The Application of Post-Market Monitoring to Novel Foods

An Expert Group Opinion,
ILSI Europe Novel Foods Task Force.

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ILSI

- Scientific Platforms > Clusters > Task Forces
- Assessment of Benefits and Risks
- Novel Foods (and Nanotechnology) Task Force

Objective

- To review how novel foods, novel food ingredients and new processing techniques should be evaluated scientifically from the safety and nutritional viewpoints
  - Expert Groups
  - Workshops
  - Concise monographs
  - ILSI Reports
  - Publications
• Approval required if not used for human consumption in the EU community before 15 May 1997 and fall into the following categories
  – new or intentionally modified primary molecular structure;
  – consisting of, or isolated from, micro-organisms, fungi or algae;
  – consisting of, or isolated from plants, or food ingredients isolated from animals except for those obtained by traditional propagating or breeding practices, and having a history of safe food use;
  – or has been applied a production process not currently used, resulting in significant changes in the composition/structure which affect their nutritional value, metabolism or level of undesirable substances;

• If substantially equivalent to existing foods with a history of safe use, then a simplified notification procedure can be used

• Produced from GM sources (EC 1829/2003)
Food and Chemical Toxicology 2007, 45: 2513-2525

History of Safe Use = Established Safety Profile

- Foods prepared and used in traditional ways (cultural practises) considered to be safe for the consuming population on basis of long-term human experience
- A level of safety, subject to appropriate risk management procedures, which is regarded as ‘acceptable’ by consumers of traditional food
- A body of knowledge on which to establish the existing safety profile of a food, with known limitations
Safety Assessment of (Novel) Foods: Case by Case

- **Analytical/compositional/nutritional characteristics of the novel food**
  - Source of material / Changes due to new processing

- **Previous history of human exposure**
  - Comparison to traditional counterpart (if available)

- **Expected applications and the *predicted* exposure**
  - Purpose
  - Food categories and Use levels (usually worst-case; over-estimates)

- **Neccessity, appropriateness and outcome of safety studies**
  - Fate in biological systems
  - Standard toxicology, feeding studies
  - Focused toxicity studies
  - Allergenicity
  - Human studies: focused effects, target populations, efficacy….

*Intern J Food Sciences and Nutrition 2003, 54: 1-32*
Ultimate Aims

• Risk Assessment (- ADI?)
  – $f$ (Hazard x Exposure)

• To inform Risk Management decisions and Risk Communication
  – Regulatory Approval (or not);
  – Conditions/ limitations,
  – labelling as conditions of approval?

• Ensure foods placed commercially on the market are safe for the consumer and do not present undue risk

• Safe for the intended uses and Compliant with legislation
Concept of Post-launch monitoring?

• No mandatory requirement

• ‘PMM should, where appropriate, be performed for foods derived from genetically modified sources, specifically where there is no traditional comparator available’. (EFSA, 2004, 2006)

• PMM data ‘will provide additional reassurance regarding long term safety of products, as well as their impact on the food supply’ (FSANZ, 2005)

• Condition for approval of phytosterol esters in fat spreads in EU
  ‘Establish a surveillance programme accompanying the marketing of the product …… in order to estimate the extent to which the product is reaching its target group, … and to estimate exposures to phytosterols from this source in other population groups……’

  (Committee Decision 2000/500/EC)
• Post Market Surveillance (PMS)
• Post Market Monitoring (PMM)
• Post Launch Monitoring (PLM)
• Pharmacovigilance for Drugs
• Cosmetovigilance for Cosmetics

• PMM : a hypothesis driven, scientific methodology for obtaining information through consumer investigations relevant to the safety of a novel food after market launch (ILSI 2008).
PMS Medicines

- Prescriptive
- Specific population
- Pharmacies
- Small patient base
- Medical condition
- Health professionals
- Clear dose, cause vs effect

PMM Foods

- No controls
- General population
- Freely available
- Large consumer base
- Health status unknown
- Consumer carelines
- Causality?
Case Study: Aspartame (additive, sweetener)

- **Reason for PMM**
  - Pre-market assessment: EDI (8.3 - 34 mg/kg bw/d) close to ADI (40 – 50 mg/kg bw/d)
  - Consumer reports of adverse health effects post-launch

- **Methodologies**
  - Intake assessment by household menu survey (market research)
  - Collection and evaluation of anecdotal reports by independent authority (CDC/FDA)

- **Outcome**
  - Intake confirmed to be within limits
  - Safety confirmed by additional targeted studies in humans and animals
  - No link between aspartame consumption and reported adverse events
Case Study: Olestra (fat replacer)

• Reasons for PMM
  – Confirmation of pre-market assumptions concerning intake and consumer nutritional status (fat soluble vitamins), GI effects
  – Precautionary labelling

• Methods
  – Intake assessment in random cross-sectional population study by FFQ
  – Passive monitoring for consumer reports of adverse effects
  – Serum micronutrient levels measured in cohort study

• Outcomes
  – Intake/usage patterns: compliant with pre-market assessment
  – Expected effects confirmed as within background
  – Reported allergic reactions: not confirmed in follow up
  – Targeted clinical study: absence of effect on anti-coagulant medication
    ➢ Labelling removed
Case Study: Fat spreads with Phytosterol esters (cholesterol reduction)

