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Setting HBEL for highly hazardous products to ensure patient safety – application of the Q&A

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Contents

History

- EU directive 2003/94 Article 8 para 2
  - ..manufacturing… laid out in such a way as to minimise the risk of error ..permit effective cleaning…..to avoid contamination, cross contamination and … any adverse effect on the quality

- Historically 1/1000th of lowest clinical dose or 10 ppm used as limits for cross contamination
- Concept paper EMA/CHMP/SWP/598303/2011
  - Limits arbitrary and not pharm/tox (science) based
    - may be too restrictive (not highly hazardous products)
    - not restrictive enough (highly hazardous products)

- Resulted in EMA/CHMP/CVMP/SWP/169430/2012
  - Objective: recommend an approach to review and evaluate pharmacological and toxicological data to enable determination of threshold levels as referred to in the GMP guideline.

Ensuring patient safety and pharmaceutical quality

- Medicinal products should
  - meet pharm/tox (science) based acceptable limits
  - meet pharmaceutical quality based acceptable limits

- Deriving HBEL from pharm/tox data
  - Calculating compound specific PDEs using all available animal and human data
- HBEL > good pharmaceutical quality limit, use good pharmaceutical quality limit
- Use adjustment factors to set cleaning limits that ensure pharmaceutical quality and acceptable risk level for patient exposure

Guideline on setting health based exposure limits

- Objective: recommend an approach to review and evaluate pharmacological and toxicological data to enable determination of threshold levels as referred to in the GMP guideline.
- Method to derive health based exposure limits for a residual active substance is based on the so-called Permitted Daily Exposure (PDE) as described in residual solvents guidance
- PDE derived assuming human exposure
    - adaptation to animal species for veterinary products
    - usually as dose/kg (VICH GL 18)
    - considering highly sensitve species
- Veterinary products for food-producing animals need to be consumer and vet-protective

HBEL needed to ensure patient safety

- To do a full toxicological assessment requires toxicological expertise and is a major task

- Full toxicological assessment or even sufficient toxicological data may not be publicly available for all pharmaceutical products to derive a HBEL

- For products with a well established clinical safety profile and favourable therapeutic window a full toxicological assessment may not be necessary to establish an acceptable HBEL

The Q&A
(EMA/CHMP/CVMP/SWP/463311/2016)

Approaches to derive a HBEL

- For highly hazardous products
  - Full toxicological assessment including all available animal and human data to derive acceptable HBEL
  - OEL data based on full risk assessment by a well known authority can be used to derive HBEL (adjustment factors usually needed to adjust for target population)
- For products not considered highly hazardous
  - Full toxicological assessment to derive HBEL
  - Use of OEL (from well known authority) to derive HBEL
  - Use of clinical data only for products with a well established clinical safety profile
    - adverse effects occur only orders of magnitude above therapeutic doses

Highly hazardous products
HHP

Highly hazardous products

EMA/CHMP/CVMP/SWP/463311/2016

- Can cause serious adverse effects at low doses
  full toxicological assessment to derive safe HBEL considered necessary

- Can in most cases be identified on their inherent pharm/tox characteristics such as e.g.
  - mutagenic compounds, potentally or know human carcinogenic
  - teratogenic and reproductive toxicants causing effects at low doses
  - seriously target organ toxic at low doses (~ < 10 mg/d clinical, ≤ 1 mg/kg/d animal)
  - Highly pharmacological potent (i.e. daily dose ≤ 1 mg/d)
  - Highly sensitising potential – should be handled in dedicated facilities (ICH Q7) unless consumer protective levels can be determined and ensured in production

Examples for highly hazardous drugs

- Cytotoxic/mutagenic anticancer drugs like alkylating cytostatics such as
  - Cyclophosphamide, temozolomide, anthracyclins like doxorubicin

- Contraceptives and sexual hormones such as
  - Cyproteronacetate, estrogens, progesterons
- Some immunosuppressive drugs such as
  - mycophenolate
- Receptor agonists such as
  - Retinoids, high potent AHR agonists and CAR agonists

Calculation of HBEL

- Derive PDE from toxicological data (NOAEL or justified BMD) with full toxicological assessment

- Use of TTC for mutagenic compounds (considered as extremely toxic)
    - This approach would be considered as conservative enough

