A detailed look at impurities in medicines

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Quality?

*Continuity* from clinical trial to supply in the year 2030? And allowing changes on the way?
<table>
<thead>
<tr>
<th>Major</th>
<th>Minor?</th>
<th>Tiny</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible?</td>
<td>UV detection</td>
<td>Mass spectrometry?</td>
</tr>
<tr>
<td>Acute?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Major

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Identification of a propantheline analog in propantheline bromide tablets
‘An official sample of propantheline bromide tablets was analyzed, using the LC method described later in this paper, and determined to contain only 60% of the stated content of propantheline bromide. The product … contained a mixture of propantheline bromide and approximately 40% of a closely related impurity.’
Propantheline Tablets

**General Notices**

**Action and use**

Anticholinergic.

**DEFINITION**

Propantheline Tablets contain Propantheline Bromide. They are coated.

*The tablets comply with the requirements stated under Tablets and with the following requirements.*

**Content of propantheline bromide, C$_{23}$H$_{30}$BrNO$_3$**

95.0 to 105.0% of the stated amount.

**IDENTIFICATION**
Minor?
Drug substances

Specifications

• Appearance
• Chemical and stereochemical identity
• Crystalline form
• Physical properties
• pH, colour and clarity of solution
• Assay
• Impurities (Inorganic, Organic)

Reduce risk
But how to set?
Drug substances

Inorganic impurities

- Moisture (≤ 0.5%)
- Sulphated ash / Residue on ignition (≤ 0.1%)
- Heavy metals (≤ 20 ppm)
- Other metals (e.g. catalyst residues)

Accepted limits reduce argument
Impurities

Australian Guidelines for the Registration of Drugs (AGRD, 1992)

BP = Official standard; ‘non-transparent’ : ‘Any secondary spot <1%’

Otherwise, the AGRD recommended the following:

**Active Ingredient:**
- Identified: each NMT 0.5%
- Unidentified: each NMT 0.1%
- also residual solvent limits

**Finished Product:**
- Any individual: NMT 1%
- Total: NMT 3%
Tryptophan continued

• essential amino acid

• eosinophilia-myalgia syndrome circa 1,500 cases permanent disability at least thirty-seven deaths
Tryptophan

Impurities now controlled in pharmacopoeial monographs

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Drug substances
Organic impurities:

How to test?

From where?

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TLC plate by Natrij 2004
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Drug substances
Organic impurities

• Solvents
• Reagents
• Starting materials
• Intermediates
• Reaction by-products
• Degradation products
• Polymorphs
New drug substance

Related substance impurities - ICH Limits

• Unidentified impurities

<table>
<thead>
<tr>
<th>Maximum daily dose¹</th>
<th>Reporting threshold²⁺³</th>
<th>Identification threshold³</th>
<th>Qualification threshold³</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2g/day</td>
<td>0.05%</td>
<td>0.10% or 1.0 mg per day intake (whichever is lower)</td>
<td>0.15% or 1.0mg per day intake (whichever is lower)</td>
</tr>
<tr>
<td>&gt; 2g/day</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>
Qualification

- Below the automatic qualification threshold of the ICH guideline
- Specified in official monograph with matching limit
- Significant metabolite
- Present in similar or higher levels in a product marketed in Australia
- Toxicological data demonstrating safety (studies or literature)
# New drug product

## Thresholds for degradation products in new drug products

**ICH Topic Q 3 B (R2)**

<table>
<thead>
<tr>
<th>Reporting Threshold</th>
<th>Maximum Daily Dose(^1)</th>
<th>Threshold(^2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 g</td>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>&gt; 1 g</td>
<td></td>
<td>0.05%</td>
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<th>Threshold(^2,3)</th>
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</thead>
<tbody>
<tr>
<td>&lt; 1 mg</td>
<td></td>
<td>1.0% or 5 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>1 mg – 10 mg</td>
<td></td>
<td>0.5% or 20 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt;10 mg – 2 g</td>
<td></td>
<td>0.2% or 2 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g</td>
<td></td>
<td>0.10%</td>
</tr>
</tbody>
</table>

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</thead>
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<tr>
<td>&lt; 10 mg</td>
<td></td>
<td>1.0% or 50 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>10 mg – 100 mg</td>
<td></td>
<td>0.5% or 200 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt;100 mg – 2 g</td>
<td></td>
<td>0.2% or 3 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g</td>
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<td>0.15%</td>
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Generic medicines

Impurities in different tablet formulations
(generalised data)
Does it work?