• **Reason for PMM**  
  – Condition of pre-market approval to confirm predictions concerning intake and target populations

• **Methods**  
  – Intake and pattern of use assessed by market research (direct survey of households)  
  – Passive monitoring for consumer reports of adverse effects

• **Outcome**  
  – Pre-market assumptions concerning intake and target group confirmed  
  – No unexpected effects of any significance observed

More products, continuing monitoring (EFSA 2008, PHYTOST..)
Case Study 4: StarLink Maize (Bt Cry9C; feed)

- **Reason**
  - Consumer complaints of adverse health effects

- **Methods**
  - Collection/evaluation of consumer reports by independent authority
  - Retrospective intake assessment in ‘positive’ cases by chemical analysis of food; measurements of biomarkers (IgE) in subjects

- **Outcome**
  - No association between putative allergic reactions and exposure to StarLink maize
  - No confirmation of allergic potential of Cry9C protein
  - No PMM strategy applied
Possible criteria to trigger a PMM?

Intake
- If EDI is close to ADI - monitor real consumption patterns
- Original application for one product; further applications leading to different exposure patterns
- Product intended for use in foods in certain populations
- Monitor potential non-intended use

Health
- Possible (side-)effects identified in pre-market
- Reassurance of no adverse effects – but need a reasoned hypothesis, system to collect signals.
- If significant number of complaints received?
- If new issues highlighted – further research?
A tool for getting market data which can be used for refinement of the risk assessment

Pre-market safety studies
- Modelling
- In-vitro
- In-vivo
- Human

Risk Assessment
- Intake Estimate
- Hazard characterisation

Risk Management
- Regulatory approval
- Limitations
- Labelling

Launch Product
- Compliance
- Advertising
- Communication

Post-Launch
- PMM
- Intakes
- Health Effects
• Food *supply* data
  – Track production of agricultural commodities
  – Measure volumes *available* for consumption

• *Household* food purchase data
  – National Food Surveys (eg UK - 6000 households since 1940)
  – Commercial market surveys
  – Retailer loyalty card info
    • Out of home?

• Survey of *individual* intake
  – Dietary recalls
• Limitations/developments
  – Traceability (occurrence, food products)
  – Sources of info: Food composition databases (e.g. EuroFIR)
  – Brands v food products v ingredients
  – Statistical modelling: improve predicted intakes
  – Harmonisation of methodologies (different countries)
Methodology : Health Effects (1)

• Company Contact Centres (channels for consumer relations)
  – Collating information from consumers
  – Surveillance, detection of signals for follow-up
    • Reactive, Proactive
    • Specific (branded) food products
    • Contact (culture, country, motivation)
    • Long term effects not identified
    • Quality of information (asked and received)
    • Expert follow-up

• Disease Registers
  – Patient Care, Public Health
    • Planning of public health care
    • Do not cover all diseases
    • Difficult to link with dietary exposures
    • Ethical/data protection
• Epidemiological Studies
  – Prospective studies (forward looking)
    • Monitor dietary practice and monitor health consequences
  – Case control studies
    • Investigate subjects with a particular disease in relation to previous dietary intake

• Needs/Developments/Improvements?
  – Detailed (accurate and continuous) dietary intakes
  – Link health effect to specific food/ingredient?
  – Early predictive (bio)markers of health effects - validation?
  – (Clinical trials in specific populations; v PMM)
Requirements for a PMM?

- Must be hypothesis driven
- Power of methodology employed must be sufficient to meet the needs of the PMM
- Study parameters must be clearly defined
- Timelines
- Adequate traceability and identification of the NF in question
- Reliable assessment of food intake
- Population must be large enough to ensure a statistically valid interpretation
- Collection, validation, recording checked for relevance and veracity by appropriate experts
- Characterised by codification in accordance with internationally recognised systems
- Transparent process fully involving all stakeholders.
- Decision making
Requirements for a hypothesis driven PMM

Regulatory (pre-market assessment)

Voluntary (Product Stewardship)

Formulation
- Generation of hypothesis;
- Agreement of objectives
- Study design/protocol
  Stakeholders
  Industry, regulatory authorities, consumers, health professionals

Contact Centres

Nutrition & Health Status

Intake data

PMM

Peer Review & Assessment
  Independent Expert Body

Options
  Stakeholders
  Industry, regulatory authorities, consumers, health professionals
PMM may be appropriate to:

- Confirm that product use is as predicted in the pre-market assessment

- Provide reassurance that effects observed in the pre-market assessment occur with no greater frequency or intensity in the post-market phase than anticipated

- Investigate the significance of any adverse effects reported by consumers after market launch
Conclusions (2)

• PMM should not replace any steps in the pre-market safety assessment

• PMM should only be used when triggered by specific evidence based questions

• Cannot be used to test hypothesis that effects are absent; it is not possible to prove a negative.
  – Outcome is limited by power and nature of a study possible (duration).
  – *(Can provide a measure of confidence that effects will not occur).*

• Methodologies place limitations on what PMM can achieve
ILSI Europe Novel Foods Expert Group on PMM

- To discuss possibilities and limitations on PMM for Novel Foods
- Discussed in workshop Barcelona 2006.

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