Migration and Exposure Considerations

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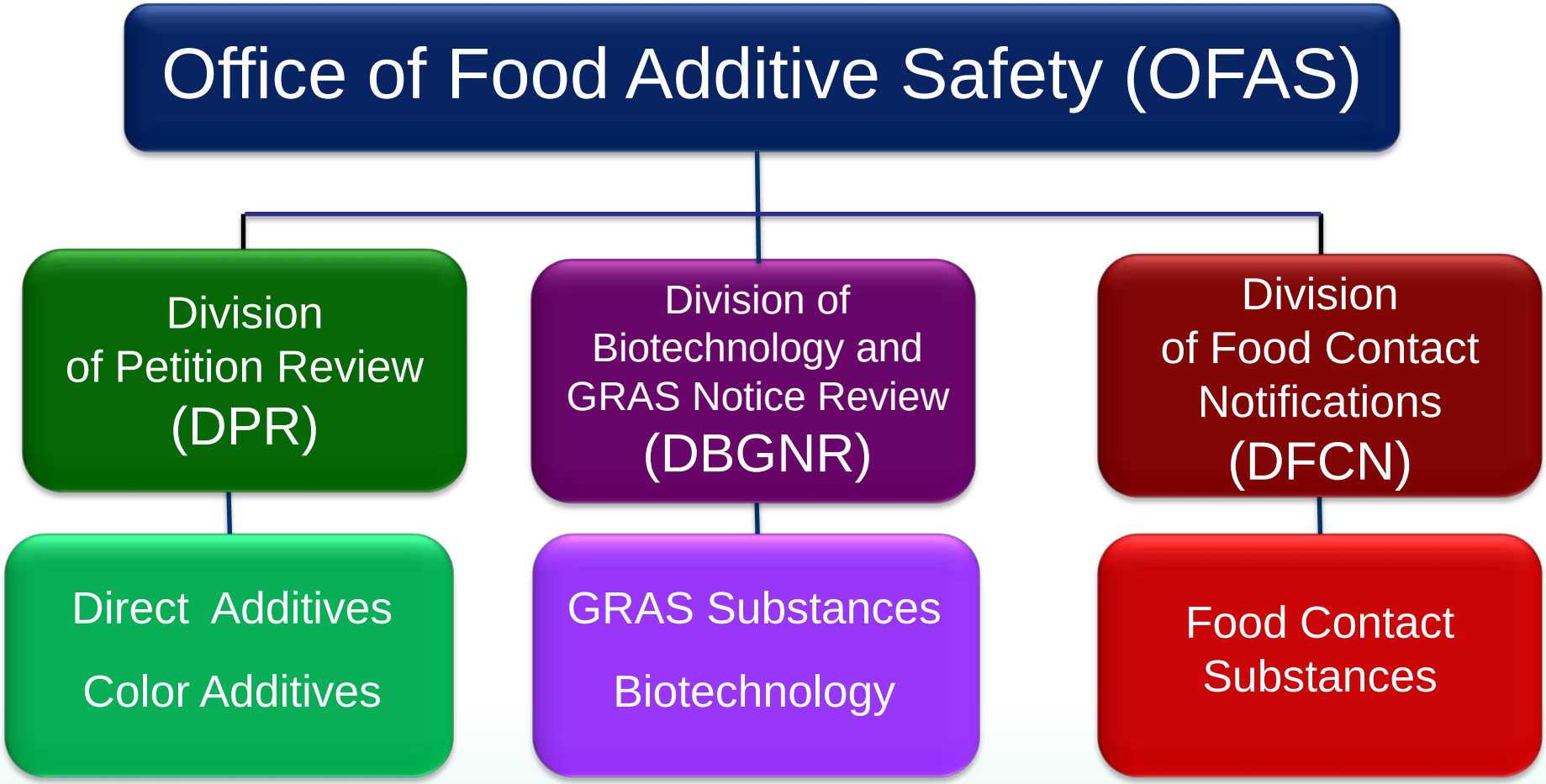

Food Additive

All substances "the intended use of which results or **may reasonably be expected** to result, directly or indirectly, in their **becoming a component of food** or otherwise affecting the characteristics of any food…"

- Defined in the Federal Food, Drug and Cosmetic Act (1958), Section 201(s)
- Require pre-market approval
  - Submission of a Food Additive Petition (FAP)
- Regulated in Title 21 of the Code of Federal Regulations (21 CFR)

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."

