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

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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)

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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

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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

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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

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Quality Data

- Quality data should be reported according 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)

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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)

2.1.S.4 Control of Drug Substance	**Phase 1**	**Phase 2**	**Phase 3**
2.1.S.4.1 Specification	X	X	X
	At least batch results	Preliminary specifications	Specifications
2.1.S.4.3 Validation of Analytical Procedures	X	X	X
	Table of acceptance limits for validation	Tabulated summary of results	Validation report to be held available
2.1.S.4.4 Batch Analyses	X	X	X
	All batches used so far	Current batch(es)	Current batch(es)

Differences in Quality Requirements between Phases (2/3)

2.1.P Medicinal Product	Phase 1	Phase 2	Phase 3
2.1.P.2 Pharmaceutical Development	**X**	X	X
	Short description, where applicable	Brief summary, taking into account changes of clinical relevance	Summary taking, into account changes of clinical relevance
2.1.P.3.3 Description of Manufacturing Process and Process Controls	**X**	X	X
	Brief description and flowchart	Description and flowchart, taking into account changes of clinical relevance	Description and flowchart, taking into account changes of clinical relevance
2.1.P.3.4 Controls of Critical Steps and Intermediates	**X**	X	X
	Provide data for non-standard processes and the manufacture of sterile products	Provide data for non-standard processes and the manufacture of sterile products	Control of critical steps and intermediates

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Differences in Quality Requirements between Phases (3/3)

2.1.P.5 Control of Medicinal Product	**Phase 1**	**Phase 2**	**Phase 3**
2.1.P.5.1 Specifications	X	**X**	**X**
	At least batch results	**Preliminary specifications**	**Specifications**
2.1.P.5.3 Validation of Analytical Procedures	**X**	**X**	**X**
	Table of acceptance limits for validation	**Tabulated summary of results**	**Validation report to be held available**
2.1.P.5.4 Justification of Specification(s)	**X**	**X**	**X**
	Brief justification for impurities	**Brief justification, taking into account changes of clinical relevance**	**Brief justification, taking into account changes of clinical relevance**

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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

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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

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Non-clinical pharmacology and toxicology data Documentation

2.2.1 Pharmacodynamics
2.2.1.1 Brief summary
2.2.1.2 Primary Pharmacodynamics
2.2.1.3 Secondary Pharmacodynamics
2.2.1.4 Safety Pharmacology
2.2.1.5 Pharmacodynamic interactions
2.2.1.6 Discussion and conclusion

2.2.2 Pharmacokinetics
2.2.2.1 Brief Summary
2.2.2.2.1 Methods of analysis
2.2.2.3 Absorption
2.2.2.4 Distribution
2.2.2.5 Metabolism
2.2.2.6 Excretion
2.2.2.7 Pharmacokinetic Drug Interactions
2.2.2.8 Other Pharmacokinetic Studies
2.2.2.9 Discussion and conclusions including evaluation of toxicokinetics

2.2.3 Toxicology
2.2.3.1 Brief Summary
2.2.3.2 Single Dose Toxicity
2.2.3.3 Repeat-Dose Toxicity*
2.2.3.4 Genotoxicity:
2.2.3.4.1. In vitro
2.2.3.4.2. In vivo *
2.2.3.5. Carcinogenicity *
2.2.3.6. Reproductive and Developmental Toxicity *
2.2.3.7. Local Tolerance
2.2.3.8. Other Toxicity Studies
2.2.3.9. Discussion and Conclusions

*Toxicokinetic evaluations required

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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/539/00)
- Pharmacodynamic interactions

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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

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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

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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)

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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)

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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)

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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

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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

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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

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