The Universe of « inactive » ingredients

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« inactives »

- Excipients
- Additives
- Processing aids

Excipients, the other essential ingredients of medicines

Already in 1721 in the Edinburgh Pharmacopoeia, it is stated in the preface :

> « Good medicines, properly administered, promise health; bad ones or such as are ill compounded, prove either productive of numerous mischiefs, or incapable of doing any real service to the sick »

A very early recognition of the importance of the quality of ingredients and of the process of manufacturing

Excipients, the Cinderella's of the Drug Industry

- The large majority of excipients has a main use in other domains :
  - food
  - cosmetics
  - paint
  - construction materials
  - ….
- They are bulk commodity products with prices in the $/kg area as compared to several k$/kg for active pharmaceutical ingredients

Excipients are not from outer space,

Origin of Excipients

- Food /agriculture

Origin of Excipients *(ctd)*

- Agriculture

Origin of Excipients *(ctd)*

- Mineral

Origin of Excipients *(ctd)*

- Examples

  Cellulose production 250 million tons/year

  Cellulose for pharmacy 0.05 million tons/year

  i.e. 0.02% !

  Propellants / Refrigerants HFA

  98 % for cooling

  2 % for pharmacy

The Excipient Universe

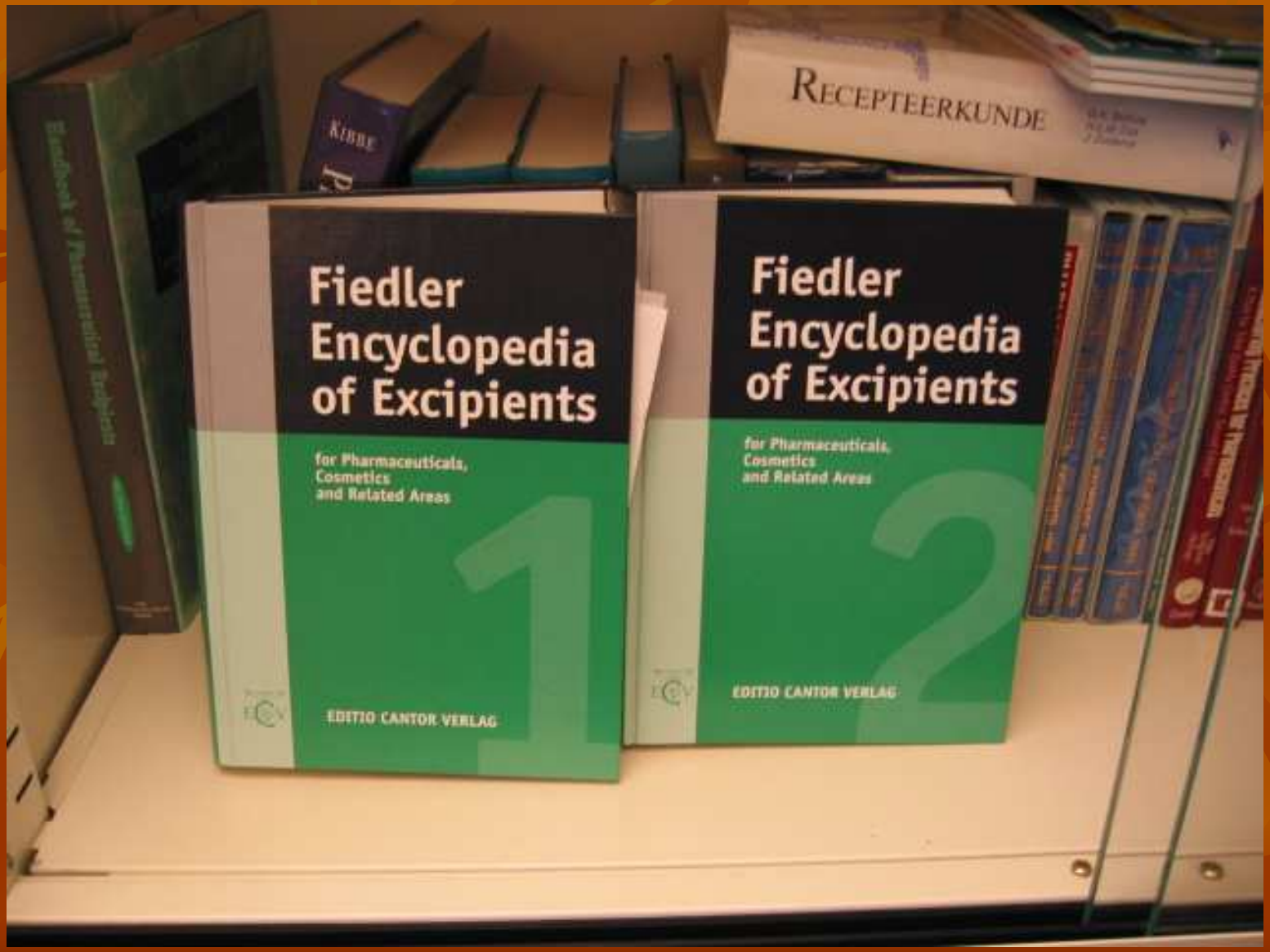
- At present about 1200 excipients in use in marketed pharmaceutical products.
  Not counting colors, flavours and fragrances
- Compendial monographs : ca. 240
- Harmonized between USA, Japan, Europe
  « almost » 40 of 61 projects, but …

