EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Preparing the CMC section of IMPD for biological/biotechnology derived substances

Dr. Una Moore
Health Products Regulatory Authority, Ireland

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Presented by Una Moore on 16th April 2014.
Health Products Regulatory Agency

Presentation Overview

EUROPEAN MEDICINES AGENCY

- Evolution of quality requirements for biological IMPs
  - Directive 2001/20/EC
  - Clinical Trials Facilitation Group (CTFG)
- Key documents to be consulted
- Key information that needs to be provided:
  - Characterisation
  - Manufacturing process development and comparability
  - Specifications
  - Stability and shelf-life claims
- Conclude with recent issues

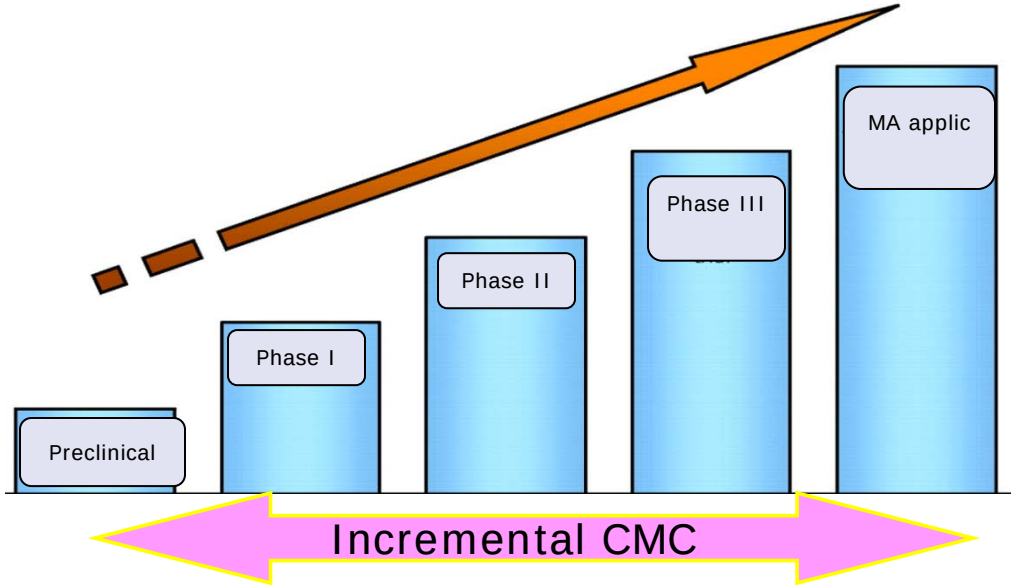
CMC information required in an IMPD for CT application

EUROPEAN MEDICINES AGENCY

• The CMC (quality) information is presented in the IMPD - is one of the core documents of CTA

•One size doesn't fit all – the information required will depend on the:

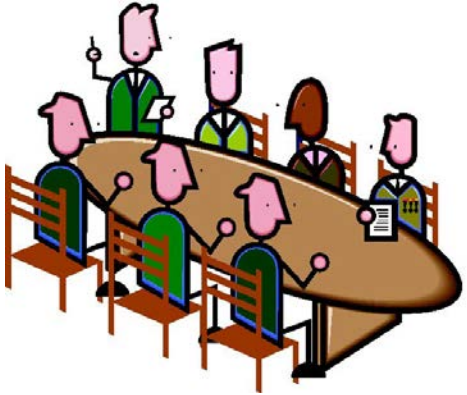
- Phase of the trial i.e. First in human, phase I, II or III.
- Nature of the product,
- Patient population,
- Nature and severity of illness
- Number of doses
- Type and duration of the CT



Evolution of quality requirements for biological IMPs

- Directive 2001/20/EC

- Clinical Trials Facilitation Group (CTFG) 2004



First in Human/Phase 1 - TeGenero

EUROPEAN MEDICINES AGENCY

- 2006: TeGenero monoclonal antibody (TNG1412) trial
- CD28 monoclonal antibody "super agonist"
- 500 times lower than the dose found safe in animals
- Caused cytokine storm resulting in multiple organ failure
- MHRA investigation - unforeseen biological action in humans
- No obvious errors in the conductance of the trial.
- Several proposals e.g. Extracellular domain only 96% homology, preclinical studies didn't include an allergy test, lower CD28 expression on the $CD4^+$ memory T-cells in non-human primates.
- International group (Gordon Duff) established to learn from this incident and to provide recommendations on how to improve the safety of FIH/Phase I trials.

Identified three categories of IMPs that are high risk:

- Biological molecules with novel mechanism of action
- New agents with a high degree of species-specificity
- New agents with immune system targets.

