

Guidance on codes of practice, standardised methods and regulations for cell-based therapeutics

– from basic research to clinical application

PAS 83:2006

PUBLICLY AVAILABLE SPECIFICATION
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Images courtesy of Dr Alex Shortt, Moorfields Eye Hospital, London

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Foreword

This Publicly Available Specification has been developed by the Department of Trade and Industry (DTI) in collaboration with the British Standards Institution (BSI). No copying without permission of BSI except as permitted by copyright law.

This PAS was researched and written by Caroline Munro and Neil Harris* with the support of the following:

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- Julian Braybrook (LGC Limited)
- Kenny Pollock (Reneuron Ltd)
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- University of Southampton

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*carried out as part of a 6 month secondment from LGC to BSI funded by the DTI Measurements for Innovators programme

As a guide, this Publicly Available Specification takes the form of guidance and recommendations: it does not contain specified requirements.

The word “should” is used to express recommendations of this Publicly Available Specification. The word “may” is used in the text to express permissibility, e.g. as an alternative to the primary recommendation of the clause. The word “can” is used to express possibility, e.g. a consequence of an action or an event.

Notes are provided throughout the text of this Publicly Available Specification to give references and additional information that are important but do not form part of the recommendations.

Contractual and legal considerations

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

Compliance with a Publicly Available Specification cannot confer immunity from legal obligations.

This Publicly Available Specification is not to be regarded as a British Standard.

Cell based therapeutics is a rapidly advancing field that offers tremendous potential for advances in healthcare. The UK benefits from a strong body of regenerative medicine expertise coupled to a supportive regulatory environment. Building on this, it is the Government's aim to make the UK a global leader in the translation of this technology into practical medical therapies.

As cell based therapeutics are moving towards the stage where products are nearing commercialisation, there has been closer scrutiny of current standardisation and regulations by researchers, manufacturers and the wider public. From this it is apparent that it would be useful to have greater clarity and a well-signposted pathway to commercialisation of cell-based therapies in the UK. As an initial response, and in support of increasing technical and regulatory demands, the Department of Trade and Industry commissioned BSI to publish a concise guidance document, a Publicly Available Specification (PAS).

Over the last 12 months, consultation has taken place with contributors from a range of organisations including academics, regulators, national research institutes and companies approaching and engaged in clinical trial and potential product release. Using this 'hands on' expertise, PAS 83 has been produced to define and capture the key stages in a product lifecycle, from cell/tissue procurement through to commercialisation and post-launch requirements. With thanks to all those who have contributed their time and expertise in the consultation process, I am delighted to introduce this document which should help ensure that any lack of clarity on the relevant legislation, guidance and standards does not act as a barrier to exploitation of this key technology.

Lord Sainsbury of Turville

Minister for Science and Innovation

Introduction

Background

As part of the DTI's national strategy to promote standardisation in support of the UK regenerative medicines industry, a workshop was held in spring of 2005 on "Standardisation to support the Regenerative Medicine Industry". This workshop was co-hosted by the DTI, National Standardisation Strategic Framework (NSSF) and BSI Standards Development. Representatives of SMEs, large businesses, academic groups, regulatory bodies and standards institutes were in attendance.

The conclusions of the workshop, together with one-to-one interviews with key stakeholders, indicated that the industry requires a higher level of clarification with respect to legislative and standardisation issues for cell-based therapies, and a considered approach to improving the quality of R&D. Ultimately the sector wanted to see an effective, clear route to commercialisation of regenerative medicine technologies.

In addition, in this rapidly evolving field, it was felt that standardisation development should occur in parallel with R&D, and that the UK should keep pace with the international arena.

This Publicly Available Specification has been written in response to these requirements of the regenerative medicine industry.

Aim of the Publicly Available Specification

For the purpose of this document a cell-based therapeutic will be defined as:

"a product in which human cells are administered to the body, for the purpose of replacing, repairing, regenerating, or enhancing function of tissues"

Blood based products and blood/organ transplantations are not included in this definition but for clarity, their relationship to the overall process map is included.