International Harmonisation

- History
- Environment
- Law
- Language

ref: C.A. Johnson
FIP Congress
Dublin, 1975

Excipients, sources of information



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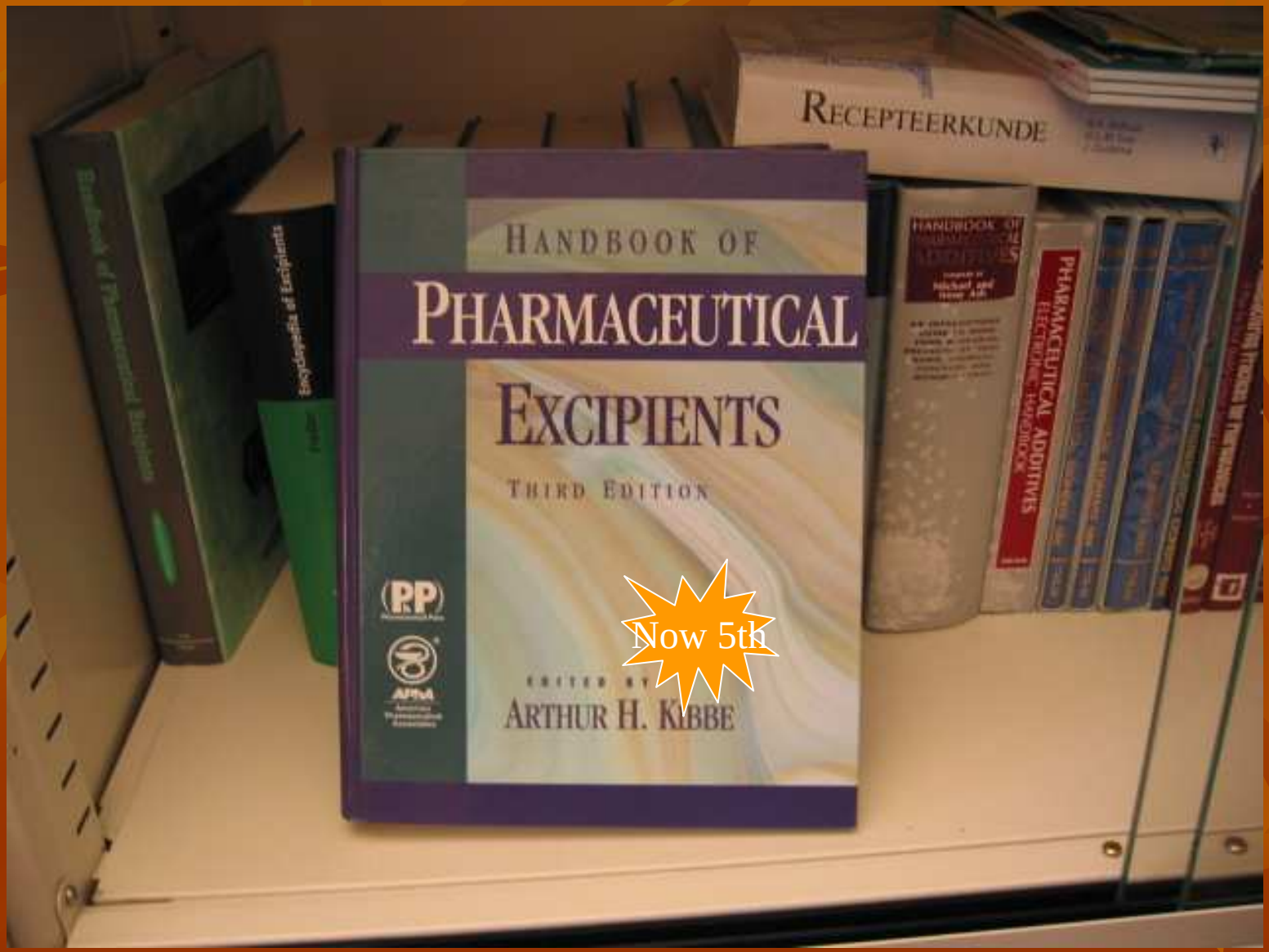

