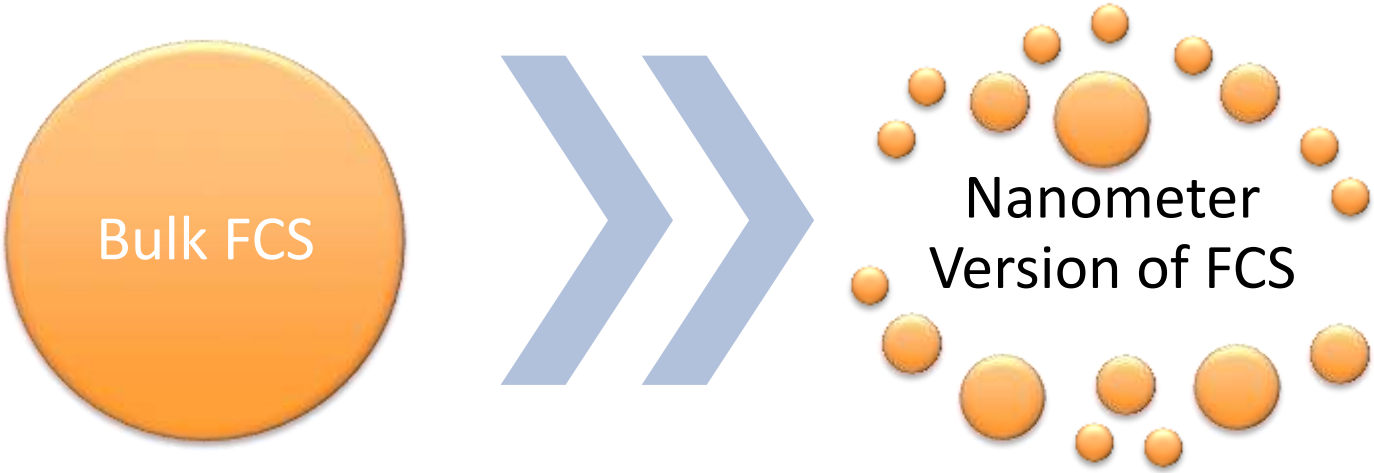


FDA's Safety Assessment

- Based on evaluating consumer exposure to a FCS and ensuring that probable dietary exposures are supported by the available toxicological information
- Consumer exposure (Cumulative EDI or CEDI) compared to Acceptable Daily Intake (ADI)



Considerations for Nanotech Products



Considerations for Nanotech Products

1. **Whether a material or end product is engineered to have at least one external dimension, or have an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm)**
2. **Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)**

Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (Finalized in June 2014)

