Expectations for Implementation in Europe

Henk de Jong
IPEC Federation Observer Q3D EWG
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ICH Q3D is here

- CHMP (committee for Medicinal Products for Human Use) approved as scientific EMA-guideline the ICH Q3D guideline
- For new marketing autorisation applications: June 2016
- For authorised medicinal products: December 2017
Q3D

- The CVMP (committee for Medicinal Products for Veterinary use) decided not to apply the guideline for « products for veterinary use only »
Guidelines for Excipient GMP

- EU Guideline, applicable by 21 March 2016:

- Appropriate GMP for Excipients, based on a risk assessment/management

- Consideration given to sharing relevant information between the excipient manufacturer and the MA holder.
Excipient GMP

For each excipient from each manufacturer used, the MA holder should identify the risks presented to the quality, safety and function from its source—be that animal, mineral, vegetable, synthetic—to its incorporation in the drug product.
Risk Identification

- Transmissible spongiform encephalopathy
- Potential for viral contamination
- Potential for microbiological or endotoxin/pyrogen contamination
- Sterility assurance for excipients claimed to be sterile
Risk Identification

- Potential, in general, for any impurity originating from the raw materials, e.g. aflatoxins or pesticides, or generated as part of the process and carried over, e.g. residual solvents and catalysts.
- Environmental control and storage/transportation conditions.
Risk Identification

- Pharmaceutical form
- Proportion of the excipient
- Daily intake
- Known defects/fraudulent adulterations, both globally and at a local company level
Risk Identification

- Is the excipient a composite?
- Known or potential impact on the critical quality attributes of the medicinal product
- Other factors as identified or known to be relevant for assuring patient safety
Analytical Results so far.....

As seen from yesterday:
- Few ingredients concerned
- Iron oxides (red, yellow and black)
- TiO2
- Calcium phosphates
- Carrageenan
- Sodium alginate
Analytical results

- Results higher than 30% of PDE limit, sometimes even far above
- However quantities used very low in % of dosage form
Pharmacopoeial activities

- Review (expert groups) the meaning of the current « heavy metal test » in the sense of the new guideline
- This comes back to knowledge of « material science »
- Where does it come from, how is it made, what are the falsifications……
- International harmonisation….WHO…?
Gap analysis

- What is needed versus what exists
- Who will be doing all the visits, write the reports……
- 3rd party inspections
- Contract laboratory data?
- Data base for excipients?
- When analysed: conformity with Q3D
JOBS

- Analysts analyze
- Formulators formulate
- Producers produce
- Suppliers provide

And they should talk together…….
Analysts have to produce:

- Qualified
- Relevant information on
- Materials and Processes
- In an Optimal way

Gottschalk 1972  Z.Anal.Chem, 258 (1972) 1
Kaiser 1974  idem, 272 (1974) 186
Compendia can be helpful

- In providing standardised methods, proven to work everywhere in a reliable way
What to analyse?

- A sufficiently **representative** sample to be **treated** in such a way that the **measurement** can yield **meaningful** results
Visual/organoleptic versus Instrumental methods

- Visual/organoleptic « simple, cheap and easy »
  In reality: not so simple, difficult to transfer, lengthy and often « dirty »

- Instrumental, expensive, need for highly skilled operators
  Investment important, however running costs usually low
Uses of results:

- « Simple » verification of acceptance criteria
- On-line feedback to control process
Formulators formulate

- Active ingredient(s)
- Excipients
- Processes & Machinery
- Container closure systems

And they need to know their ingredients
Excipients and Active’s origins:

- From deep in the earth:
- oil
Origins

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

agriculture : corn
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/corn---20 steps---sorbitol
Other origins: milk or mine
collection/transportation
Bones to Gelatin
Tallow oils to glycerin and fatty acids
Excipients

- A very diverse collection of materials
- About 1200 ingredients in use in marketed pharmaceutical products (not counting colors and flavours)
- About 250 documented in the European Pharmacopoeia
- Now 60 monographs in the international harmonisation process between: USP, JP and PhEur
Pharma use of Excipients

- Contrary to APIs, excipients are usually not specifically made for use in medicinal products:

- **Examples**:
  - Cellulose production 250 million t/y
  - Cellulose for pharma 0.05 million t/y

**Propellants/Refrigerants**:
  - HFA 134a (norflurane): 98% for cooling, 2% for pharma
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 but also construction materials
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.
Pharmacopoeial excipients

- Monograph usually sufficient to characterise safe ingredient
- Functionality related characteristics?
- Counterfeit ingredient detection?

- How well do we know our materials e.g. sodium chloride vs HPMC?
Pharmacopoeial actives

- Monograph usually sufficient to define safe ingredient
- Monograph together with a COS for an inspected manufacturer is « gold standard »
- Globalisation provokes needs for new approaches to control systems
Conclusions:

- Definition of substance composition very important
- Knowledge of origin and main use of the substance should be known, to allow for a risk analysis
- Differentiate between intrinsic composition, impurities and additives
Producers produce:

- Ideally integrating the knowledge from R&D on ingredients and process
- PAT can strongly contribute to modernise manufacturing of high quality medicinal products
New technologies to consider

- Hyphenated techniques like LC-MS and GC-MS, especially TOF-MS
- ICP-OES and ICP-MS
- X-ray fluorescence
- NIR and Raman spectrometry (and imaging)
- Solid state NMR
Hyphenated « chromato-spectro » techniques

- Qualitative or even structural information obtainable « on the fly »
- Diminishes the need for impurity reference substances (peak identification)
ICP-OES and ICP-MS

- Versatile techniques applicable to all metals including « heavy metals »
- Multi- or single-elemental analysis
- Low detection limits
- Sample preparation techniques to be standardised and simplified
X-ray fluorescence

- Versatile technique
- Single- or multi-elemental analysis
- Sample preparation simple
- Low detection limits
Merci beaucoup, from the Q3D team for your interest