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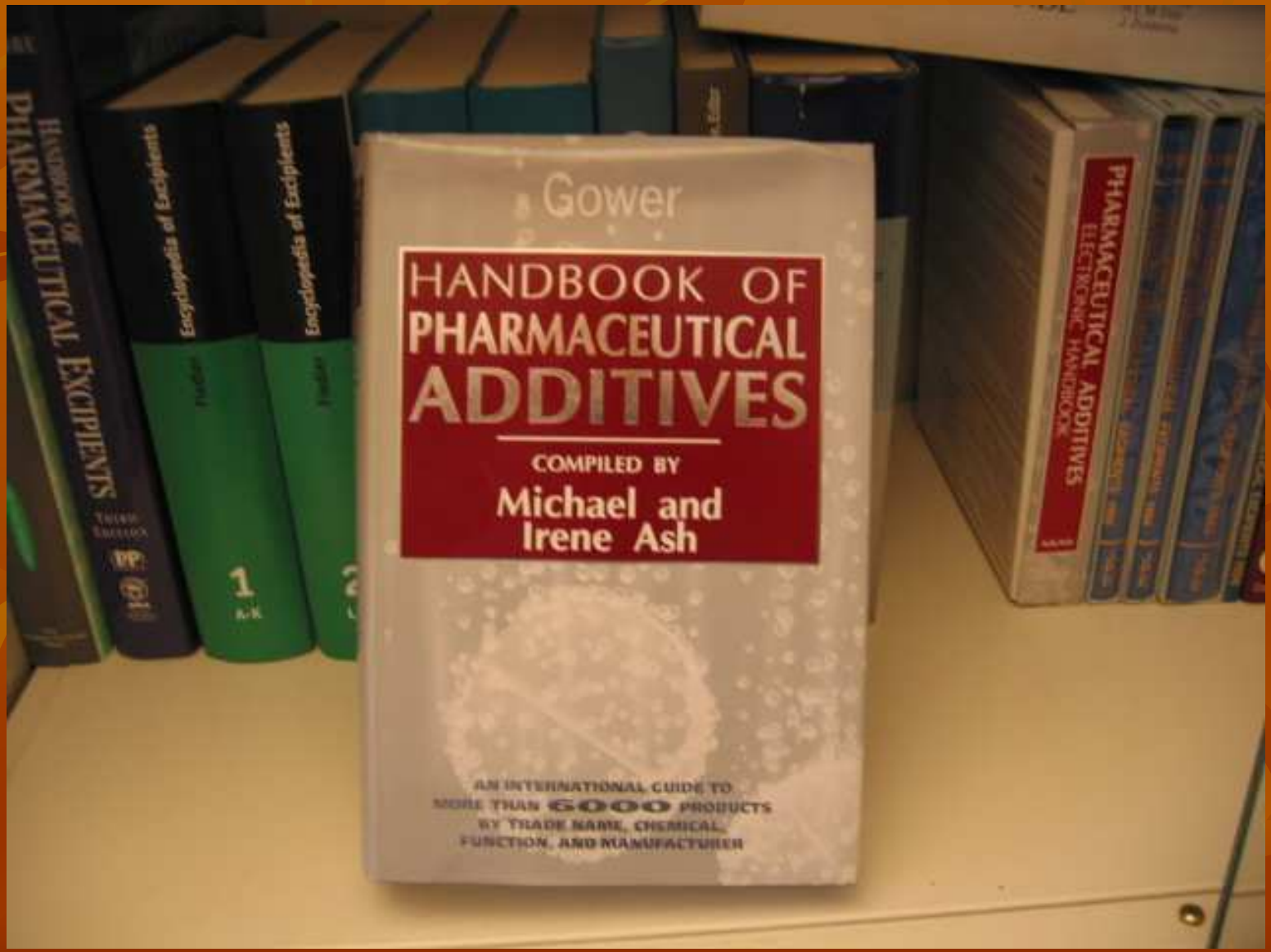