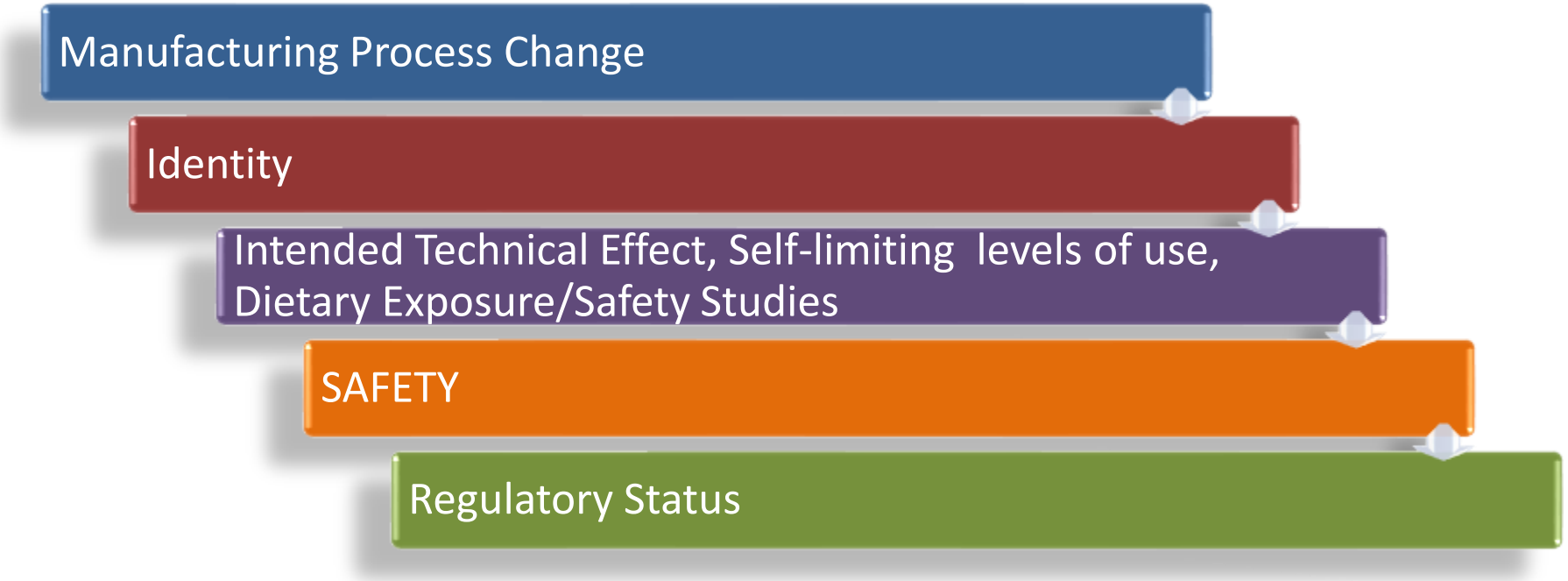
Significant Manufacturing Changes

- "Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives" (Finalized in June 2014)
- Manufacturing process for a food substance may evolve over time
- Some changes in the manufacturing process may be considered significant
- Considerations and recommendations for assessing the impact of a significant manufacturing process change on the safety and regulatory status of a food substance

Significant Manufacturing Changes

- What is a significant manufacturing process change?
  - A change in one or more starting materials
  - A change in the concentration of starting materials
  - A change in catalyst
  - A change in the source of microorganism (including a change in strain) used for a food substance derived from fermentation of a microorganisms; and
  - A change in food manufacturing or ingredient technology, such as the use of emerging technology that affects the particle size distribution of a food substance

Significant Manufacturing Changes



Nanotech and Manufacturing Changes

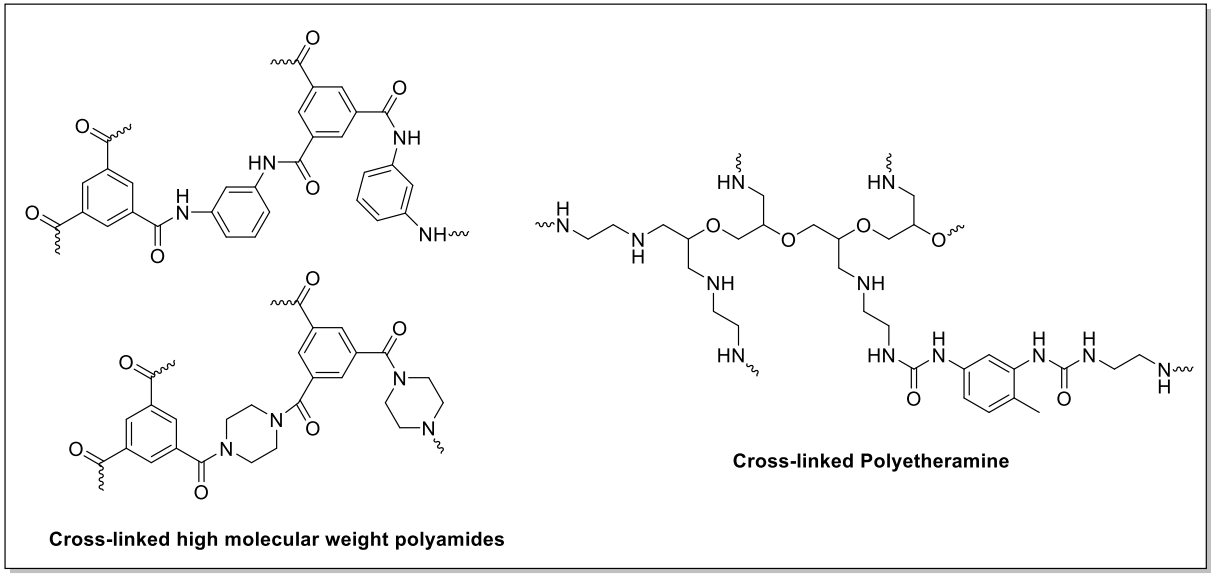
- FDA does not categorically judge all products containing nanomaterials as intrinsically benign or harmful
- Consider characteristics of the final product and safety of its intended use
- When an FCS is manufactured to include nanoparticles, safety assessments should be based on **data relevant to nanometer version of the FCS**
- If the nano-engineered FCS has new physico-chemical properties, **additional or alternative testing methods may be necessary to determine safety of the FCS**