- Defined in 1997 Food and Drug Administration Modernization Act (FDAMA)
- Require pre-market approval
  - Submission of a Food Contact Notification (FCN)
- Effective FCNs listed on FDA Website

  https://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/Notifications/ucm116567.htm

Food Contact Materials

Food Packaging
Plastics
Metal coatings
Paper coatings
Paper additives
Adhesives

Dreamstime.com

Food Processing
Filters
Lubricants
Antimicrobial Agents
Conveyor belts

Food Contact Substances

- Food Contact Substances are components of food contact materials
- Review of discrete substances–not whole packaging

Examples of Food Contact Substances

Monomer
Catalyst
Polymer
Polymer modifier
Antioxidant
Filler
Processing aid

Antimicrobial agent
Oxygen scavenger
Stabilizer
Epoxy resin
Formulation component
Colorant
Paper additive

Food Contact Notification

- Authorizes new uses of food contact substances
- Proprietary to the manufacturer / supplier
- 120-Day statutory review period (from day of acceptance)
- Must demonstrate that the FCS is safe for the intended use

FCN Submission

- FDA Form 3480
- Relevant Information
  - Regulatory → History
  - Chemistry
  - Toxicology
  - Environmental → Impact

Chemistry, Toxicology → Safety Evaluation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

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-276
5100 PAINT BRANCH PARKWAY, 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:

5a. 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

5b. Agent or Attorney or Authorized Official (if applicable)

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

5c. Identify the Manufacturer/Supplier (s) for whom the food contact notification (FCN) will be effective:

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 compared to Acceptable Daily Intake
  Consumer Exposure: EDI < ADI
  - Estimated Daily Intake (EDI) = estimate of the amount of FCS that may be consumed daily by an individual from the intended uses
  - Acceptable Daily Intake (ADI) = estimate of the amount of a FCS that may be consumed daily over a lifetime with reasonable certainty of no harm

Toxicology Review

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

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

FCN Chemistry Information

Chemistry data is reviewed to establish the identity of a FCS and for assessing potential **consumer exposure** to the FCS.

- Identity
- Physical/chemical specification
- Manufacturing Information
- Impurities
- Conditions of Use
- Technical Effect
- Stability

What is the FCS?

What has the potential to migrate?

- Migration Levels in Food

How much is migrating?

- Exposure Estimates

How much are we consuming?

Migration Levels in Food

- An FCS is reasonably expected to become a component of food through migration

- Migration data is used by FDA to assess potential **consumer exposure** to a substance (the FCS and its impurities)

- Migration levels in food may be estimated by:
  - **Migration Testing**
  - **Calculation**
    - **100% migration assumption**
    - **Diffusion theory calculation**

Typical Migration Testing

- **Accelerated temperature/time conditions** intended to simulate thermal processing and extended storage
- Consistent with the intended conditions of use with respect to **use level, food types, and temperatures**
- Use of food **simulating solvents** rather than real foods

Exposure Estimate

- Focus on the probable exposure that will result from the intended use
- Exposure Estimates are calculated by combining migration levels with information on uses of food contact articles that contain the FCS
- Estimate probable **consumer exposure** in terms of **Estimated Daily Intake** (EDI, µg/person/day) of the substance

Standard Assumptions

- All calculations are done using highest migration levels
- 100% Market capture of FCS
- All food in the diet is in contact with food-contact articles

Estimating chronic, average lifetime exposure–same exposure, same package, same additive every day, over an entire lifetime

- Refine exposure calculations for packaging
  - Use of packaging factors

Packaging Factors

- **Food-type distribution factor (f_T)**–distribution of packaging use among food types
- Example: polymer coated metal