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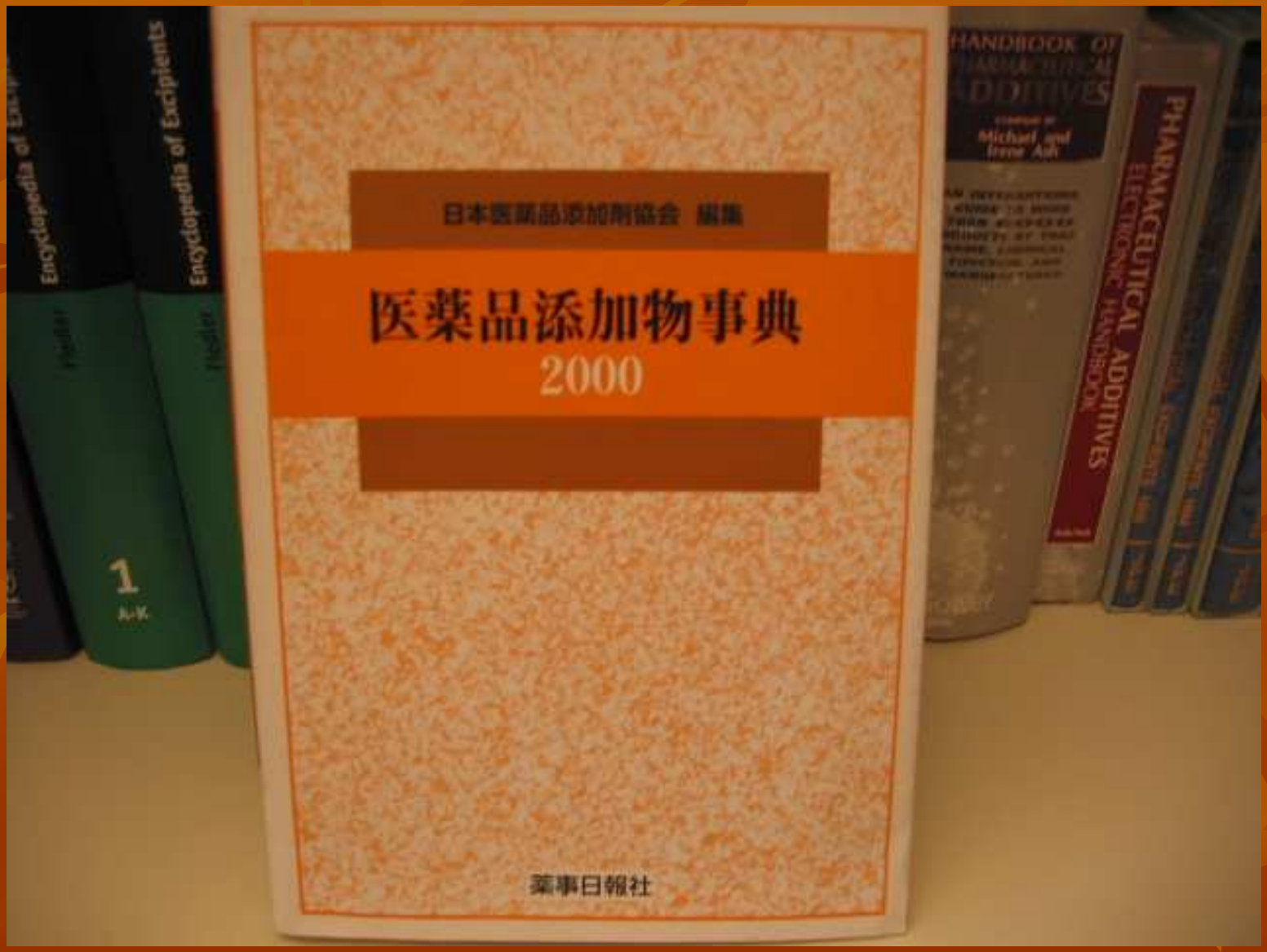