Recommendations

1) Determine changes made to the identity of the food substance as a result of change in manufacturing process
2) Conduct a safety assessment for the use of food substance
3) Depending on the type of food substance, consider the impact of significant manufacturing change to the regulatory status of the food substance
4) Consult with us
5) If warranted, make an appropriate submission

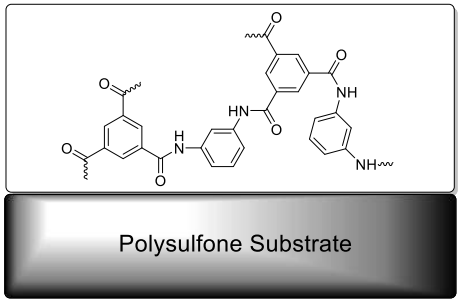
Case Study: Reverse Osmosis Membrane

- 21 Code of Federal Regulations (CFR) 177.2550; Reverse osmosis (RO) membranes.

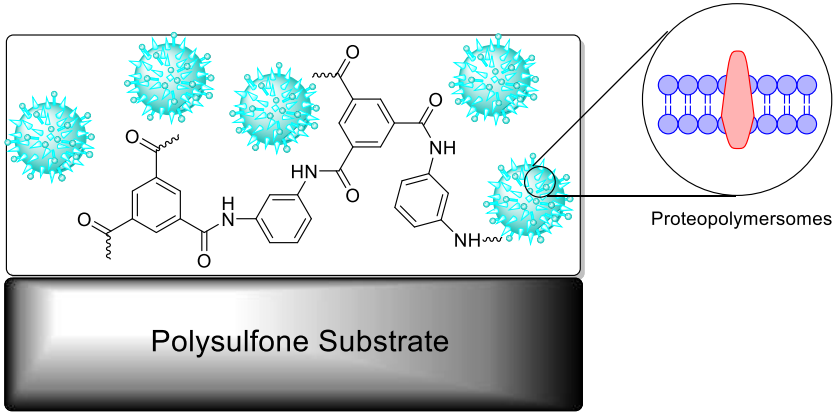


Case Study

- Typical RO membrane

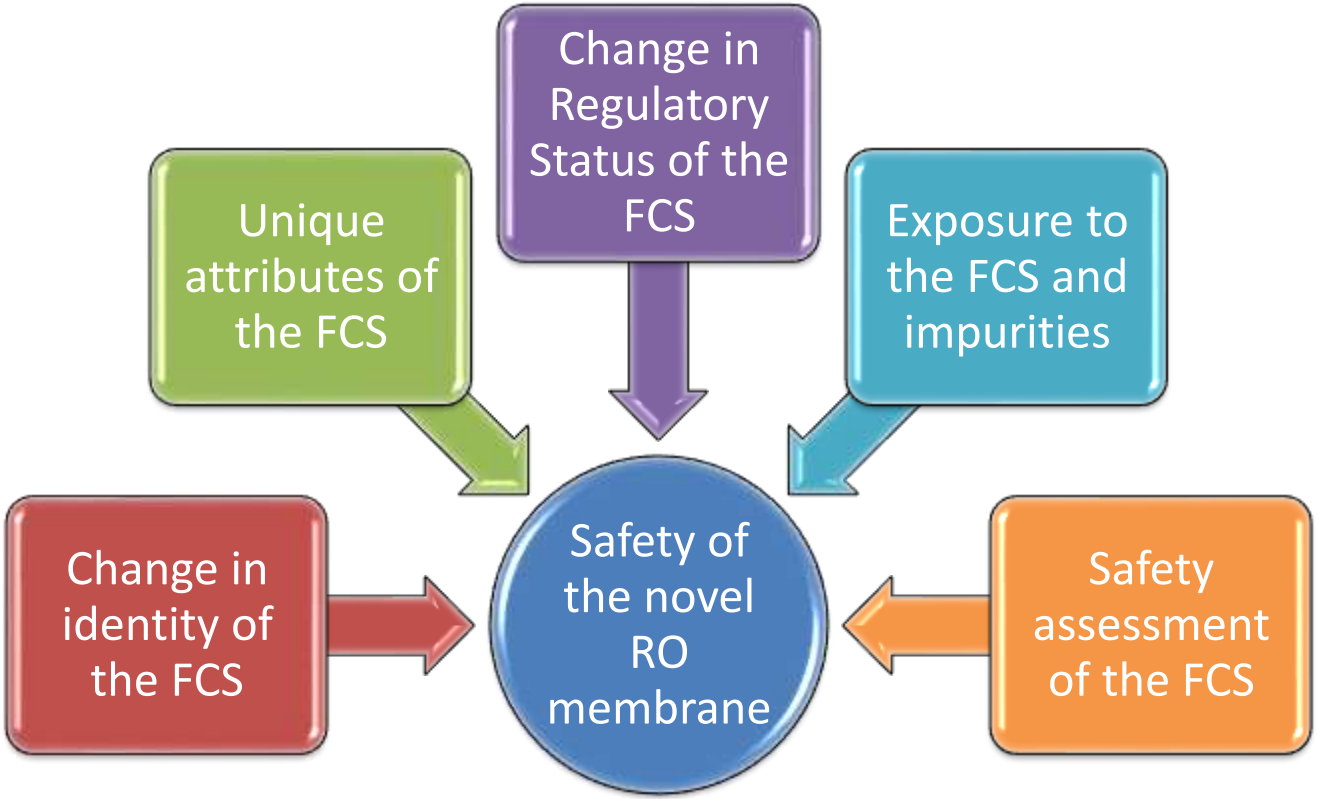


- RO membrane involving nanotechnology



Zhao, Y. et al. "Synthesis of robust and high-performance aquaporin-based biomimetic membranes by interfacial polymerization-membrane preparation and RO performance characterization" *J. Membrane Sci*. **2012**, 423-424: 422-428.

Case Study


Change in Regulatory Status of the FCS
Unique attributes of the FCS
Exposure to the FCS and impurities
Change in identity of the FCS
Safety of the novel RO membrane
Safety assessment of the FCS

Summary

- The FCN program is a pre-market authorization process by which FDA regulates FCSs (including FCSs containing nanomaterials)
- Safety assessment of the FCS involves information on the consumer exposure and toxicological data
- FDA's consideration for products containing nanomaterials involve certain dimensions and properties
- "Significant manufacturing changes" guidance document addresses changes in size distribution of the food contact substance, particularly those in the nanoscale range
- Safety assessment of an FCS containing nanomaterial involves not only evaluating changes in identity and regulatory status, but also identifying its unique attributes

FCN Guidance Documents

- **Administrative**

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparation-food-contact-substance-notifications-administrative

- **Chemistry**

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparation-premarket-submissions-food-contact-substances-chemistry

- **Toxicology**

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparation-food-contact-substance-notifications-toxicology-recommendations

- **Environmental**

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparing-claim-categorical-exclusion-or-environmental-assessment-submission-cfsan

Questions

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