What is required for first into man?

The EU IMPD

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Scope

- Structure and content of an IMPD

- What is required for first into man trial?
  - Only for IMPs that do not have a marketing authorisation within the EU
  - Quality data will primary focus on new chemical entities (NCEs)
  - No discussion of simplified IMPDs
Required IMP related Data

- Investigator’s brochure
- Trial Protocol
- Investigational Medicinal Product Dossier (IMPD)
- Examples of the label in the national language
- A copy of the manufacturing authorisation or importer’s manufacturing authorisation
- Where applicable:
  - Certificate of analysis in exceptional cases where impurities are not justified by the specification or when unexpected impurities (not covered by the specification) are detected
  - Viral safety studies and data
  - TSE Certificate

Investigational medicinal product dossier (IMPD)

- EU Directive 2001/20 (“clinical trials directive”) requires sponsors to submit information on
  - the quality and manufacture of the investigational medicinal product
  - any toxicological and pharmacological tests
  - the protocol and
  - clinical information on the investigational medicinal product including investigator’s brochure

  to the concerned competent authority (CA)

- Guidance on structure and content of an IMPD is provided in the ENTR/CT1 Guidance (REV2)
Structure of an IMPD

- **CTD structure where appropriate**
  - The Rules Governing Medicinal Products in the European Union, Volume 2, Notice to Applicants Volume 2B

- **Dossier, but not a standalone file**
  - Filing of different documents
  - Cross references to other documents (e.g. IB, Protocol)
  - Cross reference to IMPD of other sponsors require written permission

General Structure of an IMPD

- **Quality data**

- **Non-clinical pharmacology and toxicology data**

- **Previous clinical trial and human experience data**

- **Overall risk and benefit assessment**
Quality Data Requirements

- Manufacture(s) must comply with the principles of **Good Manufacturing Practice** (GMP)
  - Directive 2003/94/EC
  - Annex 13 to Volume 4
- If IMP is manufactured within the EU
  - Copy of the manufacturing authorisation stating the scope of the authorisation
- If IMP is manufactured outside the EU
  - Certification of the Qualified Person (QP) that the manufacturing site works in compliance with GMP at least equivalent to EU GMP
  - Certification of the GMP status of any active biological substance
  - Copy of the importer’s manufacturing authorisation

Quality Data

- Quality data should be reported according to the EU-Guideline on IMPs in clinical trials (CHMP/QWP/185401/2004, Draft)
  - “Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning the investigational medicinal products in clinical trials”
- Different requirements for tested IMPs and comparators
  - Phase adjusted requirements (phase I vs. phase II and III)
  - Trial type related requirements (e.g. bio-equivalence trials)
## IMPD Structure on Quality Data

2.1.S Drug Substance
- 2.1.S.1 General Information
- 2.1.S.2 Manufacture
- 2.1.S.3 Characterisation
- 2.1.S.4 Control of the Drug Substance
- 2.1.S.5 Reference Standards or Materials
- 2.1.S.6 Container Closure System
- 2.1.S.7 Stability

2.1.P IMP under Test
- 2.1.P.1 Description and Composition
- 2.1.P.2 Pharmaceutical Development
- 2.1.P.3 Manufacture
- 2.1.P.4 Control of Excipients
- 2.1.P.5 Control of the Investigational Medicinal Product
- 2.1.P.6 Reference Standards or Materials
- 2.1.P.7 Container Closure System
- 2.1.P.8 Stability

## Differences in Quality Requirements between Phases (1/3)

<table>
<thead>
<tr>
<th>2.1.S.4 Control of Drug Substance</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.S.4.1 Specification</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>All batches used so far</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>2.1.S.4.3 Validation of Analytical Procedures</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Table of acceptance limits for validation</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>2.1.S.4.4 Batch Analyses</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Current batch(es)</td>
<td>X</td>
<td>X</td>
<td>X</td>
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Differences in Quality Requirements between Phases (2/3)

