The Basics of the FDA's Food Contact Notification Process

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Moderator: Seth Goldberg

- Partner in Steptoe's Washington office
- Has practiced environmental law and litigation for 36 years
- Practice encompasses a range of subspecialties, including regulatory litigation, hazardous waste and toxic chemical regulation, environmental remediation, pesticide regulation
- Represents clients on a range of chemical regulatory issues before the US EPA, OSHA, FDA, CPSC, and a number of state regulatory agencies. His chemical regulatory practice focuses on product approval, compliance advice, and enforcement matters under a range of statutes and regulatory programs
- He regularly handles hearings, trials, and appeals before trial and appellate courts and administrative agencies

Presenter: Dr. Mitchell Cheeseman

- Managing Director in Steptoe's Washington office
- Prior to Steptoe, held Leadership positions in FDA's Foods Program for over 9 years.
- As a leader in FDA's Office of Food Additive Safety, responsible for the safety review of over 100 food and color additive petitions, over 200 GRAS notices and over 1000 food contact notifications.
- Pioneered the application of structure activity analysis in FDA's safety review of food ingredients and food-contact substances

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- Associate in Steptoe's Washington office
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- Obtained premarket clearances for FDA regulated products worldwide
- Works with clients to establish regulatory status of products for which specific premarket approval may not be necessary
- Supports companies with the development of new compliance programs in response to new laws and regulations

Today's Presentation

- Overview of the Food Contact Notification Process
  - Brief statutory background
  - How the FCN system works
  - What Data is necessary for an FCN and how does FDA conduct its review
- Common Deficiencies in FCNs and How to Avoid Them
- Your Questions and Our Answers

A Brief History of the FCN Program

And in the beginning, FDA begat …

- Food Additive Regulations
  - Found at 21 C.F.R. Part 174 – 186
  - Resulted from the submission of Food Additive Petitions
  - Process could take 2-4 years (or longer)

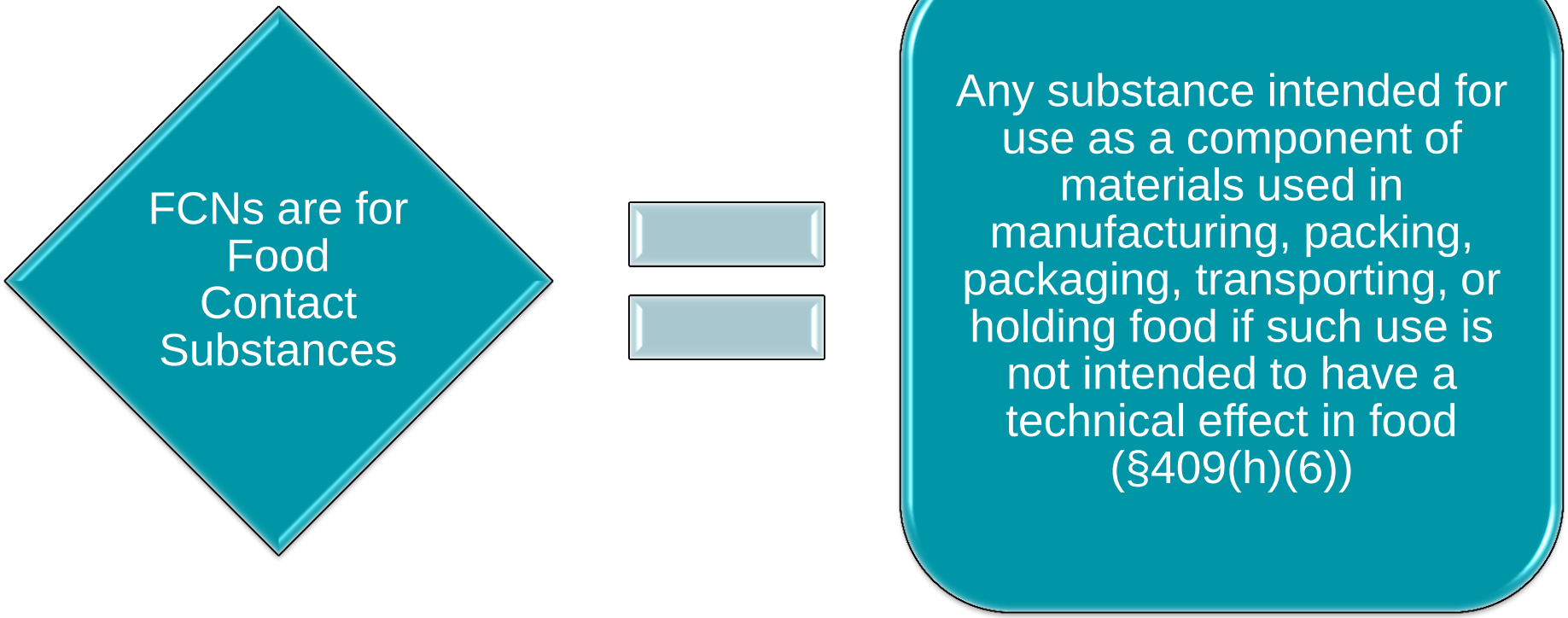
Yet fear not, for FDA overcame …

- Food Contact Notifications
  - Food and Drug Administration Modernization Act of 1997, § 409(h)
  - Program effective January 18, 2000
  - FDA regulations at: 21 C.F.R. §170.100 *et seq*.
  - 120 day review