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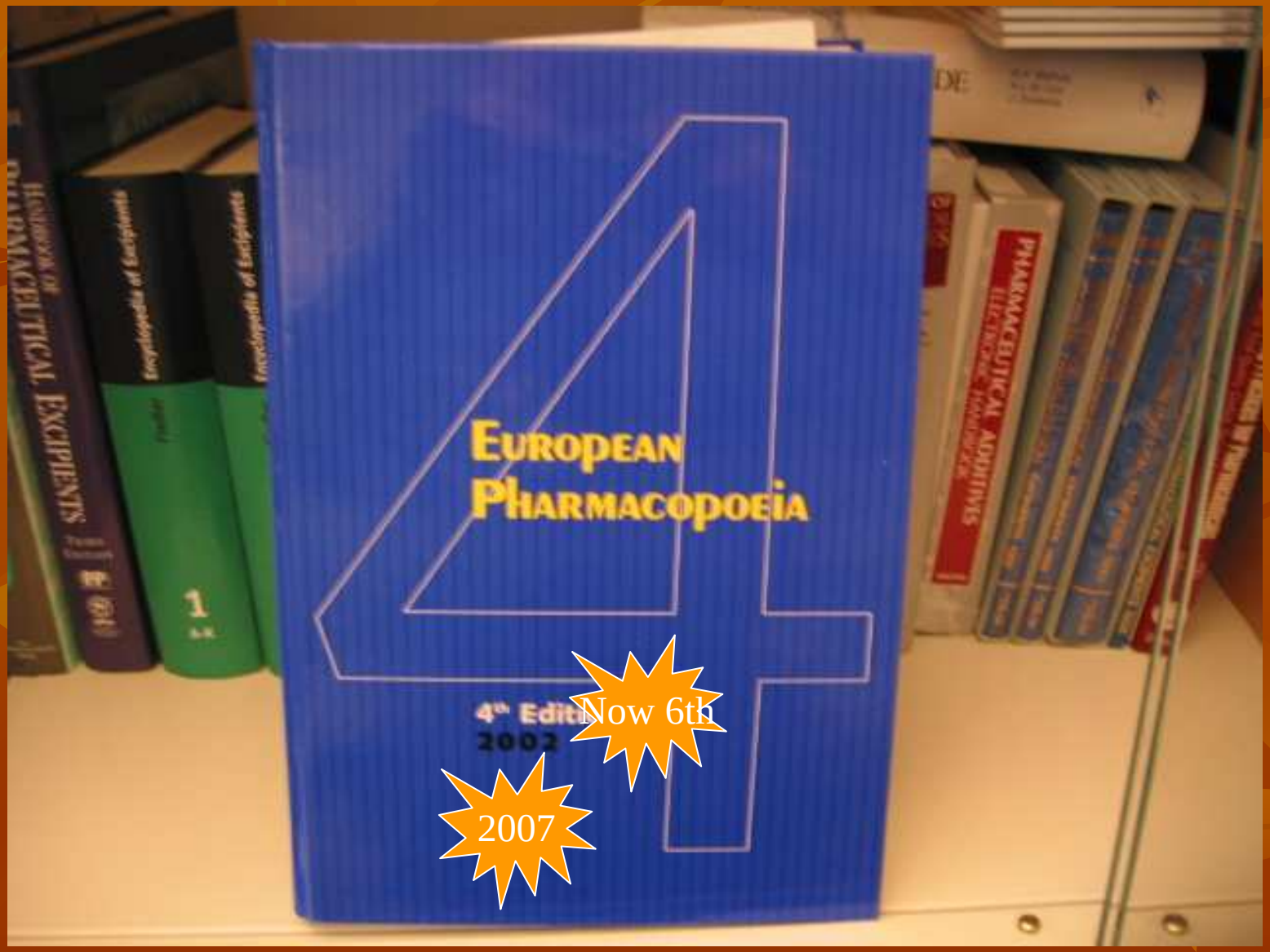

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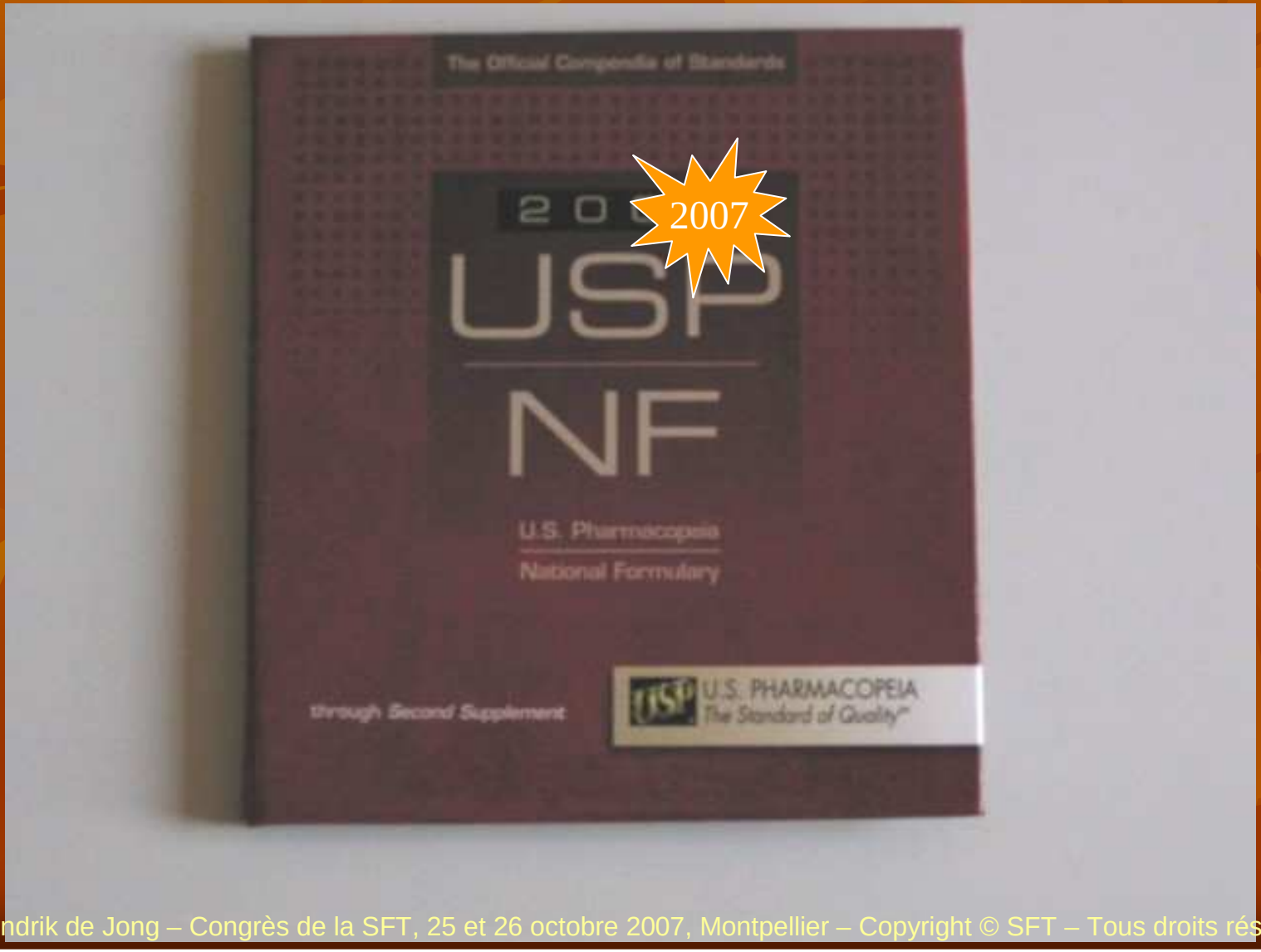