Products not considered as highly hazardous

Acceptable limits for not highly hazardous products

- 1/1000th of therapeutic lowest clinical dose

$$MACO = \frac{TDD_{previous}\ x\ MBS}{SF(1000) x\ TDDnext}$$

- Calculation of HBEL from toxicological data

$$PDE = \frac{NOAEL}{F1\ x\ F2\ x\ F3\ x\ F4\ x\ F5}$$

  - Additional factors may be for residual uncertainties

- From a toxicologic point of view
  meeting the PDE as ADI for cross-contaminants in the next product in a worst case senario (maximum daily therapeutic dose) would be sufficient.

Modifying factor used in PDE calculation

factor	range	description
F1	2-12	Interspecies extrapolation (mouse=12, dog=2)
F2	10	Inter-individual differences
F3	1-10	Accounts for study duration, 10 for ≤ 4weeks repeated dose study
F4	1-10	Severe toxicity, e.g. teratogenic = 10
F5	1-10	Account for LOEL and severity of effect (NOEL =1)

Additional modifying factors may be appropriate to account for residual uncertainties not covered by MF 1-5, e.g. lack of reprotox data

Sources for toxicological data for PDE calculation

- Pharmacological/Toxicological data
  - SmPC 5.2 and 5.3 contain data of clinical and preclinical pharmacokinetic and pharmacological data and human releant toxicological data

- Other public sources such as
  - Toxnet, ToxRefDB, ACToR
  - OELs derived by competent authorities or originator to ensure workers safety (WHO, OSHA, MAK)
  - ECHA database of registered compound data (https://echa.europa.eu/information-on-chemicals/registered-substances)

Ensure pharmaceutical quality

- EU directive 2003/94 Article 8 para 2
  - ..manufacturing… laid out in such a way as to minimise the risk of error ..permit effective cleaning…..to avoid contamination, cross contamination and … any adverse effect on the quality

- Effective process control strategies should be applied in manufacturing

Pros and Cons of these approaches

Disadvantage in having the PDE approach only for all compounds

- To perform a full toxicological assessment requires toxicological expertise
  - This expertise may not be available at all SMEs
  - Buying in of expertise needed

- Money and time consuming process for SMEs

- May not be needed for not highly hazardous products
  - 1/1000th of lowest therapeutic dose method conservative enough to ensure safe HBEL setting

Advantage of a flexible approach

- Full toxicological assessment only required for products with a real safety concern
    - Highly hazardous products
        - Mutagenic compounds
        - Highly pharmacologically potent compounds
        - High teratogenic/reproductive toxic compounds
        - Highly sensitizing compounds
- For products of low toxic concern the old 1/1000th of the therapeutic dose is considered conservative enough to derive and ensure setting of an acceptable HBEL
- Companies only producing products of low toxic concern do not need to buy in toxicological expertise

Potential points for controversy

- Q&A looks like zigzag-ing between the old approach and the guidance (EMA/CHMP/ CVMP/ SWP/169430/2012)

- The border between highly hazardous and not highly hazardous compounds cannot be clearly defined
    - The recommendation in Q&A Q2 are intended to give a conservative guide

- Defining the most relevant effect in chronic toxicology studies and the most relevant study may vary.

Examples how to derive a HBEL - Highly hazardous compound

Tacrolimus has been produced as previous product

- Tacrolimus is a potent immunosuppressant used in organ transplantation surgery
- The minimum therapeutic dose is 3.75 mg/d or (75µg/kg/d), (range 0.075-0.2 mg/kg/d, heart – kidney transplants)
- starting doses are even lower (range 0.01 – 0.05 mg/kg/d) (high pharmacol. potency)
- Kidney is a major target organ of toxicity, nephrotoxicity the most frequent adverse reaction at clinical doses
- Maternal effects, developmental effects in rabbits with LOAEL 0.32mg/kg/d (< 1mg/kg/d)
- OEL (TWA) 0.2 µg/m^3 (internal value from Astagraf Safety Data sheet, publicly available on internet, without specifying data)
  - 0.2 µg/m^3 x 10 = 2 µg/d < 10 µg/d

- Tacrolimus should be regarded as highly hazardous and a full toxicological assessment should be performed