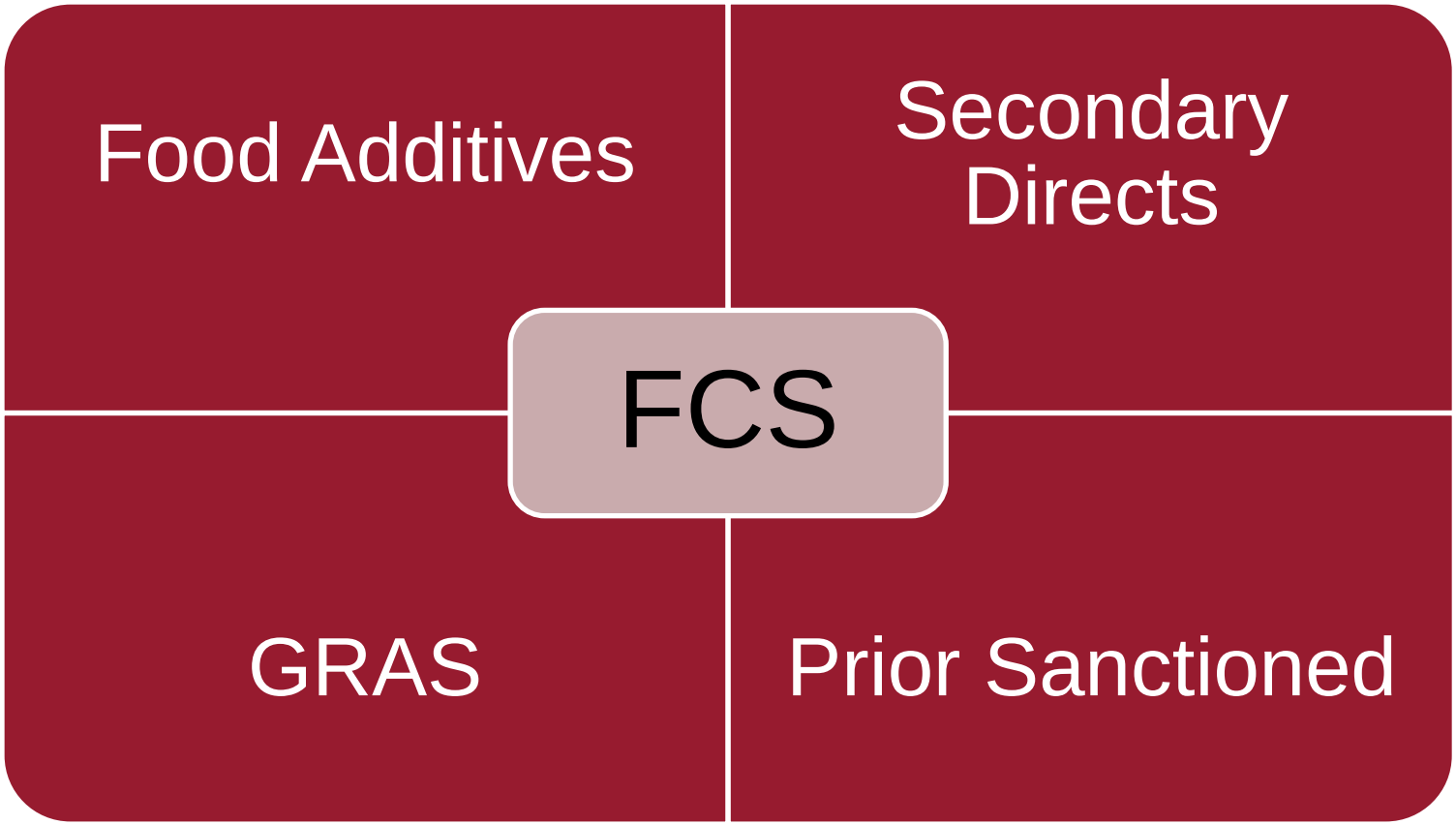
Benefits of FCNs Over FAPs

- Speed of review
  - "Self-executing" provision: FDA has 120 days to object to an FCN or it becomes effective
  - Preliminary review provided within 4-6 weeks
- Same safety standard as the petition process
- FCNs are proprietary
  - Effective only for company listed as the manufacturer in the FCN (and its customers)
  - Competitors must file their own notifications

What Can Be the Subject of an FCN?



Food Contact Substance



Subject of an FCN

Indirect additives	Polymers
	Starting substances
	Adjuvants
Secondary directs	Boiler water additives
	Ion exchange resins
Other: not “food additives”	GRAS substances
	Antimicrobials
	Substances not reasonably expected to migrate to food

Is there an ongoing technical effect in the food?

What Can't Be in an FCN?

- Direct food additives
  - FAP
- New recycling technologies
  - Not an FCS
- Formulated products consisting entirely of cleared materials
  - Form 3479
- Carcinogens
  - Barred by Delaney Clause

Who May File?

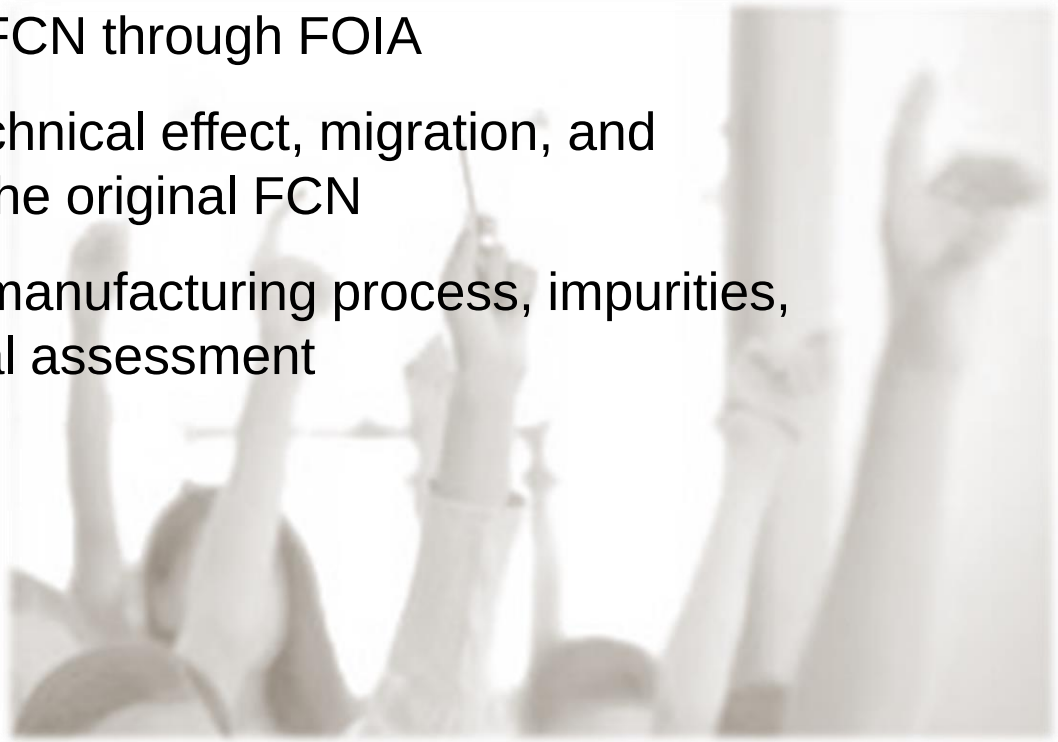
- "A manufacturer or supplier of an FCS"
  - "Supplier" – any person supplying an FCS, including "companies supplying to themselves for manufacture of a food-contact material"
  - Many FCNs are filed by companies that "supply the product to themselves" for further modification
  - A company may be the notifier but not necessarily the manufacturer of the product

When Can/Should You Submit an FCN?

