US FCN Data Requirement & Practice

-- An Overview of US FDA Food Contact Notification Program

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FDA Modernization Act (FDAMA) of 1997

- Established the FCN program as a more efficient and preferred new process
- Defined a food contact substance (FCS)

- Made approval proprietary
- Mandated confidentiality during review process
- Maintained same safety standard as FAP's
- Mandated a decision in 120 days

Food Contact Notification (FCN) Program

- Authorized by Congress under the ***Food and Drug Administration Modernization Act of 1997 (FDAMA)***
- Began operation on October 22, 1999; converting then existing FAPs to FCNs
- Began accepting new FCNs on January 18, 2000
- Division of Food Contact Notifications (DFCN) established in OFAS in 2000

Responsibilities of DFCN

- Food Contact Notifications (FCN)
- Pre-Notification Consultations (PNC)
- Other correspondence
- Threshold of Regulation exemption (TOR)
- Administrative and technical guidance
- Freedom of Information Act (FOIA)
- Division Special Projects

Definition of Food Contact Substance (FCS)

- As defined in 1997 FDAMA -- 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 a **technical effect** in food

Definitional Coverage of FCS

- **Indirect Food Additives** -- Polymers, monomers, polymerization aids, adjuvants, equipment components, packaging compounds subject to irradiation
- **Some Secondary Direct Food Additives** --boiler water additives, ion exchange resins, sugar processing additives, antimicrobials used in the processing of produces, vegetables, meats and poultries

Data Required for Safety Evaluation

- **Chemistry data** for confirming identity of a food-contact substance and for assessing potential consumer exposure to the substance and its impurities
- **Toxicology data** for use as basis for establishing a safe level of consumer exposure to the substance and its impurities
  (Chemistry and toxicology data should be on substances ***expected to migrate to food*** under the conditions of intended use)
- **Environmental data** for consideration of impact on human environment

FDA Guidance Documents for FCN Submission Process

1. **Administrative: (CSO)**
   revised Form 3480
2. **Chemistry: (Chemist)**
   revised Guidance in 2007
3. **Toxicology: (Toxicologist)**
   added Infant Guidance in 2018
4. **Environment: (EA)**
   revised in 2006

Administrative Information

Is the subject of FCN a food additive/FCS?

Regulation status - clearances

- the intended use is already covered or exempted
- some clearances are for groups of substances

Chemistry Information to be Provided in FCN

- Identity
- Manufacture
- Specifications
- Intended use and technical effect
- Stability
- Migration
- Exposure assessment

Identity

Identification of the substance:

- Name (CAS, IUPAC, common, trade)
- CAS registry number
- Composition (chemical formula, structure, molecular weight)
- Spectroscopic data (IR, NMR spectra, etc.)

Manufacture

Manufacturing process in details:

- Identify all raw materials—monomer, catalyst, solvent (CAS RNs, amounts used, specifications)
- Manufacturing process (purification steps, reaction conditions, chemical equations)
- Identify potential migrants (concentrations, supporting data)

[confidential information/trade secret]

Specifications

Physical/chemical specifications:

- Physical appearance, melting points, boiling point, density, glass transition temperature, molecular weight distribution, fraction of *low molecular weight oligomers*, impurity levels (especially *carcinogenic contaminants*).
- Properties affecting migration potential
  - Solubility, volatility

Intended Use

Description of the conditions of intended use:

- Description of proposed use
- Determines migration protocol
- Single/repeat use applications
- Typical and maximum use levels
- Maximum thickness, weight per unit area
- Limitations
  - Types of food to contact - Table 1 of § 176.170(c)
  - Conditions of use (time, temperature) - Table 2 of § 176.170(c), i.e. I & J.

Technical Effect

- Intended technical effect on the food-contact article
- Data to support
  - FCS achieves the intended technical effect
  - Proposed use level is the minimum level required for the FCS to achieve the technical effect

(No on-going effect in food)

Stability

Stability of the FCS under the conditions of intended use or during migration testing

- Describe any degradation, decomposition or chemical breakdown process (oxidation, hydrolysis, etc.) that the FCS may undergo
- Provide data to support the claim

Migration

- Description of migration experiment in details:
  - Migration cell and test sample
  - Food simulant or real foods
    - 10% ethanol - model aqueous and acidic foods
    - 50% ethanol - model alcoholic foods
    - Food oil, Miglyol 812 – model fatty foods
  - Test conditions - most severe conditions
- End tests (compliance tests) bear no relation to migration test

Migration - 2

Accelerated temperature/time conditions -- intended to simulate thermal processing and extended storage