The aim of this Publicly Available Specification is to:

- define in the form of a process map the key steps in a cell-based product lifecycle, from cell/tissue procurement through to commercialisation and post-launch activities;
- provide clear guidance to industry on the extent of standardisation that should be used during the process of research, development, trials and commercialisation of cell therapy products;
- identify which regulations, codes of practice and standards are already available in this field and link them to the lifecycle of cell-based therapy product production.

Use of the Publicly Available Specification

To this end, a detailed process map highlights the critical stages involved in the product pathway, initiated by the procurement of cells or tissue. Each stage is then accompanied by: a set of bullet points informing users of important points of awareness; a list of the accompanying legislative acts; the codes of practice and guidance documents supporting the legislation. In the case of the latter, it is intended that these will act as a navigation tool to direct the user to the relevant documents and no detailed breakdown of their contents is given. Where applicable, the supporting UK standards are also listed. A number of additional British Standards may apply in part to some of the sections of this document, but have been omitted here for clarity. However, the user is encouraged to seek additional information from standards as and when required.

1 Scope

This Publicly Available Specification (PAS) gives guidance on the product pathway from cell/tissue donation to clinical trial within the UK for cell-based therapies. It describes the accompanying legislation, codes of practice, guidance documents and standards for this process.

It is anticipated that the end-users of this document will range from academic groups who may need to implement quality systems and have an awareness of the overall process to commercialisation, to SMEs and larger industrial companies, who may liaise with academic groups or may use the document as a check list for product development. For researchers new to the field, this document will give an appreciation of the level of regulation, guidance and associated quality issues that apply to cell-based therapeutics.

The general public will have access to this document and it is anticipated that, as they understand that some of the more ethical issues are under strict regulation, they may feel more reassured about cell-based therapy research.

It is intended that this PAS will act as a quick reference source to increase clarity for users on the requirements needed for exploitation of a cell-based therapy in the UK, rather than as in depth examination of the supporting literature. The PAS will act as a guide to point readers in the direction of the relevant legislation, guidance document or standard.

This PAS does not cover xenografts, whole organ or bone marrow transplants and blood transfusions.

2 Terms, definitions and abbreviations

For the purposes of this Publicly Available Specification, the following terms, definitions and abbreviations apply.

autologous

cells in which donor and recipient are the same person

allogeneic

cells in which donor and recipient are different people

bioactives

an agent which interacts with, or has an effect upon a living organism or on living tissue or cells

biomaterial

material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body

differentiation (of cells)

process by which unspecialised cells acquire a "type" when certain genes are turned on, or become activated, while other genes are switched off, or inactivated, resulting in development of specific structures and performance of certain functions

epigenetic

reversible heritable changes in gene function that occur without a change in the sequence of nuclear DNA, often associated with acetylation of histones which cause a modification to the level of DNA folding, or changes in the methylation levels of specific DNA sequences

genotype

genetic characteristics of a cell

karyotyping

assessment of the complete set of all chromosomes of a cell to identify any chromosomal abnormalities

manipulation (of cells)

modification of cell behaviour by physical stimulus, biochemical challenge or genetic modification

Process Analytical Technology (PAT)

system of designing and controlling manufacturing through timely measurements of critical quality and performance attributes for raw and in-process materials, and also processes with the goal of ensuring final product quality

NOTE This definition is taken from

www.emea.eu.int/Inspections/PAThome.html



Documents

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pharmacovigilance

the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines

NOTE This definition is taken from The Importance of Pharmacovigilance, WHO 2002.

phenotype

detectable physical and biological characteristics

process validation

establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its pre-determined specifications and quality attributes

xenograft

material derived from one species, e.g. pig for use in another species, e.g. human

quality assurance (QA)

program for the systematic monitoring and evaluation of the various steps of production to maintain standards of quality of a product

quality control (QC)

process or set of processes or measures used to maintain proper standards to assure the quality of a product

current Good Manufacturing Practice (cGMP)

set of regulations, codes, and guidelines for the manufacture of drugs (known as medicinal products in Europe), medical devices, diagnostic products, food products and active pharmaceutical ingredients

current Good Laboratory Practice (cGLP)

regulations, codes, and guidelines for laboratories conducting non-clinical studies