Validation of analytical procedures

If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products … this should include samples

• stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis and oxidation

• peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component (e.g. diode array, mass spectrometry).

ICH Topic Q 2 (R1)
Active ingredients

Residual solvents
ICH limits based on toxicological data and permitted daily exposure (PDE) via medicine:

• **Class 1: to be avoided**
  – e.g. Benzene ≤ 2 ppm; Carbon tetrachloride ≤ 4 ppm

• **Class 2: to be limited**
  – e.g. Acetonitrile ≤ 4.1 mg/day, Methanol ≤ 30.0 mg/day

• **Class 3: to be limited by GMP considerations**
  – e.g. Acetone, Ethanol, Ethyl acetate
Guideline on the limits of genotoxic impurities
(EMEA/CHMP/QWP/251344/2006)

Genotoxicity:

- ‘positive findings in established in vitro (e.g. Ames test, chromosomal aberration test) or in vivo genotoxicity tests with the main focus on DNA reactive substances that have a potential for direct DNA damage.’
- encompasses mutagenicity through DNA reactivity, DNA damage, and chromosomal damage, both structural chromosome breakage and aneuploidy
- based on evidence for ‘threshold related mechanism’ but if a substance acts directly with DNA then there is no ‘safe exposure level’ (i.e. no threshold mechanism)
  - Type 1. With sufficient evidence, calculate PDE as per ICH Q3C for Class 2 solvents
  - Type 2. Without sufficient evidence, remove impurity or control levels to ‘as low as reasonably practicable’, i.e. apply ‘threshold of toxicological concern’ (TTC). TTC set at 1.5 µg/day
- high potency genotoxic carcinogens ‘aflatoxin-like-’, N-nitroso-, and azoxy-compounds are excluded from the TTC approach
Pethidine Hydrochloride

British Pharmacopoeia / Ph. Eur. monograph 0420

C₁₅H₂₂ClNO₂  Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride

Opioid receptor agonist; analgesic

Production

If intended for use in the manufacture of parenteral preparations, the manufacturing process is validated to show that the content of impurity B is not more than 0.1 ppm.

Impurity B Liquid chromatography

Limit: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (10 ppm) if intended for non-parenteral administration.
Epoetin-Induced Autoimmune Pure Red Cell Aplasia

- Recombinant human erythropoietin spike in cases of antibody-associated pure red cell aplasia
- Severe, isolated anaemia with sudden onset
- Significant differences between countries
- EMA request to remove human serum albumin from formulation: replaced with polysorbate 80
- Johnson & Johnson: EPO antibodies formed in mice after exposure to rubber leachates. These leachates appeared to develop in prefilled Eprex syringes with uncoated rubber stoppers
- Replaced by Teflon stoppers
Tungsten

Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity

• cases of neutralizing antibodies to epoetin alfa in investigational clinical study
• a small number of individual syringes from two batches found to contain unusually high levels of aggregation at the end of the clinical trial
• Soluble tungsten was found in the syringes

methanesulfonic acid head tank
cleaned with ethanol
ethyl methanesulfonate (alkylating agent) formed

\[
\text{H}_3\text{C}-\text{S} - \text{OH} + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{H}_3\text{C}-\text{S} - \text{OCH}_2\text{CH}_3
\]
Australian Regulatory Guidelines for Prescription Medicines (ARGPM)

Guidance 18: Impurities in drug substances and drug products

- Note for guidance on impurities testing: impurities in new drug substances ICHQ3A(R) (CPMP/ICH/2737/99)
- Guideline on control of impurities of pharmacopoeial substances: compliance with the European Pharmacopoeia general monograph ‘Substances for pharmaceutical use’ and general chapter ‘Control of impurities in substances for pharmaceutical use’ [CPMP/QWP/1529/04]
- Guideline on the specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000)
- Note for guidance on impurities in new drug products ICHQ3B(R2) (CPMP/ICH/2738/99)
- Guideline on the limits of genotoxic impurities (CPMP/SWP/5199/02)
- Guidance on limitations to the use of ethylene oxide in the manufacture of medicinal products (CPMP/QWP/159/01)
- Guideline on setting specifications for related impurities in antibiotics (EMA/CHMP/CVMP/QWP/199250/2009 Corr)
- Guideline for residual solvents ICHQ3C(R5) (EMA/CHMP/ICH/82260/2006)
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