- Room temperature: 40^0 C for 10 days
- Refrigerated food applications: 20^0 C for 10 days
- Frozen food applications: 20^0 C for 5 days
- Boiling water sterilizing: 110^0 C for 2 hours, then 40^0 C for 238 hours for a total of 10 days
- High temperature, heat sterilized or retort above 100^0 C: 121^0 C for 2 hours, then 40^0 C for 238 hours for a total of 10 days

Migration - 3

- Migration results
  - Triplicate studies
  - Analyze test solutions for FCS, TNEs, additional migrants
  - Report results in mg/in^2
- Analytical methods
  - Provide supporting data
  - Validate methods via fortification of migration solutions

Migration - 4

Alternatives to Migration Testing - 100%

- Migration calculation: worst-case scenario, assuming 100% migration of FCS or its constituents into food; i.e. repeated use articles such as conveyer belts and food processing equipment
- Diffusion theory calculation: Fick's law and diffusion coefficients

Exposure Assessment

- Critical component of FDA's safety evaluation
- Recommended toxicity tests are ***exposure driven*** for the FCS and its constituents
- Consumer exposure combines
  - Migrant levels in food
  - Information on packaging uses

Exposure Assessment - 2

- Packaging factors used in exposure assessment
  - ***Consumption factor (CF)*** - fraction of daily diet expected to contact specific packaging materials
  - ***Food-type distribution factors (f_t)*** - fraction of all food that is aqueous (aq), acidic (ac), alcoholic (al) or fatty (ft), specific for each packaging material
- Weighted-average or total migration <M>
  - Concentration of an FCS or constituents in food contacting the packaging material
  - $\langle M \rangle = f_{aq}M_{aq} + f_{ac}M_{ac} + f_{al}M_{al} + f_{ft}M_{ft}$

Exposure Assessment - 3

Dietary Concentration (DC)

DC (µg/kg food or ppb) = CF x <M>

Estimated Daily Intake (EDI)

EDI (µg/person/day) = DC x 3 kg/person/day

Normalized Estimated Daily Intake (EDI)

EDI (***µg/kg bw/day***)

= DC x 3.0 kg/60 kg person/day

= DC x 0.9 kg/6.5 kg infant/day

Exposure Assessment - 4

Cumulative EDI (CEDI)

- Cumulative exposure for all permitted uses
- Should be calculated for the FCS
- Request through a pre-notification consultation
- CEDI database on FDA's website: https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=edisrev&displayAll=false&page=3
- *All previously permitted uses do NOT include infant use. CEDI for infant is independent or separated from CEDI for general population*

Exposure Assessment - 5

Special scenarios

- Repeat use applications: latex gloves, food processing machine, conveyer belts
- Paper model (“wet-end” model): internal addition of a non-substantive paper additive to paper
- Infant use applications: infant formula is the only source of food intake

Toxicology Information to be Provided in FCN

- Toxicology data required to establish a safe level of consumer exposure to an FCS and its constituents
- The greater expected dietary exposure, the more toxicological information/data need to support the safety
- Exposure-driven, tiered approach recommended by FDA for safety testing
- Toxicology guidelines available on FDA's website

Tier-1: Toxicity tests required for DC < 0.5 ppb

- No toxicity tests needed
- Need to provide literature search information on the FCS/impurities with focus on any reports pertaining mutagenicity and carcinogenicity
- A SAR or QSAR analysis on its mutagenicity and carcinogenicity helpful (still need LCR for carcinogens)

Tier-2: Toxicity tests required for DC in 0.5 ppb to 50 ppb

Short-term tests for genetic toxicity

- Gene mutation in bacteria, i.e. Ames test
- *In vitro* cytogenetic test in mammalian cells, OR *in vitro* mouse lymphoma assay

Tier-3: Toxicity tests required for DC in 50 ppb to 1000 ppb

Battery of three genetic toxicity tests

- Gene mutation in bacteria, i.e. Ames test
- *In vitro* cytogenetic test OR *in vitro* mouse lymphoma assay
- *In vivo* micronucleus test

Two 90-day subchronic toxicity studies

One rodent species and the other in a non-rodent species

Additional studies as appropriate

Tier-4: Toxicity tests required for DC ≥ 1000 ppb

- Subchronic studies in a rodent species and a non-rodent species
- Chronic (1-year) studies in a rodent species and a non-rodent species
- Two-year carcinogenicity bioassays in 2 rodent species, with one including an *in-utero* exposure phase in its study design
- Two-generation reproductive study in rats with an attached teratology phase
- Other specialized studies, as appropriate by the indications from other studies
- Recommendation for FAP process