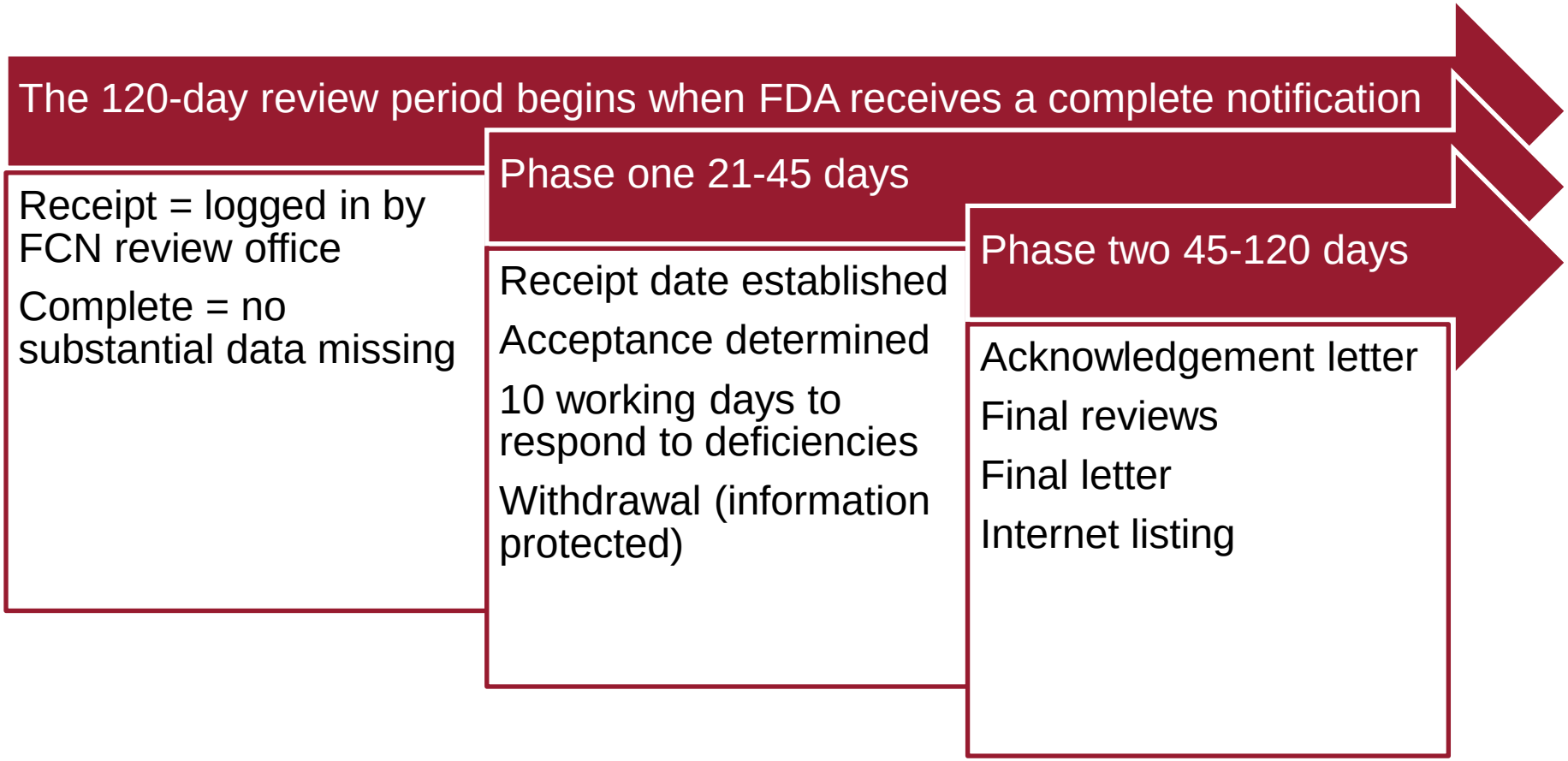
- When other methods to establish FDA status are not available
- Customer assurance
- Company preference
- FCNs are not always appropriate
  - High dietary concentration (>1 ppm)
  - Substances already regulated for the same intended use
  - Unreviewed carcinogenicity studies

Shortcut: “Me Too” FCNs

- FCNs are proprietary to the notifier, but others are not prohibited from filing an FCN for the same FCS
- A “me too” FCN often requires substantially less data
- Consider obtaining original FCN through FOIA
- May be able to utilize the technical effect, migration, and toxicology data provided in the original FCN
- Key information to provide: manufacturing process, impurities, specifications, environmental assessment