<table>
<thead>
<tr>
<th>2.1.P Medicinal Product</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>2.1.P.2 Pharmaceutical Development</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Short description, where applicable</td>
<td>Brief summary, taking into account changes of clinical relevance</td>
<td>Summary taking into account changes of clinical relevance</td>
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<tr>
<td>2.1.P.3.3 Description of Manufacturing Process and Process Controls</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Brief description and flowchart</td>
<td>Description and flowchart, taking into account changes of clinical relevance</td>
<td>Description and flowchart, taking into account changes of clinical relevance</td>
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</tr>
<tr>
<td>2.1.P.3.4 Controls of Critical Steps and Intermediates</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Provide data for non-standard processes and the manufacture of sterile products</td>
<td>Provide data for non-standard processes and the manufacture of sterile products</td>
<td>Control of critical steps and intermediates</td>
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Differences in Quality Requirements between Phases (3/3)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>2.1.P.5.1 Specifications</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>At least batch results</td>
<td>Preliminary specifications</td>
<td>Specifications</td>
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<tr>
<td>2.1.P.5.3 Validation of Analytical Procedures</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Table of acceptance limits for validation</td>
<td>Tabulated summary of results</td>
<td>Validation report to be held available</td>
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</tr>
<tr>
<td>2.1.P.5.4 Justification of Specification(s)</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Brief justification for impurities</td>
<td>Brief justification, taking into account changes of clinical relevance</td>
<td>Brief justification, taking into account changes of clinical relevance</td>
<td></td>
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</tbody>
</table>
Quality Data
From non-clinical studies to first into man trials

- If the manufacturing process differs from that used for the production of the batches used in the non-clinical studies, it
  - should be documented and
  - a flow chart of the manufacturing process used for the active substance used in the non-clinical studies should be provided

General Structure of an IMPD

- Quality data
- Non-clinical pharmacology and toxicology data
- Previous clinical trial and human experience data
- Overall risk and benefit assessment
Requirements for Non-clinical Studies

- All studies should be conducted according to currently acceptable state-of-the-art methods
- All studies should meet the requirements of Good Laboratory Practice guidelines where appropriate
- All deviations from these guidelines should be justified
- A statement of the GLP status of all studies is required

Non-clinical pharmacology and toxicology data Documentation

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<th>Pharmacodynamics</th>
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</thead>
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<tr>
<td>2.2.1.2</td>
<td>Primary Pharmacodynamics</td>
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<td>2.2.1.3</td>
<td>Secondary Pharmacodynamics</td>
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<td>2.2.1.4</td>
<td>Safety Pharmacology</td>
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<td>2.2.1.5</td>
<td>Pharmacodynamic interactions</td>
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<td>2.2.1.6</td>
<td>Discussion and conclusion</td>
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<thead>
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<th>Pharmacokinetics</th>
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<td>2.2.2.2</td>
<td>Methods of analysis</td>
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<td>2.2.2.3</td>
<td>Absorption</td>
</tr>
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<td>2.2.2.4</td>
<td>Distribution</td>
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<td>Metabolism</td>
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<td>2.2.2.6</td>
<td>Excretion</td>
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<td>2.2.2.7</td>
<td>Pharmacokinetic Drug Interactions</td>
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<td>2.2.2.8</td>
<td>Other Pharmacokinetic Studies</td>
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<tr>
<td>2.2.2.9</td>
<td>Discussion and conclusions including evaluation of toxicokinetics</td>
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<table>
<thead>
<tr>
<th>2.2.3</th>
<th>Toxicology</th>
</tr>
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<td>Brief Summary</td>
</tr>
<tr>
<td>2.2.3.2</td>
<td>Single Dose Toxicity</td>
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<td>2.2.3.3</td>
<td>Repeat-Dose Toxicity*</td>
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<td>2.2.3.4</td>
<td>Genotoxicity:</td>
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<td>2.2.3.4.1</td>
<td>In vitro</td>
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<tr>
<td>2.2.3.9</td>
<td>Discussion and Conclusions</td>
</tr>
</tbody>
</table>