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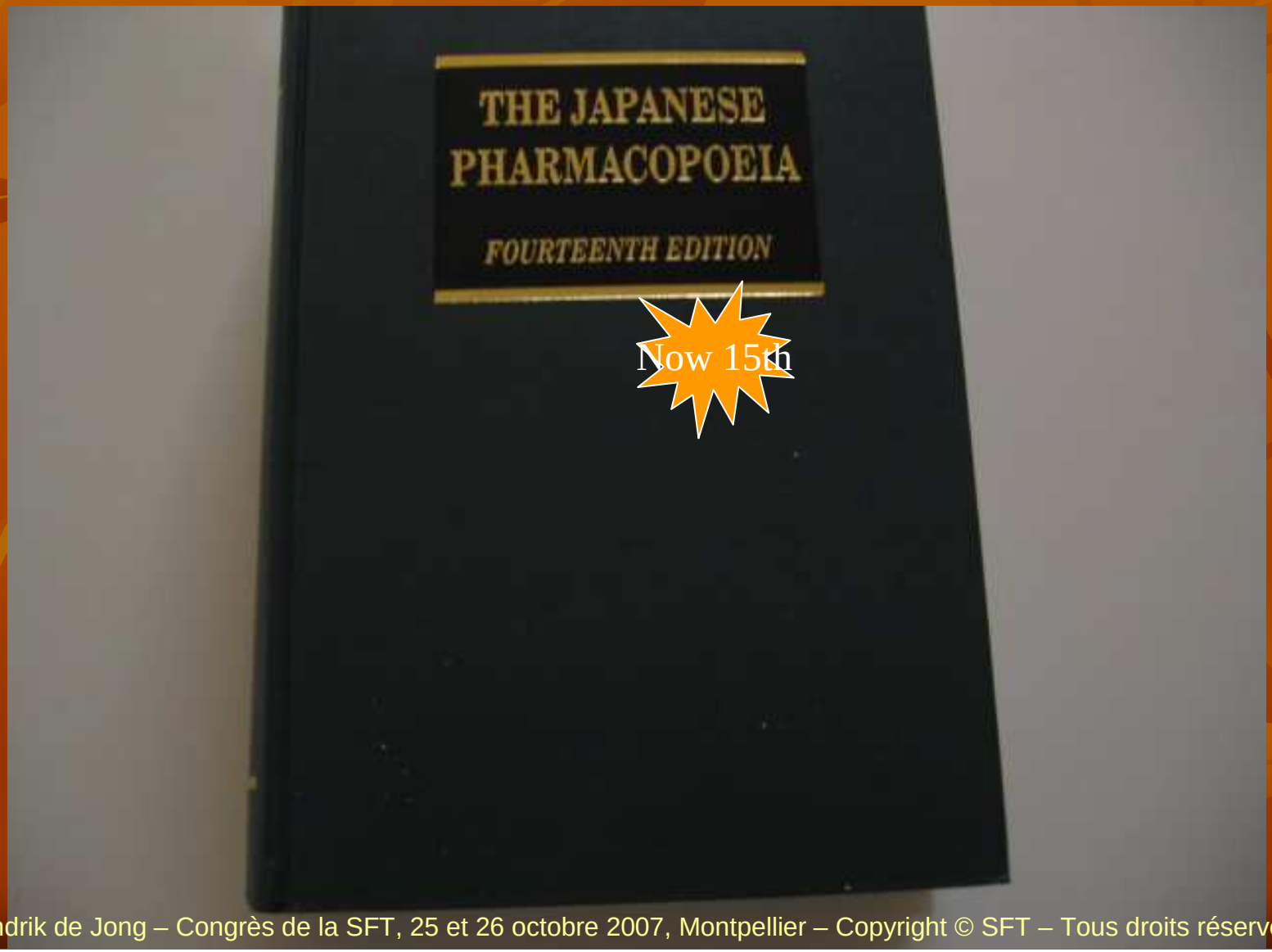