The Phases of FDA's Review



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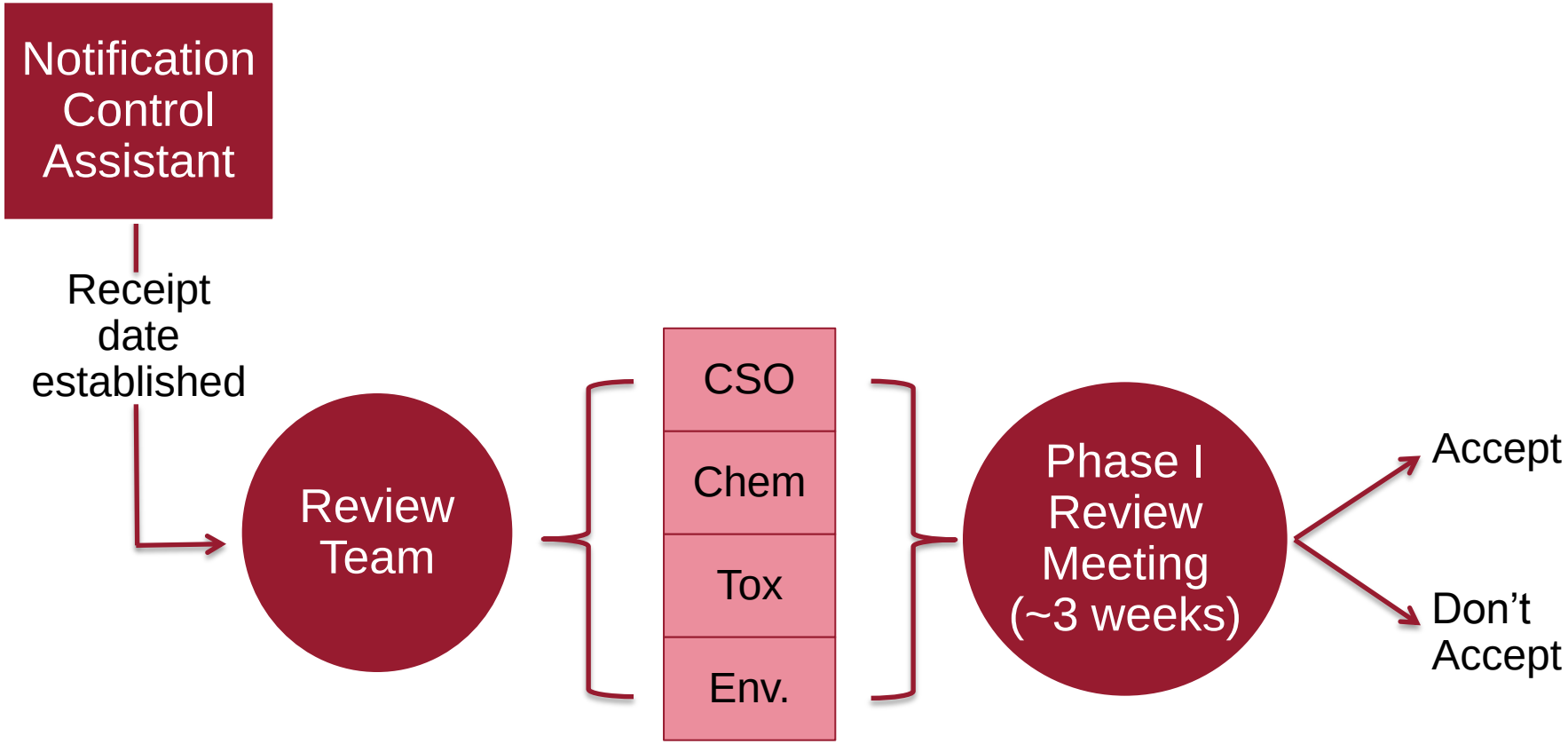
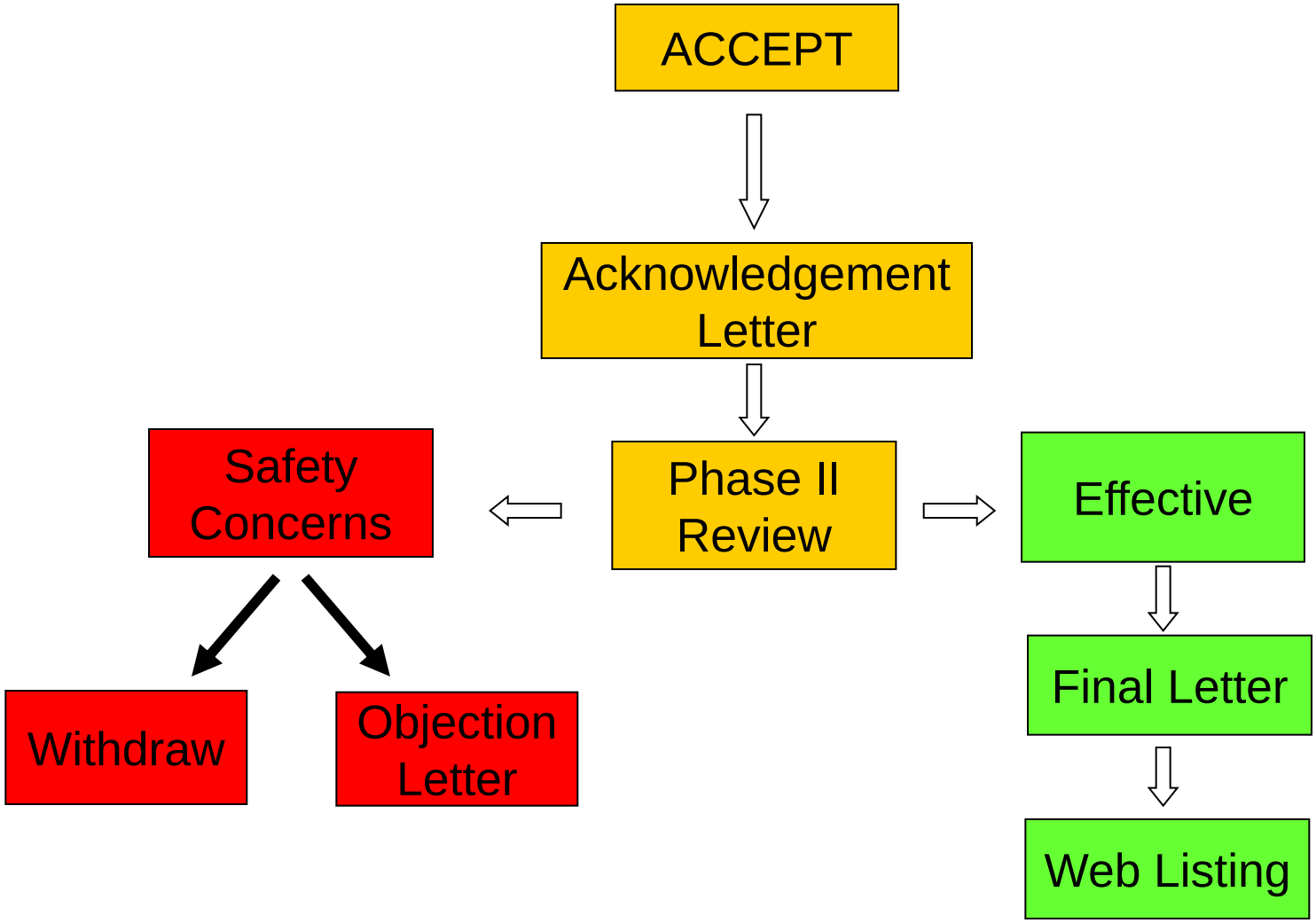
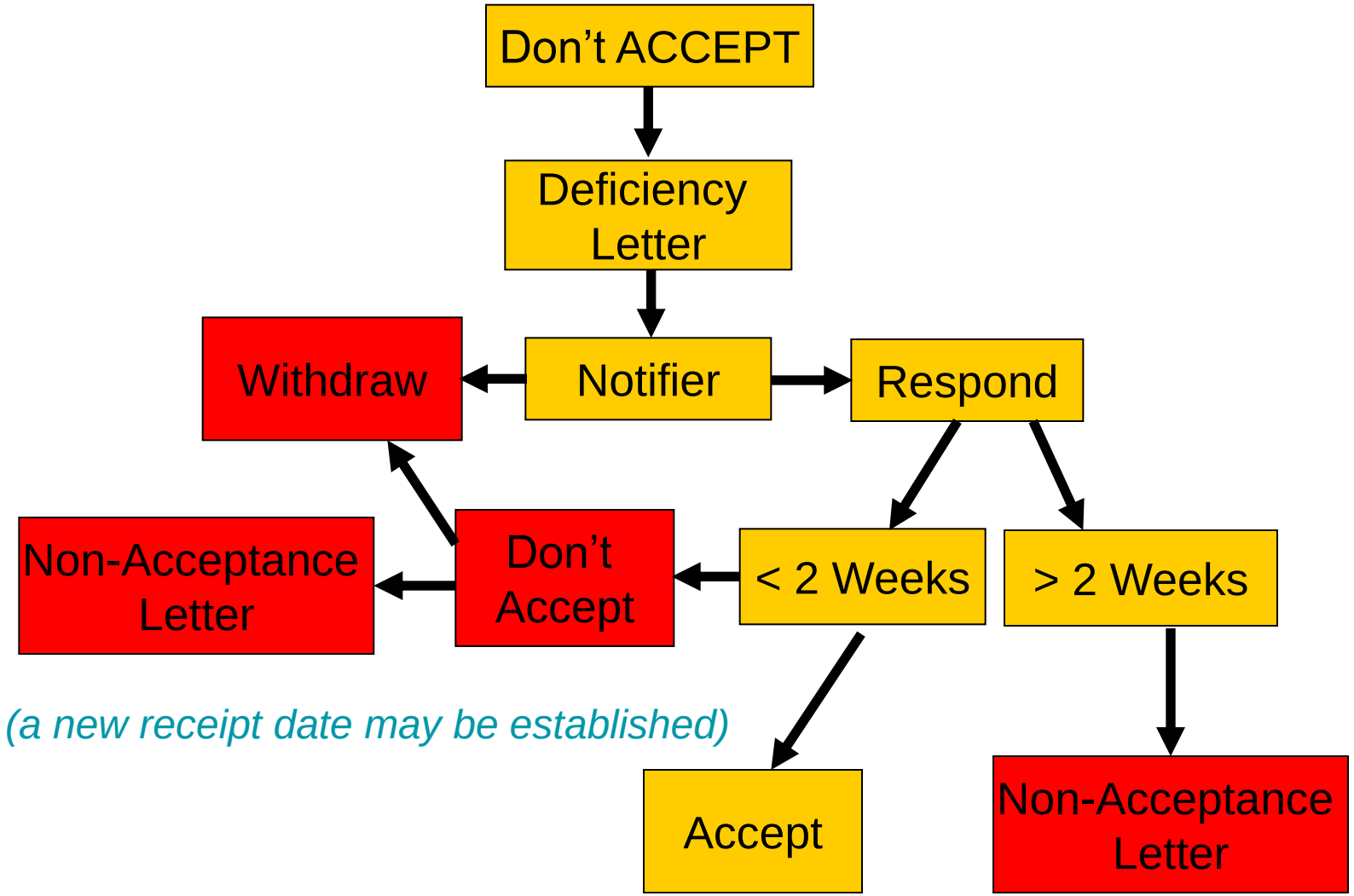
Receipt and Phase I



