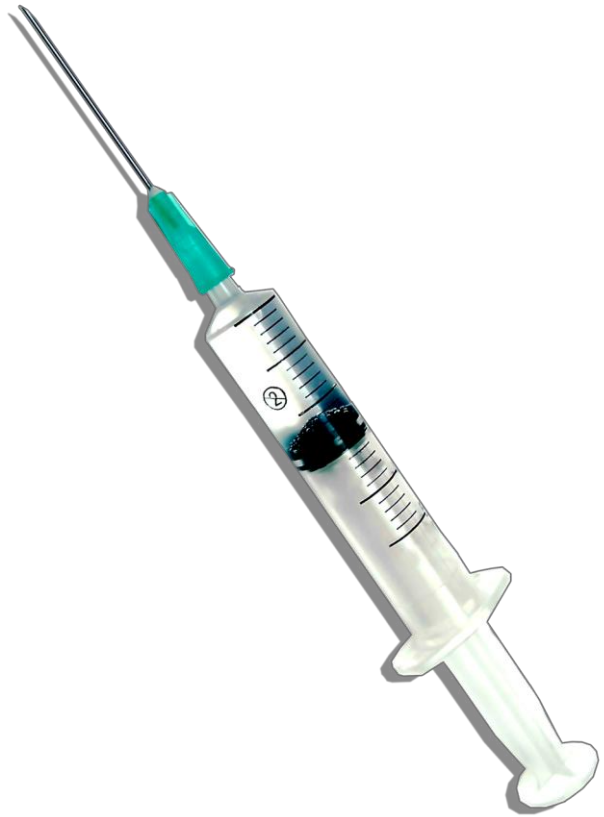
What's new in IMP preparation?

Anne Black

The first stop for professional medicines advice

24/09/2025

Changes to anticipate



- Amended UK Clinical Trials Regulation
- QAAP rewrite will include IMP reconstitution

Clinical Trials Legislation.

EU Clinical Trial Directive 2001/20/EC

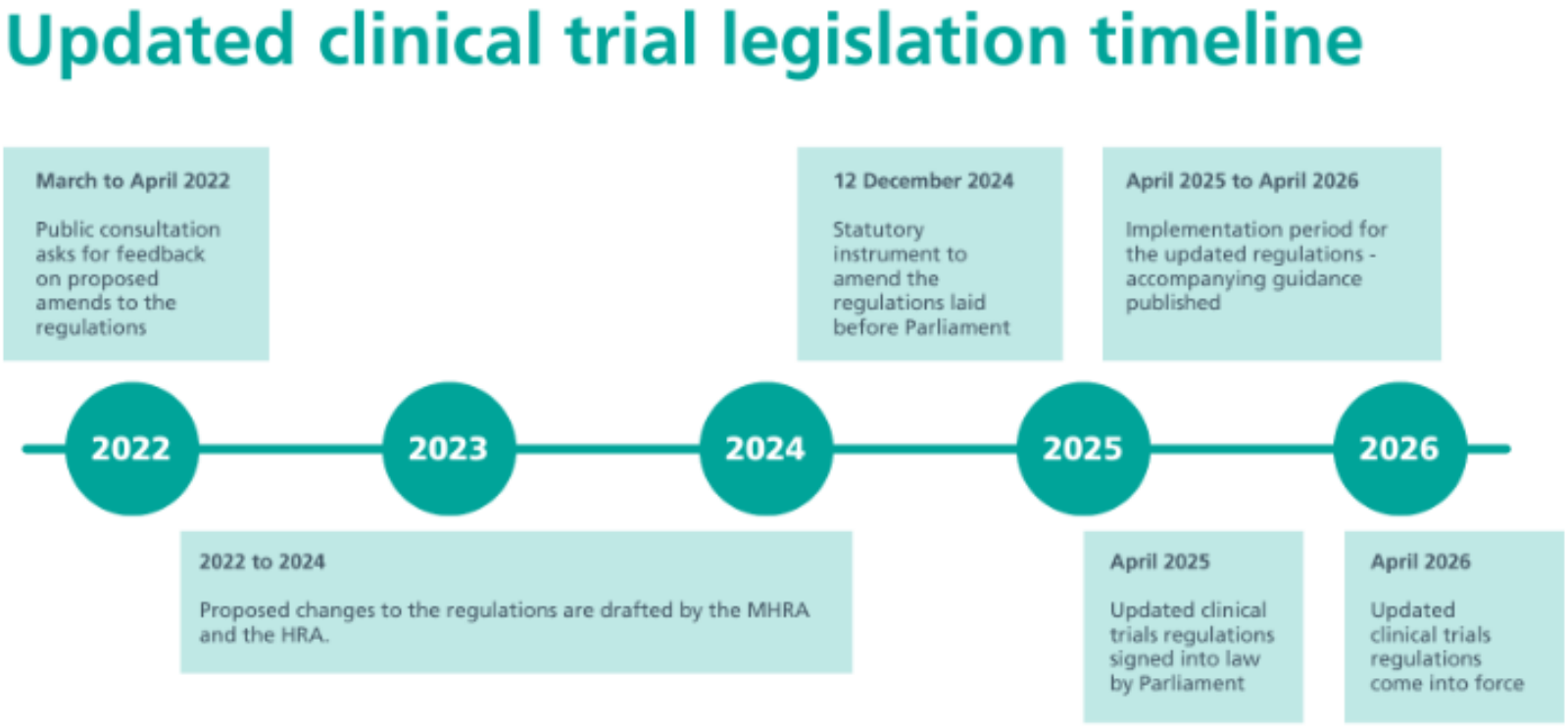
- Published in April 2001with implementation requirements by 2004
  - UK Law - The medicines for Human Use Act (Clinical Trials) Regulations 2004