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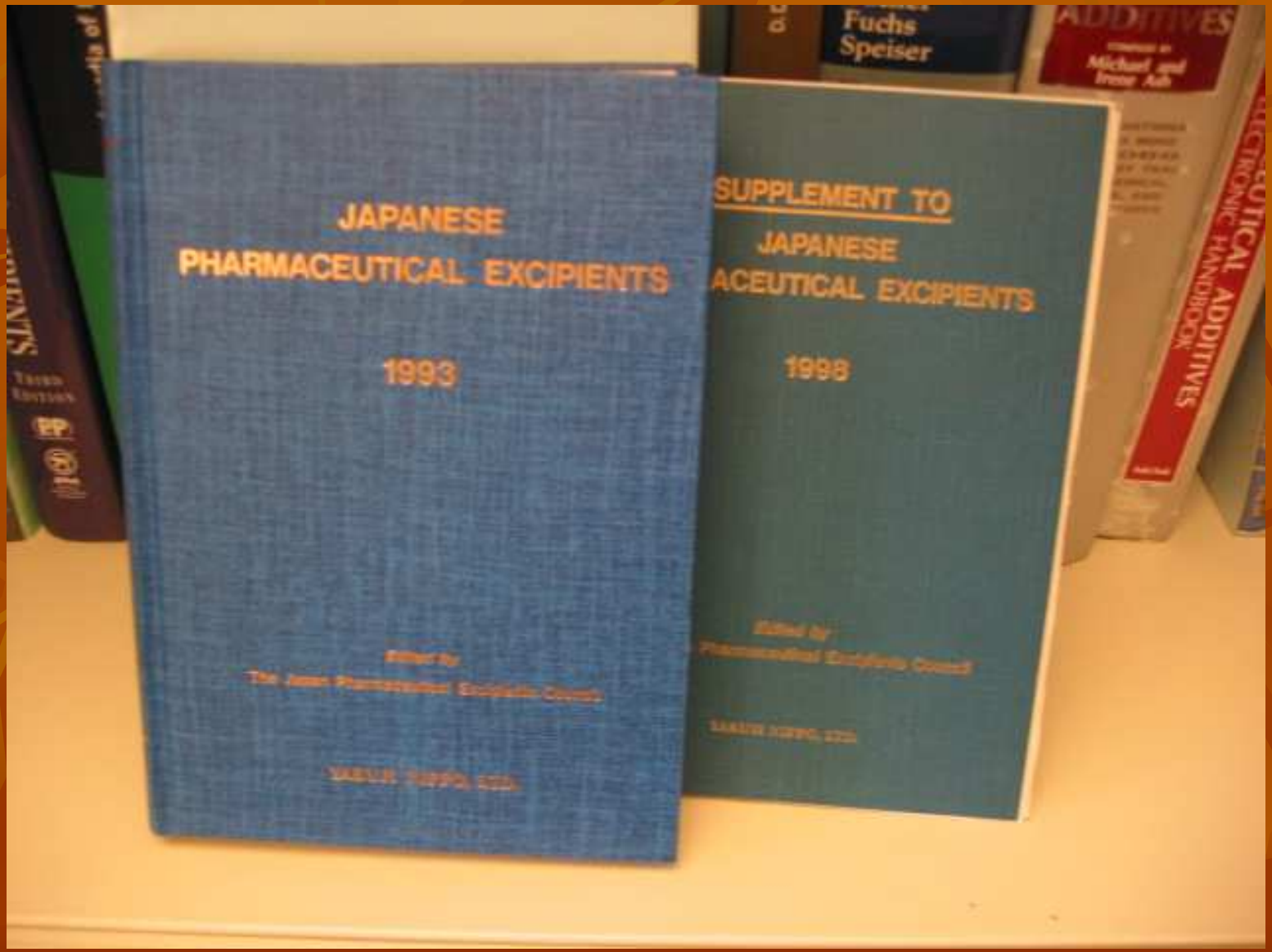