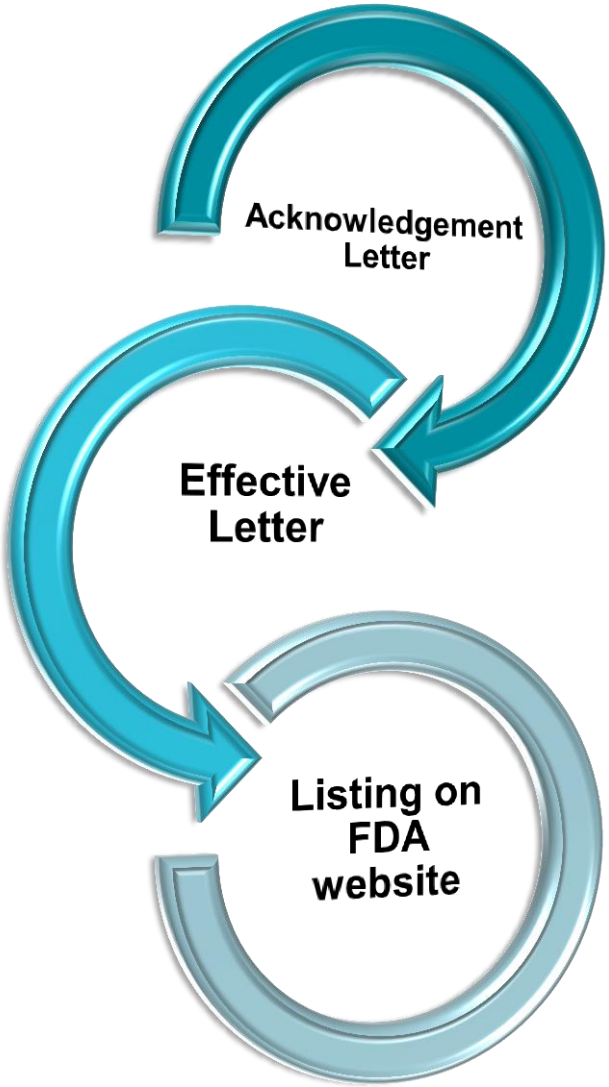
Procedure After Acceptance



The Other Case…



What Do You Get For a Successful FCN?



- Identity of the Food Contact Substance
- Name of the Notifier
- Name of the Manufacturer/Supplier
- Intended Use of the FCS
- Limitations/Specifications

The Construction And Review Of An FCN

FCN Data Requirements and Reviews

- Chemistry
- Toxicology
- Environmental Science

What's Needed for an FCN

Chemistry Information

- Chemical identity and composition of FCS
- Properties and specifications
- Manufacturing process
- Impurities and breakdown products

Intended conditions of use

- Use level
- Single/repeat use
- Food types
- Conditions of Use

Migration and Exposure

- Level of migration, as determined by calculations, modeling, or testing
- Estimation of dietary exposure, including cumulative exposure

Calculating Migration

May be able to assume 100% migration of the FCS

- Formulation information
- Analysis for concentration of residual migrant in the FCS

Migration modeling

- Fickian diffusion
- Polymer constants

Migration Testing

Repeat-Use Scenarios

- For articles intended for repeat-use, exposure over the lifetime of the material is usually calculated
- 100% migration calculations consider the service life of the article and the quantity of food processed over the same lifetime
- Should migration studies be conducted, a calculation of migration will be performed assuming equal distribution of migrants to all the food processed over the service life of the article

Consumer Exposure

Dietary Concentration (DC)

$$DC = CF \times \langle M \rangle$$

CF, the consumption factor, represents the ratio of the weight of all food contacting a specific packaging material to the weight of all food packaged

<M> is the migration into food

What Are Consumption Factors?

- Consumption factors represent the fraction of all food consumed that is packaged in a specific material

$$CF = \frac{weight\ of\ \ food\ \ contacting\ \ a\ specific\ \ packaging\ material}{weight\ of\ \ all\ \ food\ \ packaged}$$

- Based on market survey data
- Subject to change to accommodate market trends
- Can be as specific as data will allow
- Can be subdivided according to type of food or type of package

Refining Consumption Factors

From current survey data, subdivide categories when possible.

For example:

- Polymer
  - Polyolefins
    - LDPE
    - LLDPE
    - HDPE
    - PP
  - PET
- Paper
  - uncoated and clay-coated
  - polymer-coated

TABLE I - CONSUMPTION FACTORS (CF)

	Package Category	CF	Package Category	CF
A. General	Glass	0.1	Adhesives	0.14
	Metal- Polymer coated	0.17	Retort pouch	0.0004
	Metal- Uncoated	0.03	Microwave susceptor	0.001
	Paper- Polymer coated	0.2	All Polymers[a]	0.8
	Paper- Uncoated and clay-coated	0.1	Polymer	0.4
B. Polymer	Polyolefins	0.35[b]	PVC	0.1
	-LDPE	0.12	-rigid/semirigid	0.05
	-LLDPE	0.06	-plasticized	0.05
	-HDPE	0.13	PET[c,d]	0.16
	-PP	0.04	Other Polyesters	0.05
	Polystyrene	0.14	Nylon	0.02
	EVA	0.02	Acrylics, phenolics, *etc.*	0.15
	Cellophane	0.01	All Others[e]	0.05

[a]Originates from adding CFs for metal-polymer coated, paper-polymer coated, and polymer (0.17 + 0.2 + 0.4 = 0.8).
[b]Polyolefin films, 0.17 (HDPE films, 0.006; LDPE films, 0.065; LLDPE films, 0.060; and PP films, 0.037).
[c]PET-coated board, 0.013; thermoformed PET, 0.0071; PET carbonated soft drink bottles, 0.082; custom PET, 0.056; crystalline PET, 0.0023; PET films, 0.03.
[d]A CF of 0.05 is used for recycled PET applications (see the document entitled "Points to Consider for the Use of Recycled Plastics in Food Packaging: Chemistry Considerations").
[e]As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

The Alternative Consumption Factor Has Limits

- The FCS will be ***limited*** to an ***annual production volume*** at or below the maximum that has been specified
- If the market volume expands to beyond the stated production volume, a new FCN will need to be submitted to account for the increased exposure
- The market volume information will ***not*** be included in FDA's website listing of effective FCNs

