When is Adversity Legally Cognizable?

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Conflict of Interest Statement

As an attorney working in private practice, I am compensated to advise companies that manufacture and distribute food ingredients and finished foods for human and animal consumption on the requirements of the federal food, Drug, and Cosmetic Act and other federal laws. I am not receiving any compensation for this presentation.

Overview

- Foundational concepts and terms
- Ingredient safety pre-1958
- 1958 Food Additives Amendment
- General safety clause
- Definitions of “safe”
- Delaney Clause
- Case Studies
- Key Points

Civics 101

- The U.S. has a tripartite system of government
  - Legislative branch
  - Executive branch
  - Judicial branch
- FDA is an agency within the executive branch
- FDA enforces the 1938 Federal Food, Drug, and Cosmetic Act (FFDCA), which was preceded by the 1906 Pure Food and Drug Act
- FFDCA is periodically amended (e.g., as with the Food Additives Amendment in 1958)

Key Legal Terms

- Statute – a type of law
  - Must be constitutional
- Regulation – a type of law
  - Must be constitutional
  - Must be within the scope of statute
  - Must be issued in accord with procedural requirements
- Guidance – not law

Process Matters

- There are procedural requirements and constraints on the establishment of a regulation – and on its revocation
- Depending on the process – or stage of the process – the burden can shift toward or away from the regulator

Let's Start With a Historical Example

- Pure Food and Drug Act of 1906 motivated in part by concerns over the use of preservatives
- An article of food shall be deemed adulterated "if it contain any added poisonous or other added deleterious ingredient which may render such article injurious to health."
  - When is a substance poisonous or deleterious?
  - What constitutes an injury to health?
  - As a statement of probability, what does "may render" mean?
- Who bears the burden of proof?

All the Way to the Supreme Court

- U.S. v. Lexington Mill & Elevator Co. (1914)
- Nitrous oxide used to bleach flour, resulting in addition of poisonous or deleterious ingredients
- Mere presence is not enough
- Injury to health of any consumer is cognizable – “the strong and the weak, the old and the young, the well and the sick”
- “May” is used in the ordinary sense – reasonable possibility
- Government has the burden of proof

1938 - 1958

- 1938 FFDCA essentially codified Lexington Mill's interpretation of adulteration safety standard
  - Government retained burden to establish adulteration
- 1939 – *Procedures for the Appraisal of the Toxicity of Chemicals in Food* (FDA Black Book)
- 1954 - *Principles and Procedures for Evaluating the Safety of Intentional Chemical Additives in Foods (NRC Food Protection Committee)*
- Growing concern about the safety of substances added to food; years of Congressional debate provide a rich legislative history

1958 Food Additives Amendment

- Food additive: Any substance *the intended use of which* results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food
- Established a petition process for approval of food additive uses via the issuance of a regulation
- General safety clause: There can be no approval if a “fair evaluation of the data” fails to establish that the proposed use is “safe”

GRAS: An Exception to the Definition of "Food Additive"

- Generally Recognized as Safe (GRAS)
- If the use of a substance is **generally recognized** among qualified experts **as** having been adequately shown through scientific procedures to be **safe** *under the conditions of its intended use*, then that use is excepted from food additive approval.

GRAS (cont'd)

- In the case of a substance used in food prior to January 1, 1958, safety may be shown either through scientific procedures or experience based on common use in food.
- The safety requirement for food additive uses and GRAS uses is the same.
- Voluntary notification (not mandatory approval).

Statutory Context of “Safe”

- “Safe” refers to the health of man or animal
- A petition must contain full reports of investigations made with respect to safety of the proposed use
- In determining whether the proposed use is “safe,” FDA must consider:
  - Probable consumption of the additive and any substance formed in or on food
  - Cumulative effect in the diet, taking into account chemically or pharmacologically related substances
  - Safety factors appropriate for the use of animal experimentation data

Regulatory Definition of “Safe”: Take 1

- *As proposed in 1958 – "Safe" means that there is convincing evidence that no harm can come from the intended use of the food additive.*
  - Defines “scientific procedures” to include “animal, analytical, and other scientific studies,” as well as “reliable information” drawn from scientific literature
  - Setting tolerances for related food additives, use of safety factors, and qualification of experts
  - Use safety criteria in *Principles and Procedures for Evaluating the Safety of Intentional Chemical Additives in Foods (NRC, 1957),* unless evidence establishes that another approach gives equally reliable results

Regulatory Definition of “Safe”: Take 2

- *As finalized in 1959 – "Safe" means that there is convincing evidence which establishes with reasonable certainty that no harm will result from the intended use of the food additive.*
  - “Reliable information” becomes “unprejudiced…reliable information, both favorable and unfavorable”
  - Language dictating reliance on NRC publication is softened, and this is added: “FDA will give full consideration to the specific biological properties of the compound and the adequacy of the methods employed to demonstrate safety for the proposed use”

Regulatory Definition of “Safe”: Take 3

- 1970 – FDA proposes to specify GRAS eligibility criteria:
  - To ascertain that any substance is absolutely safe for human or animal consumption is impossible. This is particularly true in the case of substances intended for human consumption when animals are used to examine the effects of test substances. "Safe" must be understood to connote that [FDA], after reviewing all available evidence, can conclude there is no significant risk of harm from using the substance as intended.
- Revocation of GRAS status predicated on “a responsible and substantial question of safety”

Regulatory Definition of “Safe”: Take 4

- 1971 – Final rule revises definition of “safe”:
  - *"Safe" means that after reviewing all available evidence, including [probable consumption, cumulative effect, and safety factors], [FDA] can conclude that no significant risk of harm will result when the substance is used as intended.*
- “Reasonable certainty” language deleted, but absolute safety language remains.
- Signals intent to issue regulation “prescribing the type of toxicological data upon which the safety of a substance can be determined.”