Toxicity tests – Points to remember

- The toxicology data recommendations are applied to not only the FCS, but also its impurities/constituents
- If the FCS is a biocide, the dietary exposure levels are reduced by 5-fold for the recommended toxicity testing due to its inherent toxicity; *i.e. tier-2 DC for biocide becomes 0.1 ppb to 10 ppb*
- If the application includes infant use, make sure that the calculation for EDI and life-time cancer risk (LCR) is appropriated

Normalized Tier Values

Tier Level	Exposure Values	Normalized Exposure Values
Tier 1	**≤ 0.5 ppb OR ≤ 1.5 µg/p/d**	**≤ 0.025 µg/kg bw/day**
Tier 2	**> 0.5 ppb to < 50 ppb OR > 1.5 µg/p/d to < 150 µg/p/d**	**> 0.025 to < 2.5 µg/kg bw/day**
Tier 3	**≥ 50 ppb to < 1000 ppb OR ≥ 150 µg/p/d to < 3000 µg/p/d**	**≥ 2.5 to < 50 µg/kg bw/day**
Tier 4	**≥ 1000 ppb OR ≥ 3000 µg/p/d**	**≥ 50 µg/kg bw/day**

DC = 45 ppb

General = DC x 3.0 kg/60 kg/day = 2.25 µg/kg bw/day → Tier 2

Infant = DC x 0.9 kg/6.5 kg/day = 6.23 µg/kg bw/day → Tier 3

Acceptable Daily Intake (ADI)

- "**ADI** is an estimate of the amount of a chemical that can be ingested daily without appreciable health risk" (*R. Walker, Fd. Add. Contam. 15 (Suppl.):11-16, 1998)*
- Establish a no-effect-level **(NOEL)** for each toxic effect based on the study, species, strain and sex appearing to be most sensitive to the effect identified.
- Divide **NOEL** for each identified effect by an appropriate **safety factor (SF)**.
- The **lowest value** is the **ADI** for the chemical.

Safety Factors

- Two chronic studies – 100
- Rodent **AND** non-rodent subchronic studies – 1000
- Rodent **OR** non-rodent subchronic studies – 2000
- Reproductive/teratology studies – 100 for reversible effects and 1000 for irreversible effects

Safety Determination of a Food Contact Substance

A food-contact substance (FCS) is considered safe for its intended use if the probable estimated consumer dietary exposure (EDI) to the FCS is less than or approximates the Acceptable Daily Intake (ADI)

Margin of Exposure (MOE): if the MOE is adequate - large enough

Different Nomenclature (Jargon)

NOEL: No-Observed-Effect-Level
NOAEL: No-Observed-Adverse-Effect-Level
SF: Safety Factor
UF: Uncertainty Factor
MOE: Margin of Exposure
MOS: Margin of Safety
RfD: Reference Dose
ADI: Acceptable Daily Intake

Carcinogenic Risk Assessment

Constituents can be carcinogenic

- Unreacted monomers: vinyl chloride, ethylene oxide, acrylamide, 1,3-butadiene, acrylonitrile, epichlorohydrin
- Residual solvent: methylene chloride, benzene, chloroform
- Manufacture side products: 1,4-dioxane, 2,4-diaminotoluene
- Contaminating impurities: PAHs, PCBs, TCDD

Carcinogenic Risk Assessment-2

- **Calculation of Unit Cancer Risk (UCR):** Defined as the sum of the slopes of lines drawn from the lowest apparent effective dose of the chemical through zero for each tumor site in a carcinogenicity study
- **Upper-bound Lifetime Cancer Risk (LCR):** multiplying the UCR by the EDI of the constituent (*Infant LCR is calculated in a different way, see infant Guidance for details*)
- **Acceptable LCR:** in general as the LCR is less than 1×10^{-6} for trace level of a carcinogenic constituent in food

Environmental Assessment
(21 CFR 25.40)

- The FDA will not accept an industry submission for review if the environmental component is missing or deficient (21 CFR 25.40)
- The environmental component is either a claim of Categorical Exclusion or an Environmental Assessment

Environmental Assessment - 2

- A brief discussion for the need for the proposed action
- Introduction, fate, and effects of the substances in the environment
- Alternatives to the proposed action
- Environmental impact of the proposed action as a result of use and disposal of the food contact substance

Pre-notification Consultation

By a letter, E-mail or on site meeting

- Provide technical information and assistance; i.e. cumulative dietary exposure (CEDI) and Acceptable Daily Intake (ADI) for a food contact substance; factors/models used in dietary exposure calculation, FDA's UCRs, etc.
- Provide technical advice on types and level of chemistry and/or toxicity testing needed to support the safety of a food contact substance

Thank you for your Time and Attention

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Any questions?

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