

# Nutraceuticals & New Dietary Ingredients The Swiss Perspective

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# Raison d'Être for Nutraceuticals

- *Nutrition and Health*
  - A large body of scientific literature substantiates a relation between nutrition and health
  - Health benefits are the result of a “continued” ingestion of specific substances (or combination of substances) contained in (or related to) the human food chain
- *Disease risk reduction*
  - The health benefits are mostly achieved by a reduction in the risk for specific diseases
  - Nutraceuticals are the substances in the food providing such health benefits

# Raison d'Être for Nutraceuticals

## *continued...*

- *Public Health & Nutraceuticals*
  - Disease risk reduction at low cost is an attractive way to slow the continuous rise in the health care cost of the aging population in the Western world
- *Safety of Nutraceuticals*
  - The food chain is a positive selection of substances having a low toxicity profile in the dose range of a normal diet
  - There is a history of safe human use of these substances at the exposure level obtained by the respective food
  - That's a good basis for safety but might not be quite enough
- *Efficacy of Nutraceuticals*
  - Needs scientific substantiation by mechanistic rationale and/or clinical studies
  - Authorized health claims are desired to guide consumers

# Data Package for a Nutraceutical - A Scientists View -

- *Substance Source and available data*
  - Its presence in the human food chain
  - Other documented evidence of safe human use
  - Its documented evidence for efficacy (mechanistic plausibility and/or clinical data)
  - The safety profile of the substance
- *The conditions of use should be guided by*
  - The levels of chronic human exposure (plasma concentration) via the respective diets
  - The target tissue concentrations reached by the respective diets
  - The safety profile of the substance
  - The target organ concentrations needed for efficacy

# Data Package for a Nutraceutical

## - The Industry's View -

- *Establishing safety and efficacy data is fine, but how do we get the investment back?*
  - Competitors can piggyback on established safety and efficacy data
  - Tight patent protection is rarely possible for nutraceuticals
  - Industry shies away from making the necessary investment
- ***Proposal for legislation***
  - Time limited market exclusivity for the “first mover” similar to the “orphan drug” regulation
  - Prohibition of data piggybacking
  - Authorized brand-specific efficacy claims
  - Other...

# Definitions

- *Nutraceuticals* (health-promoting micronutrients)
  - *DIs (dietary ingredients)*:
    - a vitamin,
    - a mineral,
    - an herb or other botanical,
    - an amino acid,
    - a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or
    - a concentrate, metabolite, constituent or extract.
  - *NDIs ("new dietary ingredients")*:
    - meets above definition and was not sold in the U.S. in a dietary supplement before October 15, 1994.

# When does a DI become a NDI?

- *By a significant change in the conditions of use leading to an increase in exposure*
  - A newly recommended dose, composition or galenic form, if it results in a DI **exposure that is significantly higher** than that obtained by the old dose, composition or formulation or that obtained by consumption of the respective food.
  - The safety profile of the DI
- *By a significant chemical modification of the DI*
  - that is not readily converted back to the original DI by the body (i.e. ester)
  - Modifications leading to metabolites not produced by the original DI require special attention

# What information on the chemical nature of the NDI should be provided?

- *Origin:*
  - extract, (raw, enriched, purified)
  - fermentation,
  - chemical synthesis
  - Chemical name of efficacious molecule
- *Impurity profile*
- *In case of “non-single compound” NDI*
  - standardize dose/content on efficacious molecule
  - provide evidence on role of other compounds with high prevalence in the mixture and/or with relevant effect
- *Stability of compound in the galenic form(s) chosen*
- *Bioavailability data in humans*

# What is an acceptable ratio of the intended dose to the dietary intake?

- **Assumption:**

- The safe human use of an NDI is documented by food-based exposure data (human plasma levels)
- Additional preclinical (Tox) and clinical safety data (SAD, MAD) is available

- **Proposal:**

- The dietary intake of the population with highest safe & beneficial dietary intake of the compound is used as a basis to define the intended dose
- The intended dose can be significantly higher (>3-fold) than the dietary intake, if supported by additional safety data
- The recommended dose must be at least a small multiple below the safe upper limit of the DI

# What is adequate safety evidence?

- Safety is a must *for nutraceuticals*
- *Provided that for a food chain compound there is evidence for a **beneficial effect and it has a wide safety window**, it should receive **approval as NDI***

# Proposal for “Must Do” safety studies for NDIs

- *ADME in rats*
- *13-weeks oral toxicity study in rats*
- *developmental/teratogenicity study in rats*
- *genotoxicity studies:*
  - Ames test
  - mouse lymphoma V79 assay (in vitro) or COMET assay

# Proposal for “Conditional” safety studies for NDIs

- *Depending on*
  - outcome of abovementioned studies,
  - accumulation potential,
  - known side effects of related compounds:
- *52 weeks toxicity study in rats*
- *2 generation study in rats*
- *Standard carcinogenicity study: overkill.*
- *Replace by **SHE assay** (Syrian hamster embryonic cell assay). The result has to be judged in context of structure –activity characteristics and potential toxicological mechanisms*
- ***Important: Official guideline on which studies are expected under which conditions (decision tree)***

# Safety Factor for NDIs?

- *Food additives*
  - A standard “safety factor” of 100 is applied for estimation of an “upper safe level” in humans from the NOAEL found in rodent studies
  - These are substances which are “new to the human body” i.e. without a history of safe human use
- ***Proposal for DIs: No standard safety factor***
  - These substances have a history of safe human use
- *The upper safe dose for humans is derived from*
  - Pharmacokinetic data in both humans and rodents,
  - Plus data from rodent tox studies
  - Also considering the exposure needed for efficacy

# Safety Factor for NDIs *continued...*

- *This data allows to determine the upper safe dose*
  - which in humans leads to plasma levels not exceeding the NOAEL found in the rodent tox studies.
- *Intended dose should be*
  - X-times (e.g. 3-times) below the upper safe level
  - And allow for the desired efficacy

# Consistent Regulatory Hurdles

- Currently, an approved DI becomes an unapproved drug, if a disease claim is made - independent of whether the claim is based on scientific evidence
- ***Proposal:***
- Extend allowed health claims for dietary supplements according to level of evidence for their efficacy
- Requirements for safety data should be consistent, independent of the claim made
- Regulatory hurdle should be identical for NDIs independent of their origin (extracts, fermentation, or chemical synthesis)

# Summary

- *Nutraceuticals can provide a risk reduction for disease, thus they make sense from a public health point of view*
- *They must be safe in the recommended dose as evidenced by appropriate safety data*
- *Efficacy should be evidenced by mechanistic plausibility and/or clinical data, serving as a basis for honest claims*
- *Legislation together with the Industries have to find ways that allow the first mover to protect his investment in safety & efficacy studies*

**Thank you!!!**