Tacrolimus data sources

- Good sources for medicinal products are
  - Toxnet
    - Summarizes data of various free databases, mostly detailed study information
  - PI (US-FDA) or SmPC (Europe)
    - Available in the world wide web, PDR, pharma companies
    - Clinical as well as relevant preclinical data however sometimes without dose details
  - Occupational limits (OEL)
    - Data used for calculation of the OEL should be available (this is not the case for the OEL set for Astagraf found on the safety data sheet)

Tacrolimus PDE calculation

- Min therapeutic dose 3.75 mg/d
- PDE calculated from preclinical animal data
  - the reprotox study in rabbits is considered as the most relevant tox study here
  - rabbit reprotox LOAEL 0.32 mg/kg/d (Toxnet HSDB)
    - $PDE = \frac{0.32 \frac{mg}{kg}/d}{2.5\ x\ 10\ x\ 1\ x\ 10\ x\ 10}$ = 0.13 µg/kg/d or 6.5 µg/d for an adult

F1 = 2.5 for rabbit, F2 = 10 for interindividual variance, F3 = 1 for reprotox study covering full organogenesis, F4 = 10 teratogenic effects, F5 = 10 for LOAEL

Examples how to derive a HBEL - Low hazardous compound

Lithium carbonate has been produced as the previous product

- Lithium salts are use as antipsychotic drugs (mania, bipolar disorder recurrent unipolar depression)
- Recommended therapeutic doses 900 – 2400 mg/d of lithium carbonate
- Major target organs for toxicity under therapy are kidney and thyroid
- Full two generation reprotox-study (GLP) in rat publicly available [https://echa.europa.eu/registration-dossier/-/registered-dossier/15034/7/9/2]
    - NOAEL determined with 45 mg/kg/d
- OEL 2.34 mg/m^3 (SER Netherlands)

- Data justify lithium corbonate to considered as low hazardous compound

Lithium data sources

- Toxnet
  - No relevant animal data available
- SmPC at [www.medicines.org.uk]
  - No relevant preclinical data
- ECHA registered substances database
  - Full mixed dossier with a GLP 2 generation reprotox study [https://echa.europa.eu/registration-dossier/-/registered-dossier/15034/7/9/2]

Lithium carbonate PDE calculation

In this case the extensive human data available clearly require a safety assessment based on human data

- PDE (oral) calculated from human clinical data
  - recommended approach: use 1/3 of the lowest human daily dose
  - $PDE = \frac{300\ mg/d}{1\ x\ 10\ x\ 1\ x\ 1\ x\ 10}$ = 3 mg/d or 60 µg/kg/d

What would be the PDE derived from animal data

- PDE calculated from preclinical animal data
  - the reprotox study in rats is considered as the most (only) relevant tox study available
  - rat reprotox NOAEL 45 mg/kg/d (ECHA)
    - $PDE = \frac{45\ \frac{mg}{kg}/d}{5\ x\ 10\ x\ 1\ x\ 1\ x\ 2\ (x10)}$ = 450 (45) µg/kg/d

F1 = 5 for rat, F2 = 10 for interindividual variance, F3 = 1 for reprotox study covering full organogenesis, F4 = 1, F5 = 2 for NOAEL

- Due to the limited animal data available an additional modifying factor of up to 10 for residual uncertainty may apply

HBEL using the 1/1000th approach

- 1/1000th of therapeutic lowest clinical dose

$$\text{HBEL} = \frac{900\ mg/d}{1000} = 900\ \mu g/d \text{ or } 18\ \mu g/kg/d$$

This approach would also ensure a conservative and protective setting of a HBEL

Conclusion and future needs

- The flexible approach dependent on product potency as outlined in the Q&A provides a pragmatic approach to ensure HBEL for cross-contaminants
- Need for full toxicological assessment for products of high concern (highly hazardous products)
  - the 1/1000th of the therapeutic dose may not ensure setting of HBEL for these products
- Flexible approach for not highly hazardous products
  - Full toxicological assessment or
  - 1/1000th of the therapeutic dose
  - Both methods are considered to be sufficient to ensure HBEL, however also pharmaceutical quality needs to be ensured

- Pragmatic approach to avoid full toxicological assessment when not needed for setting of HBEL

Thank you very much for your attention!

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