Migration into Food <M>

- Based on results from migration studies and FDA food type distribution factors (f_T)
- Concentration in food:

$$<M> = (f_{aq}+f_{ac})M_{10\%\ EtOH} + (f_{al})M_{50\%\ EtOH} + (f_{fat})M_{fat}$$

(μg/kg food)

- 100% migration
- Migration modeling
  - Fickian diffusion
  - Migration database

$$DC = CF \times <M>$$

100% Migration

In some cases where the use level of the FCS is low, it may be possible to dispense with migration studies altogether by assuming 100% migration of the FCS to food

- Single-use articles require:
  formulation information or
  chemical analysis for concentration of residual migrant in the FCS

100% Migration Calculation

An example: Adjuvant Y is added at a level not to exceed 0.01 wt-% to polypropylene (PP) films (not to exceed 2 mil, or 0.002 in)

-the CF for PP is 0.04

-the density of PP is 0.9 g/cm^3

-assume 10 g of food contacts 1 in^2 of PP

Migration is calculated as follows:

$$\langle M \rangle = \frac{0.01 \text{ g Y}}{100 \text{ g PP}} \times \frac{0.9 \text{ g PP}}{\text{cm}^3} \times \frac{16.4 \text{ cm}^3}{\text{in}^3} \times 0.002 \text{ in} \times \frac{1 \text{ in}^2}{10 \text{ g food}} = 2.95 \times 10^{-7} \frac{\text{g Y}}{\text{g food}}$$

= 300 ppb

Dietary Concentration (DC) is calculated as follows:

DC = CF x <M> = 0.04 x 300 ppb = 12 ppb

Consumer Exposure

Dietary Concentration (DC)

DC = CF x <M>

(μg/kg food)

Estimated Daily Intake (EDI)

EDI = DC x 3 kg/person/day

(μg/p/d)

Consumer Exposure

Minimum Toxicity Tests	Exposure Level (micrograms/person/day)
Literature Search	<1.5
Ames Assay	<150
Mouse Lymphoma Assay or In vitro Chromosome Aberration test	<150
In vivo Chromosome Aberration Test	>150 <3000
Subchronic Toxicity Test with Rodents	>150 <3000
Subchronic Toxicity Test with Non-rodents	>150 <3000
Repro study w/ teratology phase	>3000
One-Yr toxicity test with non-rodents	>3000
Carcinogenicity study with rodents	>3000
Chronic tox/ carcinogenicity study with rodents	>3000

Toxicology Data Cont'd

- Notifiers must identify all relevant toxicology available
- All (relevant) available toxicology data must be submitted
- Comprehensive toxicology profile
- Safety narrative
- Studies are sometimes requested below recommended levels

Bailey et al. 2005. Reg. Tox. Pharm. 42: 225-235.

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Regulatory Toxicology and Pharmacology 42 (2005) 225–235

Regulatory Toxicology and Pharmacology

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The use of structure–activity relationship analysis in the food contact notification program

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Abstract

Food contact substances (FCS) include polymers, paper and paperboard, and substances used in their manufacture, that do not impart a technical effect on food. Moreover, FCSs are industrial chemicals generally consumed at dietary concentrations (DC) of less than 1 mg/kg food (ppm), and more commonly at less than 0.05 ppm (50 ppb), in the daily diet. As such, many industrial chemicals have been analyzed for toxicological concern, some of which may share structural similarity with FCSs or their constituents, and the majority of these studies are available in the public domain. The DCs of these compounds lend themselves to using structure–activity relationship (SAR) analysis, as the available "expert systems" and use of analogs allows for prediction and management of potential carcinogens. This paper describes the newly implemented food contact notification (FCN) program, the program by which FDA reviews FCSs for safe use, the administrative review of FCSs, the SAR tools available to FDA, and qualitative and quantitative risk assessments using SAR analysis within the regulatory framework of reviewing the safety of FCSs.
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Keywords: Structure–activity relationship; Food and drug administration; Threshold of regulation; Food contact substances; Food contact notification; Mutagenicity; TD50; MCASE; OncoLogic; Structure alerts

FDA's FCN Program: Toxicology Review

- Review of pivotal data and minimal SAR review may be performed on all significant migrants
- Positive or equivocal results in genetic toxicity testing may result in a need for detailed SAR analysis of likely carcinogenic risk
- Detailed SAR analysis can incorporate analogue analysis or the use of commercially available software for predictive toxicology
- Minimal SAR review may indicate a need for in-depth SAR review or for additional specialized testing

Estimation of an ADI

- Lowest no effect level
  - Generally NOAEL not considered
- Safety factor
  - 100-fold for chronic data
  - 1000-fold for less than chronic data
  - Additional factors to account for deficiencies
- CEDI/ADI database/ PNC

Risk Management Decision

- Comparison of Estimated Daily intake to Acceptable Daily Intake
  - ADI from data on the food contact substance
  - ADI from read across to data on a structurally similar substance
  - Testing Threshold
  - Threshold of Toxicological Concern
- Risk assessment for any constituents of concern
  - Carcinogenic unit risks
  - Classical safety assessment
- Consideration of how conservative estimates of the EDI and ADI are

FDA's FCN Program: Safety Review Polymers

- The main exposures are generally to oligomers and monomers
- Oligomer exposure to species below MW of 1000. (Based on H atomic weight, halogen substitution may increase this limit)
- Chemist, toxicologist, and SAR analyst consider likely structure
- Comparative SAR can be performed
- Analysis determines acceptability of data

FDA's FCN Program: Safety Review Polymers

- Safety data specifically on oligomers is acceptable
- Safety data on monomers may be acceptable depending on structural analysis
- If safety review has been previously performed on some oligomers only new oligomers considered

FDA's FCN Program: Safety Review of Polymers

Food and Chemical Toxicology 49 (2011) 1877–1897

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Assessing the toxicity of polymeric food-contact substances ☆

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ABSTRACT

The US Food and Drug Administration's Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition conducts safety assessments of food additives, including food-contact substances such as polymeric and oligomeric materials that have the potential to migrate to food. Traditionally, little toxicity testing has been conducted on the low-molecular weight oligomeric fraction (<1000 Da) of these food-contact substances. At lower exposures (⩽150 μg/person/day), safety has been assessed based on the use of toxicity data on the monomeric components of these polymers as a sufficiently conservative approach for addressing the concern for genetic toxicity and carcinogenicity of the low-molecular weight oligomers (LMWOs). This paper discusses this assumption relative to the available data on these substances and their monomeric components in the context of exposures of ⩽150 μg/person/day with emphasis on the evaluation of the potential genetic toxicity of these compounds. In most instances, data are available on either the monomers or the monomers' structural class to conservatively address the potential genetic toxicity of the LMWOs. Caveats to this generalization are also discussed. The assessment of LMWOs is important because they can be one of the primary migrants to food from a polymeric food-contact substance.