Resulted in the release of the EMA guidance note

Guideline on strategies to identify and mitigate risks for first in human CTs with IMPD (EMEA/CHMP/SWP/28367/07). Effective date September 2007.

'Quality aspects, should not in themselves, be a source of risk for first-in-human studies'
Physico-chemical and biological characterisation requirements are the same for all IMPs.

1. Determination of strength and potency

Safe starting dose – methods need to be relevant, reliable and qualified.

Where the dose assay is

- Based on biological activity and activity based on arbitrary units,
- Not qualified and/or validated

Result: poorly defined dose in preclinical study

Use of a reference biological standard from early in development to ensure reproducible measurement of biological activity.

A test for biological activity should be available unless otherwise justified

Available information should be provided in the IMPD

2. Qualification of the material used

Material used in non-clinical studies should be representative of the material used in first in human studies

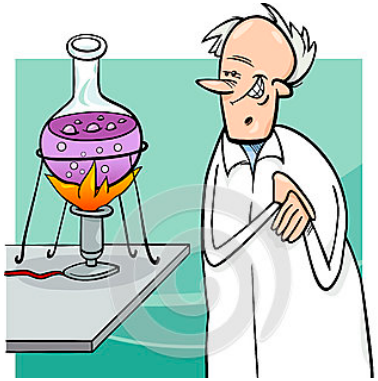
Adequate level of quality characterisation required including heterogeneity, degradation profile and process-related impurities

Particular attention to impurities that could be pharmaceutically active/toxic

Methods for characterisation should be suitable and qualified.

Manufacturing changes – have product characteristics changed? Assurance that product safety has not altered.

Are additional preclinical studies needed?



Available information should be provided in the IMPD

3. Reliability of very small doses

Intended formulation of the dose provides the intended dose

Risks:

- Concentrated product needs to be diluted,
- Preparation of very small doses,
- Product is absorbed to the sides of the container/infusion system

Result:

Overestimation of the safety of the initial dose and non-clinical safety data.

Compatibility with primary packaging and administration systems should be investigated.

Available information should be provided in the IMPD

Preparation of the IMPD

EUROPEAN MEDICINES AGENCY

- **Guideline on strategies to identify and mitigate risks for first in human CTs with IMPD (EMEA/CHMP/SWP/28367/07)**
- **Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008). Effective date 2012.**

  - Outlines the specific quality (biological, chemical and pharmaceutical) documentation required for an IMPD for a biological/biotechnology derived IMP
  - Applies to proteins/peptides produced from recombinant or non recombinant cell culture systems that can be highly purified and characterised
  - Highlights the different levels of information required for different phases of CTs
  - Provides the opportunity to qualify and validate assays progressively throughout development

- **Reference to an ASMF or a CEP (Ph. Eur.) is not acceptable or applicable**

Characterisation – structural, biological and impurities

EUROPEAN MEDICINES AGENCY

Provides additional guidance on the quality characterisation data required in guideline EMEA/CHMP/SWP/28367/07

- Prior to Phase 1 and after significant process changes information should be provided on:
  - Primary, secondary and higher-order structure
  - Post translational modifications e.g. glycoforms, C & N-terminal variants, deamidation, oxidation, charged variants
  - Physicochemical properties
  - Biological activity - Relevant, reliable and qualified method – absence can be justified
- Recognises that the amount of characterisation data and the validation of assays will increase as the IMP develops – i.e. a staged approach
- Presence of process-related and product related substances – staged approach for product related substances.
- Reference to literature data is not acceptable

For early phase CTs all available information should be provided

Process-related and product related impurities

EUROPEAN MEDICINES AGENCY

Process related	Range of limits (quantitative)	Provided
*Host cell DNA (mammalian cell lines)	***Phase 1– quantitative FIO Phase II/III ≤5 to 70 pg/mg	In-process control/ DS specification
Host Cell Proteins (All Cell Systems)	***Phase 1– quantitative FIO Phase II- III ≤ 100 ng/mg	DS specification
**Media residues/ column leachables/ Protein A	***Phase 1– quantitative FIO Phase II/III -quantitative limits Protein A - Phase II- III ≤ 5 ng/mg	In-process control/ DS specification
Product related		
Aggregates	Phase 1– quantitative FIO Phase II/III -quantitative limits (≤5%)	DS/DP specification
%Fragments	Phase I – available information Phase II/III -quantitative FIO (≤5%)	DS/DP specification
%Acidic and basic variants	Phase I – available information Phase II and III– quantitative FIO/limits	DS/DP specification
LMW reduced and non-reduced	Phase I – available information Phase II and III– quantitative FIO/limits	DS/DP specification

*WHO guideline specifies total DNA limit of 10 ng per dose, **Discussion of the removal of process related impurities, ***Upper limits should be specified

Manufacturing Process Development and Comparability

EUROPEAN MEDICINES AGENCY

Upstream and downstream manufacturing details and control strategy clearly described

Preferably in a flow chart

Manufacturing process and control strategies are continuously improving
Scale-up, possible change in site of manufacture
Changes and rationale presented in dossier

Maintain link between new process and preclinical and clinical trial batches

Necessary to demonstrate that the batches manufactured using the modified process are comparable to the batches used in clinical and non-clinical studies.