*Toxicokinetic evaluations required
Pharmacodynamics

- Primary Pharmacodynamics
  - Should be assessed in appropriate animal models if possible
  - Studies should be performed prior to first into man trials (if possible)

- Secondary Pharmacodynamics

- Safety Pharmacology
  - Should be performed in accordance with the ICH S7A
    - „Note for guidance on safety pharmacology studies for human pharmaceuticals“ (CPMP/ICH/333/00)

- Pharmacodynamic interactions

Pharmacokinetics & Toxicology

- Pharmacokinetics
  - ADME from non-clinical studies are usually not required for “first into man” trials

- Toxicology
  - ICH M3 (CPMP/ICH/286/95): Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals
  - Note for guidance on single dose toxicity (Notice to applicants 3BS1A)
  - Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99)
  - Duration:
    - 14 days in rodents and non-rodents
Genotoxicity

- Notes for Guidance
  - Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (ICH 2SA, CPMP/ICH/141/95)
  - A standard battery for genotoxicity testing of pharmaceuticals (ICH 2SB, CPMP/ICH/174/95)
- First into man trials:
  - At least two in-vitro tests
    - A test for gene mutation in bacteria
    - An in-vitro test for cytogenetic evaluation of chromosomal damage with mammalian cell
    - or –
    - An in-vitro mouse lymphoma tk assay
  - In-vivo test for chromosomal damage in rodent hematopoetic cells
    - Phase 2

Carcinogenicity

Reproductive and Developmental Toxicity

- Carcinogenicity
  - Usually not requested for first into man trials
  - See Note for guidance on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95)
- Reproductive and Developmental Toxicity
  - Phase 1 in male volunteers
    - Statement on the reproductive toxicity in males may be requested (necessary in multiple dosing)
  - Notes for Guidance:
    - Note for guidance on specific reproductive toxicology: Detection of toxicity to reproduction for medicinal products (CPMP/ICH/386/95)
    - Note for guidance on reproductive toxicology: Toxicity on male fertility (CPMP/ICH/136/95, modification)
Local Tolerance

- Prior first into man trials local tolerance should be assessed
  - Site of administration
    - Ocular tolerance
    - Dermal tolerance
    - Parenteral tolerance
    - ...
- Sensitising potential
  - Required for substances applied to skin or mucous membranes

- Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00)

Phototoxicity

- Photo safety testing required, if
  - Substance absorbs light in the wavelength of 290-700 nm and
    - Topically/locally applied or
    - Substance reaches skin or eyes after systemic exposure

- Requirements for first into man trials
  - Absorption spectra (?)

- Note for guidance on photosafety testing (CPMP/SWP/398/01)
General Structure of an IMPD

- Quality data
- Non-clinical pharmacology and toxicology data
- Previous clinical trial and human experience data
- Overall risk and benefit assessment

Previous clinical trial and human experience data

- In first into man trials usually no clinical data available
  - Summaries of clinical data of related drugs might be helpful where appropriate
  - Clinical trials should be conduct in accordance with the principles of GCP (ICH E6, CPMP/ICH/291/95)
  - Cross reference to IB
Overall risk and benefit assessment

- Analysis of the non-clinical and clinical data in relation to the potential risks and benefits of the proposed trial
  - Any prematurely terminated studies should be identified under discussion of the reason(s)
- Identification of principal hazards of the new IMP
- All relevant pharmacology, toxicology and kinetic data should be extrapolated to indicate possible risks in humans
- Safety margins should be defined where appropriate
  - Based on systemic exposure if possible

The IMPD in Europe

- While regulatory requirements for Marketing Authorisation are well defined requirements for clinical trials are less clear
  - “When do we need what?”
  - Less stricter rules allow more flexibility
  - The IMPD is a growing file during clinical development
- European harmonisation process is still ongoing
  - ENTR / CT documents
  - QWP Guidelines under development
  - Guidance documents for biotechnical products under development