- CT Regulation (EU) 536/2014 implemented in EU on 31/1 /2022

- EU Exit: 31/1/2020 Transitional arrangements for 2 years.

- UK Public Consultation on new UK Clinical Trial Regulation during 2022.
- SI to amend UK 2004 Regulation laid before Parliament in Dec 2024, approved in April 2025.
- UK The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.
- Clinical Trials Hub Guidance published August 2025 Medicines: clinical trials hub - GOV.UK

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 Pathway.



The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.

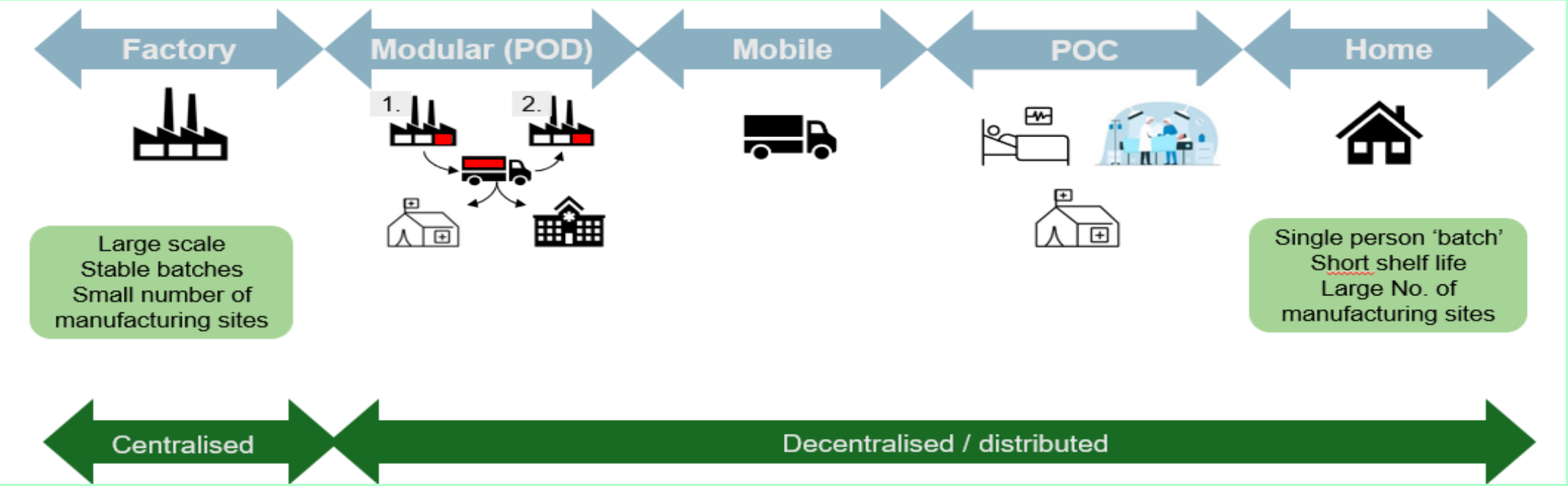
- Ensure patients and their safety are at the focus of all clinical trials and bring the benefits of clinical trials to everyone
- Create a proportionate and flexible regulatory environment
- Cement the UK as a destination for international trials
- Provide a framework that is streamlined, agile and responsive to innovation