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Environmental Recommendations

Allowing an FCN to become effective is an agency action and the FCN must contain:

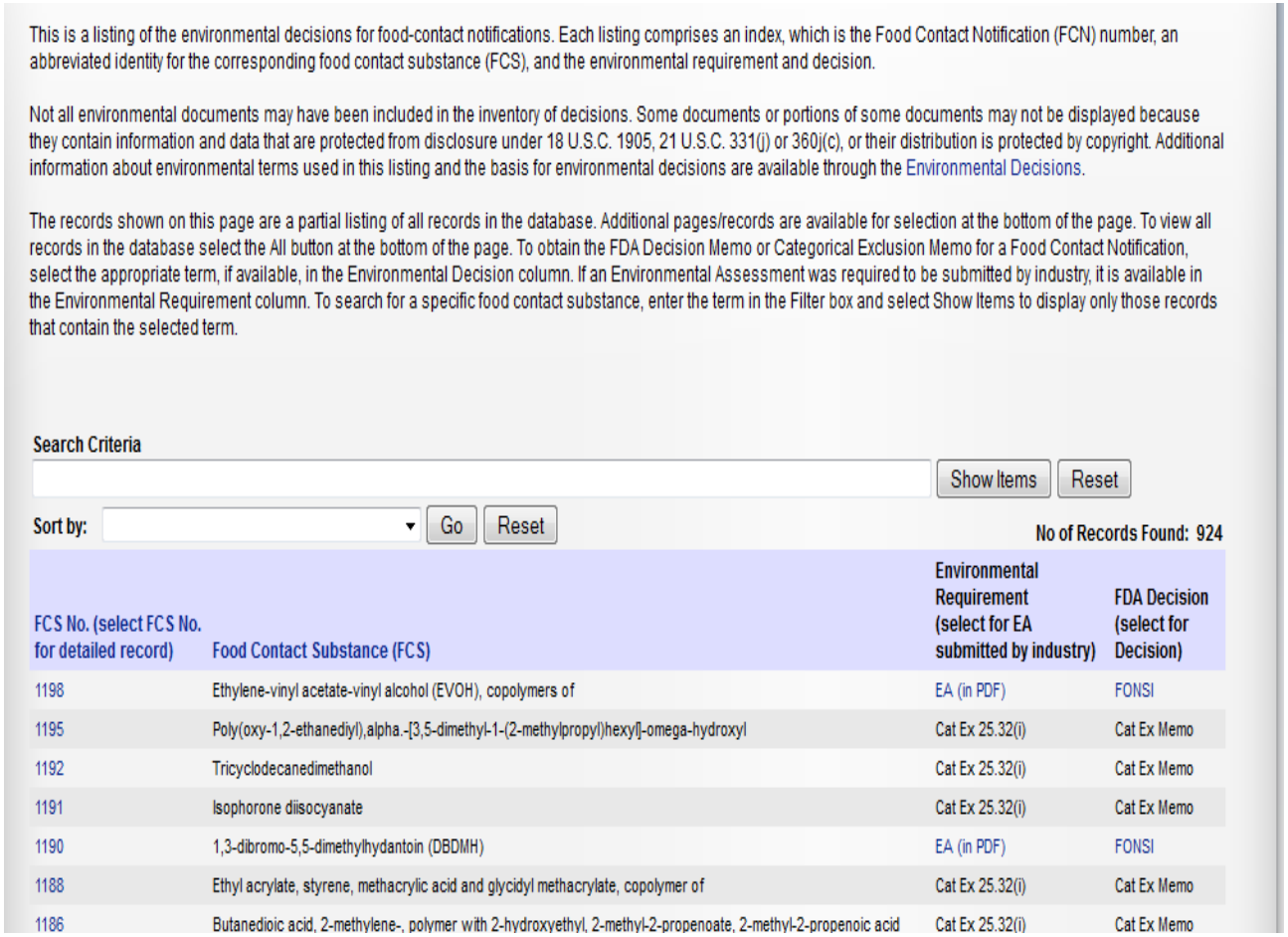
- An Environmental Assessment (EA)

or

- A warranted claim of categorical exclusion from the requirement to prepare an EA (21 CFR 25.15)

Environmental Guidance: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081049.htm

Inventory of Environmental Impact Decisions for Food Contact Substance Notifications



This is a listing of the environmental decisions for food-contact notifications. Each listing comprises an index, which is the Food Contact Notification (FCN) number, an abbreviated identity for the corresponding food contact substance (FCS), and the environmental requirement and decision.

Not all environmental documents may have been included in the inventory of decisions. Some documents or portions of some documents may not be displayed because they contain information and data that are protected from disclosure under 18 U.S.C. 1905, 21 U.S.C. 331(j) or 360j(c), or their distribution is protected by copyright. Additional information about environmental terms used in this listing and the basis for environmental decisions are available through the Environmental Decisions.

The records shown on this page are a partial listing of all records in the database. Additional pages/records are available for selection at the bottom of the page. To view all records in the database select the All button at the bottom of the page. To obtain the FDA Decision Memo or Categorical Exclusion Memo for a Food Contact Notification, select the appropriate term, if available, in the Environmental Decision column. If an Environmental Assessment was required to be submitted by industry, it is available in the Environmental Requirement column. To search for a specific food contact substance, enter the term in the Filter box and select Show Items to display only those records that contain the selected term.

Search Criteria

Show Items Reset

Sort by: Go Reset

No of Records Found: 924

FCS No. (select FCS No. for detailed record)	Food Contact Substance (FCS)	Environmental Requirement (select for EA submitted by industry)	FDA Decision (select for Decision)
1198	Ethylene-vinyl acetate-vinyl alcohol (EVOH), copolymers of	EA (in PDF)	FONSI
1195	Poly(oxy-1,2-ethanediyl),alpha.-[3,5-dimethyl-1-(2-methylpropyl)hexyl]-omega-hydroxyl	Cat Ex 25.32(i)	Cat Ex Memo
1192	Tricyclodecanedimethanol	Cat Ex 25.32(i)	Cat Ex Memo
1191	Isophorone diisocyanate	Cat Ex 25.32(i)	Cat Ex Memo
1190	1,3-dibromo-5,5-dimethylhydantoin (DBDMH)	EA (in PDF)	FONSI
1188	Ethyl acrylate, styrene, methacrylic acid and glycidyl methacrylate, copolymer of	Cat Ex 25.32(i)	Cat Ex Memo
1186	Butanedioic acid, 2-methylene-, polymer with 2-hydroxyethyl, 2-methyl-2-propenoate, 2-methyl-2-propenoic acid	Cat Ex 25.32(i)	Cat Ex Memo

http://www.accessdata.fda.gov/scripts/fdcc/?set=ENV-FCN

FCN Strategy

- Start with use and exposure
- Consider what data exists and what approvals you can accomplish
- Consider GRAS in the interim
- Plan toxicological testing, use read across and don't create more data than you need
- Protect your data
- Tell a good story; tell it how FDA would tell it

Common FCN Issues and Tips and Tricks for Preparing Your FCN

Common Chemistry Deficiencies

- Missing data components
  - MW data without information on the low MW fraction
  - Batch data without analytical methods
- Lack of manufacturing information
- Missing information on migration testing methodology
  - No validation
  - No example calculations
  - No raw data, or information on LOD/LOQ
- No exposure estimates for minor components or constituents
  - Catalysts, other manufacturing aids
  - Impurities and breakdown products