NOTE This includes toxicology and pharmacology studies in animals.

current Good Clinical Practice (cGCP)

regulations, codes, and guidelines for hospitals and clinicians conducting clinical studies in humans

current Good Cell Culture Practice (cGCCP)

guidelines to define minimum standards in cell and tissue culture

current Good Tissue Practice (cGTP)

regulations, codes, and guidelines for the manufacture of cell-based therapeutic products

statutory instrument (SI)

named and numbered piece of legislation applicable to the UK, Great Britain or England and/or Wales

CHMP

EMA Committee for Medicinal Products for Human Use

DH

UK Department of Health

EMA

European Medicines Agency

EU

European Union

FDA

US Food and Drugs Administration

HFEA

Human Fertilisation and Embryology Authority

HTA

Human Tissue Authority

ICH

International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use

ISO

International Organization for Standardization

MHRA

Medicines and Healthcare Products Regulatory Agency

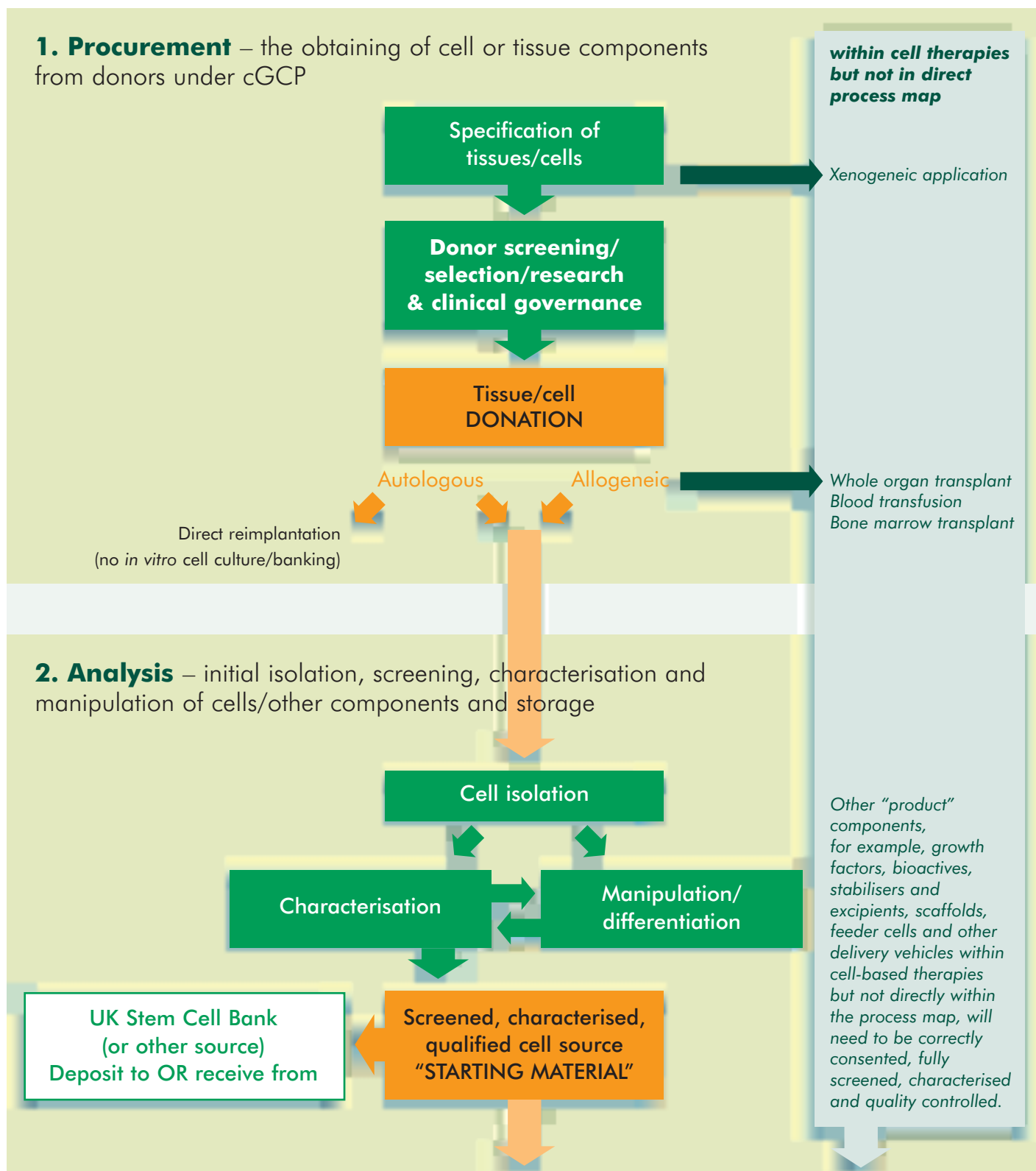
SME

small and medium sized enterprise

3 Cell-based therapeutics production – Process map

PAS 83 is intended to guide users on the requirements for the series of steps contained within a cell therapy product development pathway. To facilitate this, a detailed process map has been produced that illustrates the critical steps

involved in the product pathway starting with cell or tissue procurement through to clinical trial and eventual product release.



3. Confirmed proof of product and process

– initial-to-final screening for potential use

Initial phase

Screened, characterised, validated cell source