Confirm safety profile of the product remains unchanged

Need to demonstrate comparability

- Stepwise approach
- Analytical and orthogonal physiochemical and biological analytical methods
- Stressed stability studies
- Possibility non-clinical and/or clinical studies

This information needs to be presented in the dossier

Specifications

EUROPEAN MEDICINES AGENCY

Why are they so important?

Part of the control strategy deigned to ensure product quality and consistency of manufacture
Chosen to confirm the quality of DS/DP which ensures safety and efficacy of the product.

What are specifications?

List of tests, analytical procedures, acceptance criteria (numerical limits)
(i) Proposed by the manufacturer &
(ii) Approved by the regulator
as conditions of approval

Settings specifications:

1. Identify test that's important to ensure the quality of the product.
2. Define the analytical method of the test
3. Propose acceptance criteria which should be established and justified on:
   (a) Preclinical and clinical studies
   (b) Relevant developmental data
   (c) Stability studies
   (d) Methods used

This information needs to be presented in the dossier

Specifications

EUROPEAN MEDICINES AGENCY

Tests required within specifications	
DS	**DP**
Quantity	Content
Identity	
Purity	
Biological activity	
Microbiological quality	Sterility
Impurities	Endotoxin
Appearance & description	
pH, osmolality	

DP: Extractable volume, particles, residual moisture

Acceptance criteria:

Preliminary specification limits - need to be reviewed and will be phase dependent

- Phase I/II wider limits than data support
- Product characteristics for which there is insufficient knowledge to set a predefined limit include with limit of 'for information only'

-Batch data (consistency) need to be submitted.

Phase I all available data including batch intended for clinical trial (awaiting data). Phase II/III not necessary to provide all batch data.

Analytical Procedures:

Validation is an evolving process

Phase 1: Confirm suitability,

Phase II/III: assay validation results

Content assay should allow for correct dosing

EUROPEAN MEDICINES AGENCY

Directive 2010/63/EU – protection of animals used for Scientific Purposes

Legal requirement to consider the principle of three R's (replace, reduce and refine) when designing scientific experiments.

Potency assays – recommend use of cell based biological assay

Endotoxin/Pyrogens - limulus amoebocyte lysate test used instead of rabbit pyrogen test – consult Ph.Eur. for guidance on conductance of the LAL test

Move towards assessors questioning the use of animals when *in-vitro* tests are available.

Stability and shelf-life claims

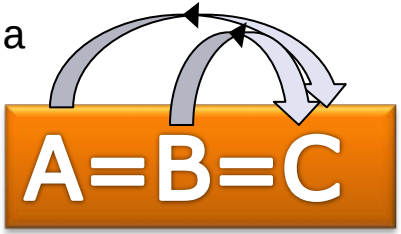
Clearly state the shelf-life being requested

In support of shelf-life:

- Provide stability protocol, specification, analytical tests and test interval times
- Quality reflective of the batches used in clinical trials
- Claim should be based on real time and real temperature studies - need at least 1 batch of CT material + previous batches
- Phase II/III: recommend data from accelerated and stressed conditions are available
- Methods should be stability indicating.
- Would expect a potency assay in protocol
- Re-test period does not apply to biological/ biotechnology drug substances.

Extension of Shelf-life

- Acceptable if supported by relevant data
  - Real-time data
  - Accelerated studies
  - Developmental batches/batch using earlier manufacturing process
  - Justification why early stability data applies to changed process



  - Commitment to complete the proposed protocol studies
- Maximum extension
  - Not exceed two-fold
  - Not more than 12 month
  - Not beyond the proposed protocol
  - Extension by non-substantial amendment if shelf-life extensions are clearly stated in the protocol

Recent Issues

Monoclonality of Cell Banks

EUROPEAN MEDICINES AGENCY

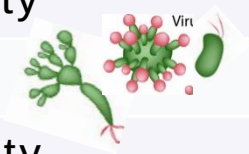
Summary description of the history, source and generation of the cell banks

MCB (an aliquot of a **single pool of cells**) should be established before phase I trials

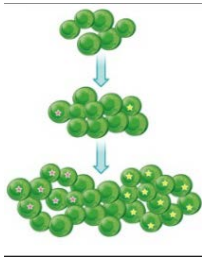
Working cell bank not always needed.

