CBC-PROCOS S.p.A.

Strategies to minimize the impact of presence of residual solvents in APIs

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Agenda

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Definitions

***Organic volatile chemicals*:**

- **used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products**
- **not completely removed by practical manufacturing techniques.**

Relevant CTD sections for solvents

MODULE 3

Module 3	
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Main relevant API DMF sections for solvents

3.2.S.2.2 Description of manufacturing process and in process control

3.2.S.3.2 Impurities

3.2.S.4.1 Specification

3.2.S.4.2 Analytical procedure

3.2.S.4.3 Validation of analytical procedure

3.2.S.4.5 Justification of specification

Where to start?

- **ICH guideline Q3C**
  http://www.ich.org/home.html
- **USP <467> (Chemical tests – Residual solvents)**
- **EP <5.4> Limiting residual solvents level in active substances, excipient and medicinal products**
- **Annexes to:**

  CPMP/ICH/283/95 Impurities: Guidelines for residual solvents

  CVMP/VICH/502/99 Guidelines on impurities: Residual solvents

But….more if genotoxic compounds

Guideline approach

- **Classification of solvents based on their severity**
  - ***Class 1 solvents: Solvents to be avoided***
  - ***Class 2 solvents: Solvents to be limited***
  - ***Class 3 solvents: Solvents with low toxic potential***
  - ***Others***

- **Limit definition**
  - ***ESTABLISHED IN TABLES (based on daily dosage of 10 g)***
    NO FURTHER CALCULATION IS REQUIRED
  - ***CASE BY CASE : ON PDE and DAILY DOSAGE***

Recent Updatings (June 2015)

- **MIBK will be placed into Class 2 (limited by health-basis) from Class 3 (no health-based).**

- **New solvent Triethylamine has also been included in Class 3.**
  - **New limit: ≤ 0,5%**
  - **Q&A EDQM (320 ppm for 10 g daily dose, based on a Permitted Daily Exposure of 3.2 mg/day)**

TABLE 1. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	*Concentration limit (ppm)*	*Concern*
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

TABLE 3. Class 3 solvents which should be limited by GMP or other quality-based requirements.

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Dimethyl sulfoxide	2-Methyl-1-propanol
Ethanol	Pentane
Ethyl acetate	1-Pentanol
Ethyl ether	1-Propanol
Ethyl formate	2-Propanol
Formic acid	Propyl acetate

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	*PDE (mg/day)*	*Concentration limit (ppm)*
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene[1]	0.7	70
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone[2]	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran[3]	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene*	21.7	2170

*usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene

Strategy of control & impact at API level for solvents used in manufacturing

- Knowledge of the solvents used in the manufacturing process (and preferably in the key starting material)
- Evaluation of the capability of the manufacturing process to remove them by:
  - Distillation
  - Drying

  ...

  Class 2, 3 if demonstration of absence at intermediate or API level (≤10%ICH limit)

  ⇩

  NO NEED OF ROUTINE ANALYTICAL CHECK
- Scientific identification of solvents « likely to be present» to be included in the API specification

Strategy of control & impact at API level: solvents used

API specifications

***Class 1*: normally absent**

***Class 2*: listed with ICH limits, GC routinely tested**

***Class 3 (only)*: monitored by LOD**

If *Class 2* + *Class 3 solvents*: listed with ICH by GC + LOD or only GC

***Other solvents (only)*: listed with justified limit; skip test could be accepted**

Strategy of control & impact at API level : toxic solvents as «by products» or used

- Limits set as for TTC approach (ICH M7 or Guideline on the limits of genotoxic impurities' EMEA/CHMP/QWP/251344/2006),
- GC validated analythical method
- Routinely check, if present
- If introduced at intermediates :demonstrated ≤30% below the ICH limit on 6 pilot or 3 industrial batches for API, API no routine test is required (Skip test)+ limit at intermediate
- If introduced at final stage :skip test if demonstrated ≤ 30% below the ICH limit at API

Strategy of control & impact at API level: example of toxic solvents as by products

- **Benzene**
  - Acetone
  - Methanol
  - Toluene
  - Epthane
  - …

- **Mesityl oxide**
  - Acetone

Equipments

- **GC systems with different injection mode and detectors**
  - Injection mode
    - Liquid (direct) injection
    - Head space (HS)
  - Detectors
    - Flame ionization detector (FID)
    - Thermal conductivity detector (TCD)
    - Mass spectrometer (MS)
- **LC systems equipped with UV/PDA detectors for particular applications (es. Formamide)**

Solvents may impact on physical properties of API

- **Caking (the formation of lumps or hard blocks which reduce the flowability of solids) is produced by bulk cohesive strength between particles named as "solid bonds"**

- **Residual of solvents facilitate to create the solid bonds as for the follow:**

Understanding powder caking: Predicting caking strength from individual particle contacts

M. Wahl [a], U. Bröckel [a], L. Brendel [b], H.J. Feise [c,*], B. Weigl [c], M. Röck [d], J. Schwedes [d]

[a] University of Applied Science Trier, Germany
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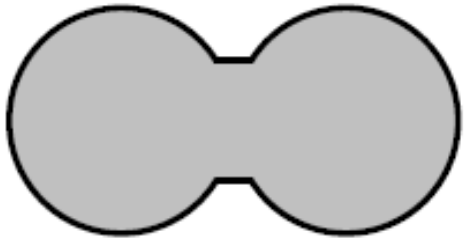
[c] BASF SE, Ludwigshafen, Germany
[d] Technical University Braunschweig, Germany

Impact on physical properties of API: caking

Solid bond bridge

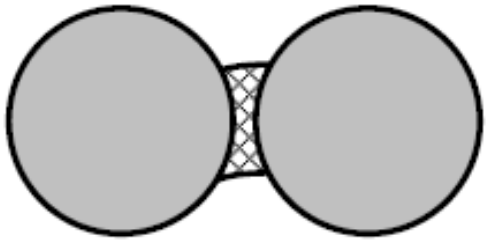
a) Sinter bridge, melt bridge



Solid partially melt and solidify again. During melting and solidification solid bonds are formed.

Temperatures of 1/3 – 2/3 of melting temperature cause solid bond during long time storages

b) Catalyzed solid, crysallising binder



Solid partially dissolves into the water or solvent adsorbed onto the surface and then precipitate again. During dissolution and precipitation solid bonds are formed

0.1% - 0.5% of water / solvent are enough for solid bonds formation.

Post approval changes for solvent EU vs US: an evaluation

Change description	US	EU
Solvent change before final intermediate	CBE 30	II or IB
Solvent change after final intermediate	PAS	II or IB
Solvent change with impact on impurity profile	PAS	II

Guidance for Industry - Changes to an approved NDA or ANDA

Reg CE 1234/2008

QUESTIONS?

Thanks for your attention!

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