"STARTING MATERIAL" from stage 2

Other "product" components

In-house knowledge
Background IP
Know-how

Lab-based research
experimentation
(*in vitro*, *in vivo*)

Process engineering
Knowledge

IDENTIFIED PROTOCOL and PRODUCT COMPONENTS (any combination)
– may include BUT NOT LIMITED TO CELLS – SCAFFOLDS – BIOACTIVES – GROWTH FACTORS

Confirmation of lead candidate and process

Proof of concept

Proof of process

Assessment of
commercialisation potential

Cell and product analysis

- Ongoing characterisation
- Stability
- Reproducibility
- Purity
- Contamination

Product performance

- *In vitro* assays (potency/dose)
- Delivery systems
- Screening systems

Processing

- Scale up (allogeneic potential)
- Scale out (autologous potential)
- Logistics
- Cost
- Repeats of analysis and performance
- specifications

Business strategy

- Market
- Health economics
- Logistics (shelf life, distribution)
- Cost of product vs cost of goods
- Reimbursement
- Regulatory
- Cost of QA/QC
- Public opinion

Product and process confirmed
Manufacturing process locked
"ACTIVE SUBSTANCE"

4. Product manufacturing – production of clinical grade material under cGMP

Pilot scale manufacture

Product analysis and performance

- Confirm release criteria
- Stability
- Reproducibility
- Potency
- Purity
- Contamination

Manufacture/processing

- Critical in process control point identified
- Scale up/out to required volumes

Process analysis

- Stability
- Validation runs
- Contaminations
- Sterility
- Incorporation/use of PAT
- Risk assessments

QC Check and release

Conformity of the product and process to its specifications against release criteria