Regulatory Definition of “Safe”: Take 5

1975 proposed redefinition: "Safe" or "safety" means that there Is a reasonable certainty in the minds of competent scientists that the substance is not harmful. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

- probable consumption
- cumulative effect
- safety factors
- benefit contributed by the substance

Regulatory Definition of “Safe”: Take 6

As finalized in 1976: "Safe" or "safety" means that **there** is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It Is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined **by** scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

- probable consumption
- cumulative effect
- safety factors
- [but NOT benefits]

Interpretive Statements

- Regarding the scope of “safe” – The general safety clause applies to “all types of health risks.”
- Regarding interpretation of data – “[T]he methods and criteria for interpreting data are up to the discretion and expertise of the agency.”

FDA Guidance: The Redbook

- 1939 – Procedures for the Appraisal of the Toxicity of Chemicals in Food (Black Book)
- 1982 – Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Red Book)
- Current edition: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000)
- Request for comments on potential updates published in October 2014

The Redbook (cont'd)

- "FDA consistently has taken the position that various types of scientifically valid information may be used to support a determination that the proposed use of an ingredient is safe."
- "Flexibility in Guidance for Toxicity Testing. FDA's guidance for toxicity studies for food ingredients continue to emphasize that there is no substitute for sound scientific judgment. This guidance presents recommendations--not hard and fast rules."

Delaney Clause

- General safety clause: There can be no approval if a “fair evaluation of the data” fails to establish that the proposed use is “safe”
- Delaney clause: “no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal”
- There actually are three Delaney clauses.

Delaney Clause

- Reflected increasing concern over cancer
- Parent agency initially objected to clause as unnecessary and unduly restrictive
- Has begotten many questions
  - When does a substance “induce cancer”?
  - Which tests are “appropriate”?
  - What about carcinogenic constituents?
  - Does the clause apply to GRAS determinations?
  - Does it apply to agency-initiated rulemakings?

Allocation of Burden

- Food Additive Petition (FAP) approval: “[B]y requiring that the data ‘establish’ safety, Congress clearly placed the burden of proving safety on the sponsor of a food additive petition... FDA does not have to prove that the product is unsafe. This distinction is very important because it is possible that the data may fall in the ‘grey area’ where the food additive has not been shown convincingly either to be safe or unsafe. In such a situation further testing may be necessary to resolve the issue.”
- Compare with revocation of approved/GRAS use

“Fair Evaluation”

There must be an “objective basis for the evaluation of the data presented” for a scientist to conclude that a substance has not been shown to be safe. The “requirement of objectivity is met. . . if the agency reviews the evidence carefully, conducts a fair evaluation of the evidence, states its reasons for crediting or not crediting a piece of evidence, weighs all the evidence, applies the correct statutory standards, and decides.”

Procedural Safeguards

- Order regarding FAP is effective on publication
- Any person adversely affected may file objections and request a public hearing
- If granted, formal procedures will govern hearing
- Order acting on objections is subject to judicial review
- Findings of fact will be sustained if “based upon a fair evaluation of the entire record”
- Challenges can take years to resolve

Case Study: Approval Contingent on Labeling

- 1987 – FAP filed for Olestra; FDA embarked on 8-year review
- 1995 – Food Advisory Committee (FAC) recommended approval
- 1996 – FDA approved some uses, contingent on label statement & review of post-market studies
- 1998 – FAC reaffirmed original recommendation
- 2003 – FDA eliminated label statement requirement
- 2004 – FDA approved additional uses
- 2008 – Additional uses self-determined GRAS and notified to FDA

Case Study: GRAS Revocation and Attempted Ban

- 1958 – Saccharin listed as GRAS by FDA
- 1972 – FDA revoked GRAS status and issued interim food additive regulation
- 1977 – Rat studies revealed bladder cancer; FDA proposed ban; Congress imposed moratorium and mandated studies and a labeling statement
- Studies demonstrated irrelevance of 1977 findings
- 1991 – FDA withdrew ban proposal
- 2000 – NTP removed saccharin from its Report on Carcinogens; labeling statement requirement was removed

Case Study: Abandonment of Challenged Uses

- 1960s – FDA approved first uses of BPA
- 2008 – FDA issues draft report affirming safety; FDA Science Board Subcommittee on BPA questioned comprehensiveness of review; consumer group submitted citizen petition (CP) requesting prohibition
- 2009 – FDA embarked on 4-year review
- 2010 – FDA sued to compel response to CP
- 2012 – FDA denied CP; amended regulation to prohibit use in bottles and drinking cups used by infants and children

Key Points

- Determination of whether an effect is adverse is only the beginning
- Determination of adversity must be placed in context of governing standard
- The likelihood of controversy depends in part on the quantity and quality of underlying evidence
- “Safety” can have economic and political dimensions
- The pace at which science evolves argues in favor of flexibility and discretion – within limits

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Questions

At this time, please limit questions to those specific to this presentation, and save general questions for the Roundtable Discussion with all the presenters.