Sources of information

- USA FDA Inactive Ingredient List
- Canadian « non medicinal ingredients » list
- Japanese pharmaceutical excipients Directory, by JPEC but Official
- Tentative by IPEC-Europe based on drug catalogues e.g. VIDAL, but not complete

Documentation and Specifications needed for Regulatory Acceptance

- ICH guidance
- In EU – Notice to Applicants & Guidance
  - Pharmaceutical Development
  - Excipients described in Pharmacopoeia
  - Excipients not described in Pharmacopoeia
  - Novel Excipients

Some Issues regarding Novel Excipients

- In Europe no DMF-system (yet)
- Full submission by applicant necessary (stand alone document possible)
- Development of a new excipient is a long-term process (3 – 7 years)
- Return on investment …
- Close cooperation between manufacturer and user indispensable

Excipients origins:

- From deep in the earth: oil

Excipient origins

- From crude to refined starting materials:
- Petrolatum
- Polyglycols
- Starting materials for synthetic chemistry

Excipient origins agriculture : corn

agriculture : wheat

agriculture : sugar beet

agriculture : cotton

Excipients:
sugar, starch, cellulose
small packages and big bags

Agriculture derived excipients

- Maize, Potato, Wheat, Sugar beet, Sugar cane

  -starches

  -dextrins

  -cyclodextrins

  -sucrose

  -sorbitol

Minerals

- Talc
- Kaolin
- Sodium chloride

Processes

- From very simple to complex e.g.

Talc:

mining—drying-- milling

Sorbitol:

maize---20 steps---sorbitol

Other origins: milk or mine

collection/transportation

Bones to Gelatin

Tallow oils to glycerin and fatty acids

Types of Excipients

- Excipients also in use as API: usually one (pharma)grade is made
- Excipients developed and manufactured specifically for pharma use: special grade or grades
- Excipients coming from other areas e.g food ingredients

Excipient grade considerations

- Material should be fit for its intended use
- Food grade material usually acceptable for (oral) pharma use, however consider: functionality, interactions, stability issues
- Special grades needed for parenterals, inhalation products

Impurities in Excipients

- General:

  impurities related to

  -starting materials

  -manufacturing

  -processing aids

  contaminants to be controlled

  by GMP/ GDP

Impurities in Excipients

- Definition of the material: single or multiple component substance
- Related substances from the starting materials, the process or instability
- Additives, components added intentionally

Impurities in Excipients

- Organic impurities
- Inorganic impurities
- Residual solvents

- Pesticides, anti-fungals……
- Microbial contamination

Pharmacopoeial Excipients

- Monograph in general sufficient to distinguish technical grades from pharma
- Monograph represents acceptance criteria for general use
- Debate on functionality related characteristics ongoing
- Heavy metals test not satisfactory

Pharmacopoeial Excipients, issues

- Genotoxic impurities
- Heavy metals (residues of catalysts)
- Mycotoxins

Non pharmacopoeial excipients

- Well known substances: reference to literature
- Novel excipients: follow ICH guidance as for API, but adapted to « special case » i.e. quality, safety and functionality

Some examples:

- Inorganic impurities

-heavy metals in minerals

inorganics

hydrogenated fats

gelatin, acacia,…..

stearates

polymers

liquids (containers)

Examples:

- Inorganic impurities:

  -sulfites processing aid starches

  -radioactive nuclides

Examples:

- Organic impurities:

-proteins e.g. gluten

prion protein

-additives e.g. silicon dioxide

BHT

Tocopherol

Hydrogen peroxide

Examples:

- Organic impurities:

-monomers and processing aids in polymers; special instructions on ethylene oxide residues

-residual solvents

-pesticides

Examples:

- Organic impurities:

  -microbial contamination

  -mycotoxins

  -residues from antimicrobial treatment

Conclusions

- Definition of substance composition very important
- Knowledge of origin and main use of the substance
- Differentiate between intrinsic composition, impurities and additives
- Apply general ICH guidance for novel materials

Aknowledgments

- Thanks to my colleagues from IPEC the International Pharmaceutical Excipients Council

&

- The late Dr Dankward Jaekel (Novartis) co-founder of IPEC-Europe, author of chapter in: » Excipient Toxicity and Safety » ISBN 0-8247-8210-0 (1999)

Thank You for listening