In vitro diagnostic products

Availability of "PRODUCT"
for clinical studies

5. Pre-clinical trials – assessment of safety and performance for regulatory submission

Perform risk assessments

Identify appropriate pre-clinical models

Use data for discussions with regulatory bodies

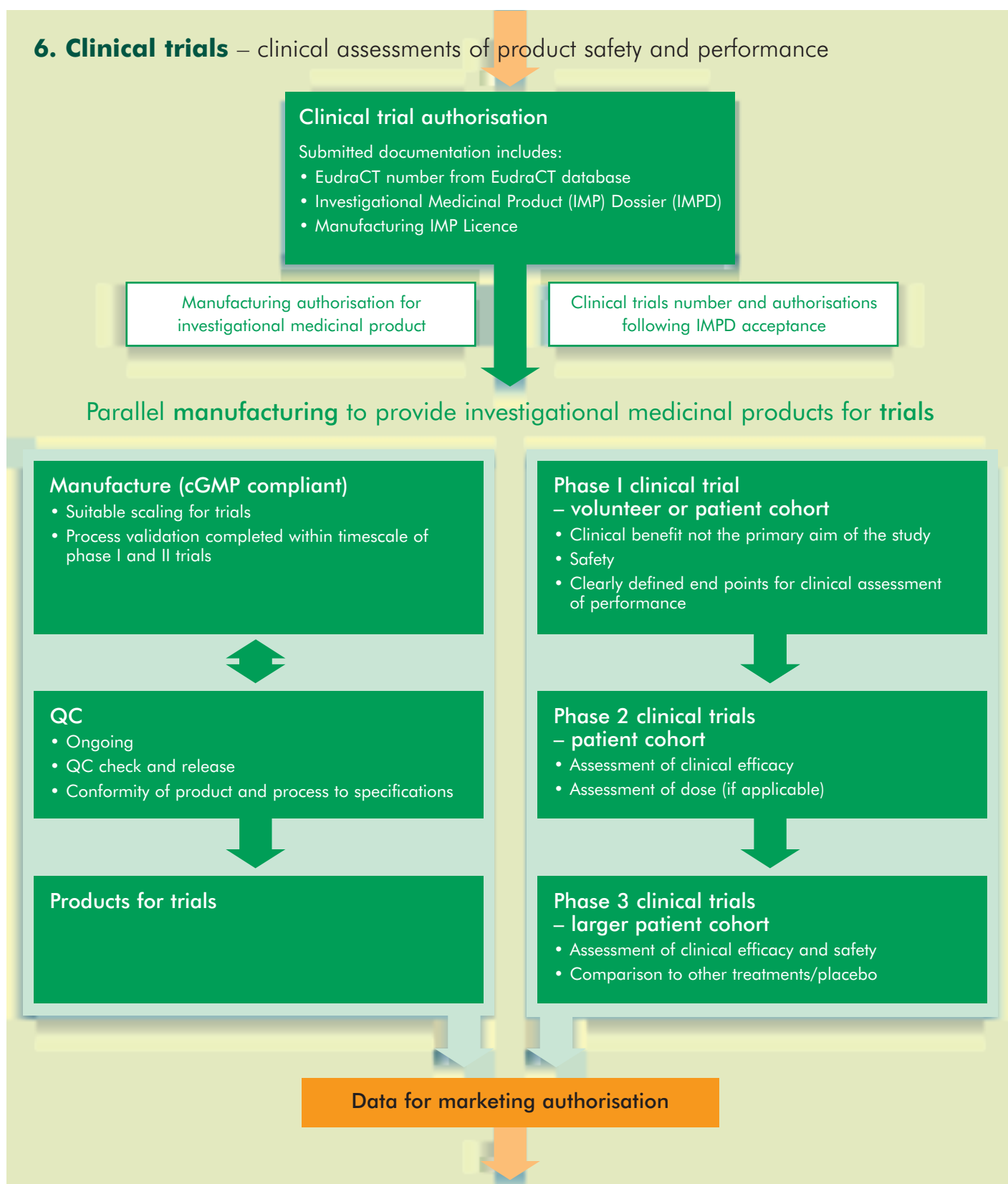
Perform pre-clinical studies to GLP

NOTE Manufacturing IMP licence

As the process of manufacture is a component of the product it may be beneficial in some cases to gain manufacturing authorisation prior to performing pre-clinical studies. This should be assessed on a case-by-case basis

Pre-clinical data available

6. Clinical trials – clinical assessments of product safety and performance



7. Launch – commercially available product

Pre-launch authorisations

Ongoing manufacturing

- In line with manufacturing licence
- Associated QC, cGMP, cGLP

Production of a site master file SMF and information for marketing authorisation or marketing and wholesale authorisation

8. Post-market – ongoing processes following commercialisation of product

Manufacture

Data storage

- QC and QA of manufacturing process for marketing licence
- Patient registry – benefit assessment
- Risk management

Licensing

- Post-authorisation renewals and updates to marketing licences

Pharmacovigilance

- Periodic safety update reports
- Adverse event reporting
- Post-authorisation safety studies (Phase 4)

Clinical

Data storage

- Product information
- Donation information
- Complete traceability patient/product
- Data protection