  $f_{(aq)} = 0.16$, $f_{(acidic)} = 0.35$, $f_{(al)} = 0.40$, $f_{(fatty)} = 0.09$

- **Consumption factor (CF)**–fraction of the daily diet expected to contact specific packaging materials
- Example: Metal (polymer coated) 0.17
  Metal (uncoated) 0.03

Packaging Factors are applied only to food packaging applications

Exposure Estimate

- **Total migration of the FCS (<M>)**

$$\langle M \rangle = F_{aq}(M_{aq}) + F_{acidic}(M_{acidic}) + F_{alcohol}(M_{alcohol}) + F_{fatty}(M_{fatty})$$

- **Estimated Daily Intake (EDI)**

EDI = <M> x CF x 3000 g food/person/day

= µg FCS/person/day

An exposure estimate is calculated for each of the possible migrants (FCS and its impurities)

Exposure Estimate: Example

- FCS is copolymer intended for use as component in can coatings
- Food types: aqueous, acidic, and fatty foods
- Maximum temperature of 121 ºC (250 ºF)
  (High temperature, heat sterilized or retorted)
- Possible migrants:
  FCS oligomers (LMWO), monomer A, monomer B, Impurity C

Exposure Estimate: Example

Migration Testing

- Test sample: Coating containing FCS
- Food simulants: 10% ethanol–aqueous and acidic foods, miglyol–fatty foods
- Test conditions: High temperature, heat sterilized or retort
  - Test sample heated 121^0 C and held for 2 hours, then 40^o C for 238 hours for a total of 10 days
  - Tests are conducted in triplicate
  - Samples taken at 2, 24, 96, and 240 hours
- Test samples analyzed for possible migrants

Exposure Estimate: Example

Migration Testing

Migrant	Migration 10% Ethanol (µg/kg)	Migration Miglyol (µg/kg)
FCS LMWO	500	600
Monomer A	50	60
Monomer B	40	80
Impurity C	< 5.0	< 5

Exposure Calculation

For FCS LMWO:

$\langle M \rangle = \Sigma Fi\,(M_i)$

$\langle M \rangle = F_{aq}\,(M_{aq}) + F_{acidic}(M_{acidic}) + F_{fatty}\,(M_{fatty})$

$\langle M \rangle = (0.16)(500\ \mu g/kg) +$
$(0.35)(500 \mu g/kg) + (0.09)(600\ \mu g/kg)$

$\langle M \rangle = 309\ \mu g/kg = 309\ ppb$

EDI = CF x <M> x (3kg/p/d)
= 0.05 (309 µg/kg) (3kg/p/d)
= 46.4 µg LMWO/p/d

Exposure Estimate: Example

Chemical	Migration 10% Ethanol (µg/kg)	Migration Miglyol (µg/kg)	<M> (µg/kg) (ppb)	EDI (µg/p/d)
FCS LMWO	500	600	309	46.5
Monomer A	50	60	31	4.7
Monomer B	40	50	27.6	4.1
Impurity C	< 5.0	< 5	<3	<0.5

Application of Packaging Factors

- Packaging Factors (CF and f_T) are applied for single-use food packaging scenarios

- Scenarios where Packaging Factors are **not** applied:
  - Repeat-use scenarios
  - Scenarios where a “direct additive” calculation might be more appropriate
    - Example: microwave popcorn bag

      EDI = <M> x g food/p/day (consumption of popcorn)
  - FCS in contact with infant formula and/or human milk

FCS in Contact With Infant Formula or Human Milk

- Examples of food-contact articles: packaged formula, baby bottles, bottle inserts
- Infant (up to 6 months)
- Migration Testing Protocols are consistent with general protocols in Chemistry Guidance depending on intended use time and temperatures
- Exposure estimates account for only one source of food: consumption-to-mass ratio of 140 g/kg bw/d

FCN – Guidance Documents

- **Administrative**

  http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081807.htm

- **Chemistry**

  http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081818.htm

- **Toxicology**

  http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081825.htm

- **Environmental**

  http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081049.htm

Thank you