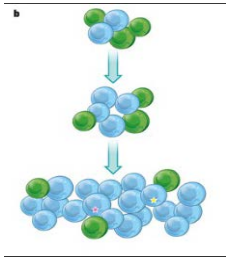
Characterisation - in line with CHMP/ICH Q5D guideline.

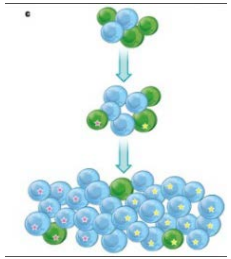
Characterisation	MCB	WCB
Identity	X	X
Purity	X	X
Viability	X	X



Emerging evidence that not all cell banks are monoclonal – techniques such as FISH analysis – identifying genetic heterogeneity.

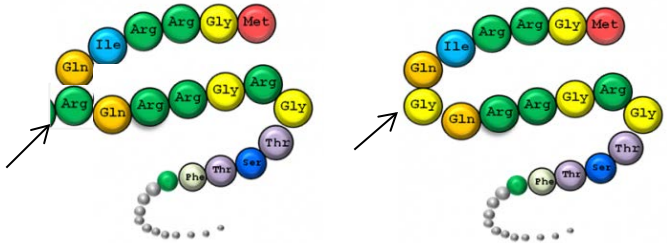






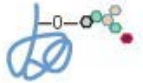
Monoclonality of Cell Banks

The DS could be a mixture e.g.



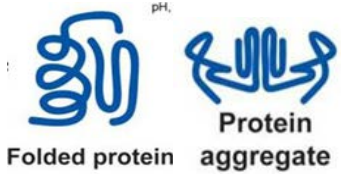
Different amino acid sequence

Different post translational modifications e.g. N or O linked glycosylation



Different impurity profile e.g. deamidation, oxidation, aggregation profile

Different functional activity



Consequences:

Complete physical, chemical and functional characterisation to confirm same DS

Investigations into the source of DS/DP (i.e. which clone) used in each CT

Possible repetition of CTs, rejection of MAH

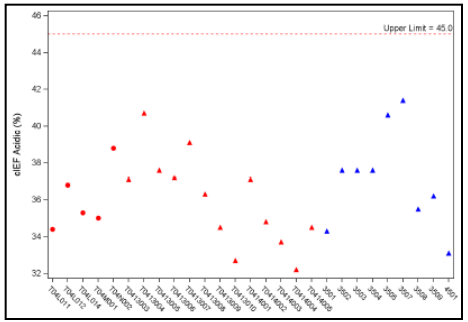
Monoclonality should be confirmed before phase 1 CT

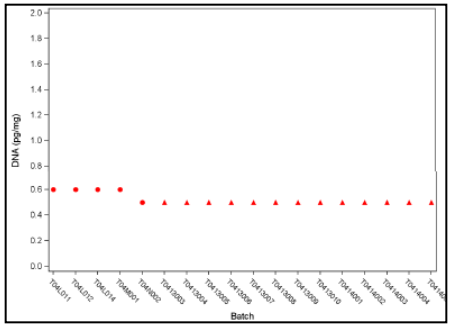
Leachables

- Changes to product quality may occur due to interactions between the product and container closure.
- Leachable issues should be addressed early in the manufacturing process
- Source from container, syringe, storage bags, closures (rubber stoppers)
- Stability studies should include samples maintained in the inverted and horizontal position.
- CT conducted in IE where contaminants leached from the stopper
  - Zinc leached from stopper – observed visible insoluble zinc phosphate particles in placebo resulted in voluntary suspension to trial recruitment
  - Significant delay to completion of the trial.
- If uncoated stoppers are proposed for use with the excipient polysorbate 80 particular focus should be placed on leachables studies as early in development as possible.

Less significant issues

- Justification for hold time and process intermediates
- Justification of specification limits particularly for phase III CTs.
- Justification 'for information only' when numerical acceptance criteria could be provided





- Justification of extension of shelf-life – comparability of batches manufactured using different processes
- DP sterilisation by filtration; maximum bioburden limit NMT 10 CFU/100 ml. *Due to limited availability of the formulated medicinal product, a pre-filtration volume of less than 100 ml may be tested if justified*.

Helpful guidelines

- Guideline on strategies to identify and mitigate risks for first in human CTs with IMPD (EMEA/CHMP/SWP/28367/07)
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008). Effective date 2012
- Guideline on Development, production, characterisation and specifications for monoclonal antibodies and related products - EMA/CHMP/BWP/157653/200/2008)
- ICH Q5B – Expression Construct in Cell Lines
- ICHQ5C – Stability Testing
- ICHQ5D – derivation and Characterisation of Cell Substrates
- ICH Q5E - Comparability
- ICHQ6B - Specifications

Thank you for your attention

Any Questions?