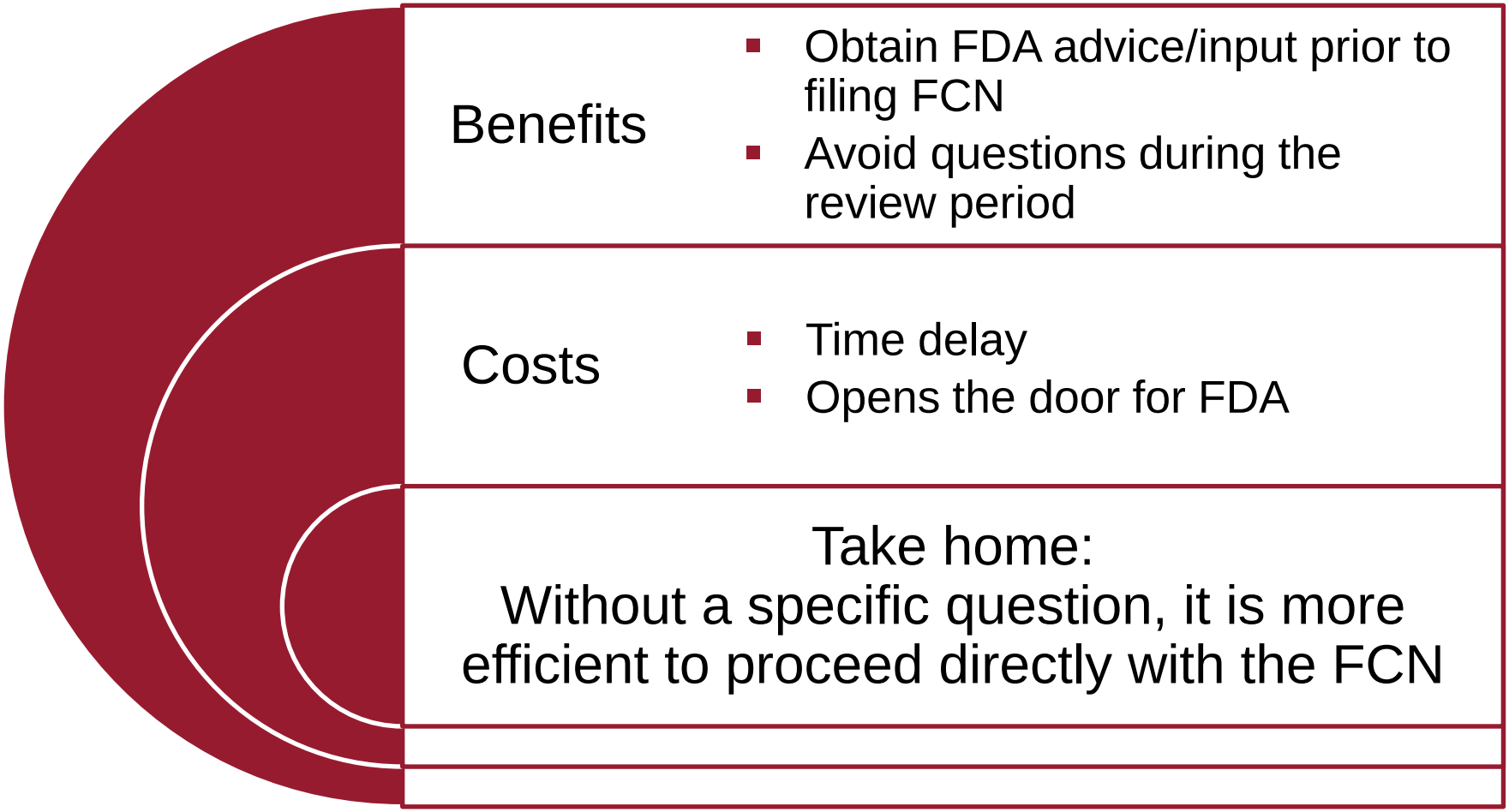
Common Toxicology Deficiencies

- Inadequate quantitative and qualitative information on what migrates into food
- Inadequate review of pivotal toxicity data (PNC?)
  - Inadequate explanation of why negative data is dismissed
  - Incorrect selection of a NOEL
  - Incorrect safety factor or safety margin
- Inadequate toxicology studies

Common Environmental Deficiencies

- Incorrect categorical exclusion claimed or only one CE claimed when multiple apply
- Requested use not consistent only partially consistent with the claimed CE
- Use requested not consistent throughout submission
- No discussion of potential impacts on solid waste strategies (recycling)
- No statement that extraordinary circumstances regarding sites of production don’t exist
- Includes confidential information

Prenotification Consultations



Confidential Business Information

CBI in an FCN can be protected

When can FDA disclose CBI?

- After effective date: everything other than CBI
- Upon FDA's formal objection to the FCN
- If an FCN is withdrawn prior to effective date its contents cannot be disclosed under FOIA

What can be protected?

- Manufacturing details: process, specifications (maybe), analytical test methods
- Impurities
- Production quantities

Take Steps to Help Protect CBI

CONFIDENTIAL

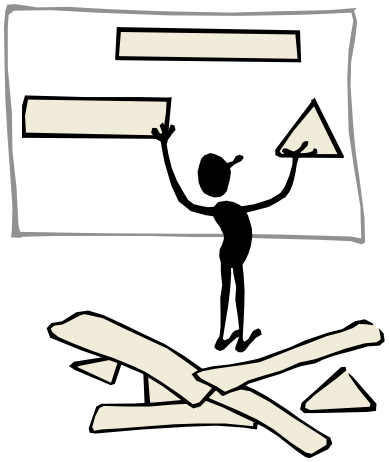
- Clearly mark material in FCN considered to be confidential
- Submit sanitized version of FCN (redact [redacted] information)
- Ask FDA to advise in advance if information marked "confidential" is to be released
- Request a copy of your FCN and all related correspondence under FOIA

Special Concerns

Infant formula	• Exposure: formula is the sole food being consumed • Biological impact: developing physiology and systems • Safety assessment considerations: additional toxicity data?
Nanotechnology	• Safety assessment proceeds as normal • Consider any unique properties and behaviors • FDA guidance available
Environmental Assessment	• Standards for assessment increasingly stringent • Use and provide references • New issue: greenhouse gases

Changes to an Effective FCN

- Substantive changes may require a new FCN
  - E.g., manufacturing process, specifications
  - Changes to the identity of the FCS or its impurities
  - Deviations within GMP are not substantive
- Minor change may need to be notified to FDA
  - Is the change “significant”?
- Change in the intended use does require a new FCN
  - E.g., use level, food types, conditions of use)



Conclusions

- FCN program considered very successful both domestically and internationally
- Today there are 1174 effective FCNs listed on FDA's website and the number being submitted is increasing
- Tell the story

Questions?

Upcoming Events

- November 12: Recent Developments in EU and US Food Law

Thank You for Joining Us

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