Main Changes

- The approval process
  - Simplify and streamline – single application MHRA and REC 30 days turnaround.
  - Notification Scheme for low risk trials
- Research Transparency
  - Registries and publishing results
- Good Clinical Practice
  - Aligns with ICH guidelines
- Manufacturing and Assembly
  - Brings in exemption for diagnostic radiopharmaceuticals
  - Brings in Decentralised Manufacturing Legislation
- Safety Reporting and Pharmacovigilance

Guidance running alongside. Inclusivity.

What is Decentralised Manufacture?



MHRA. Oct 2024.

Background

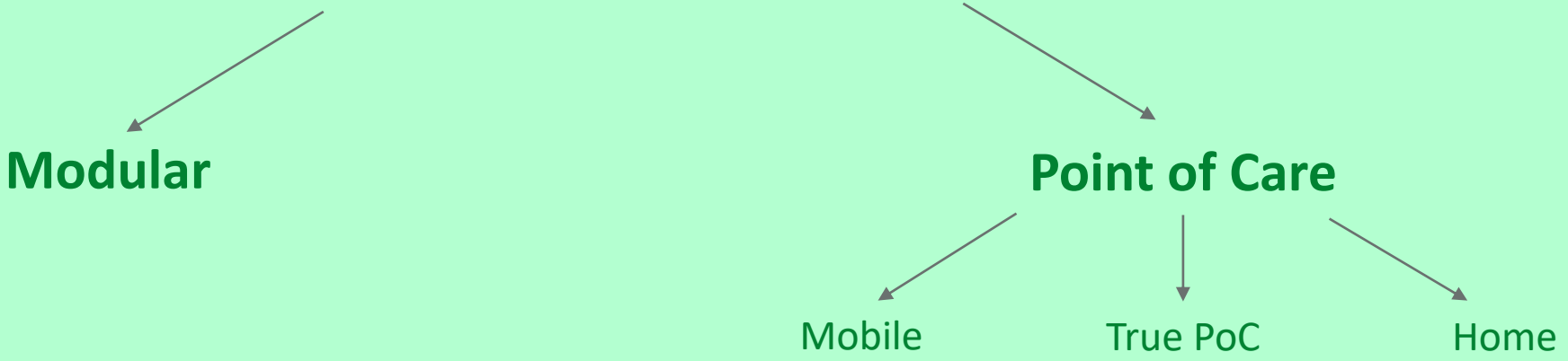
A pioneering legislative framework; 23rd July 2025: The Human Medicines (Amendment) (Modular Manufacture and Point of Care) Regulations 2024 Statutory Instrument 2025 No. 87[1]

- Patient-centric , flexible, safe and regulatory compliant.
- Applies to MA, IMP and ULM
- Facilitates manufacture of more safe high-quality medicines
- Will not override conventional manufacturing regulations or processes.
- Challenges for successful implementation in the NHS.
- Complex to implement
- Shared responsibility with industry
- Training and alignment across all parts of the system.

- It is not Preparation /recon and cannot occur under the S10 or Reg 37 exemption.

Accountability for governance of all such activities in will rest with Pharmacists, Hospital Chiefs or Superintendents?

Decentralised Manufacture



Legal Test = Product qualifies where, for reasons of deployment it is deemed necessary or expedient by the MHRA to be manufactured or assembled in a modular unit.

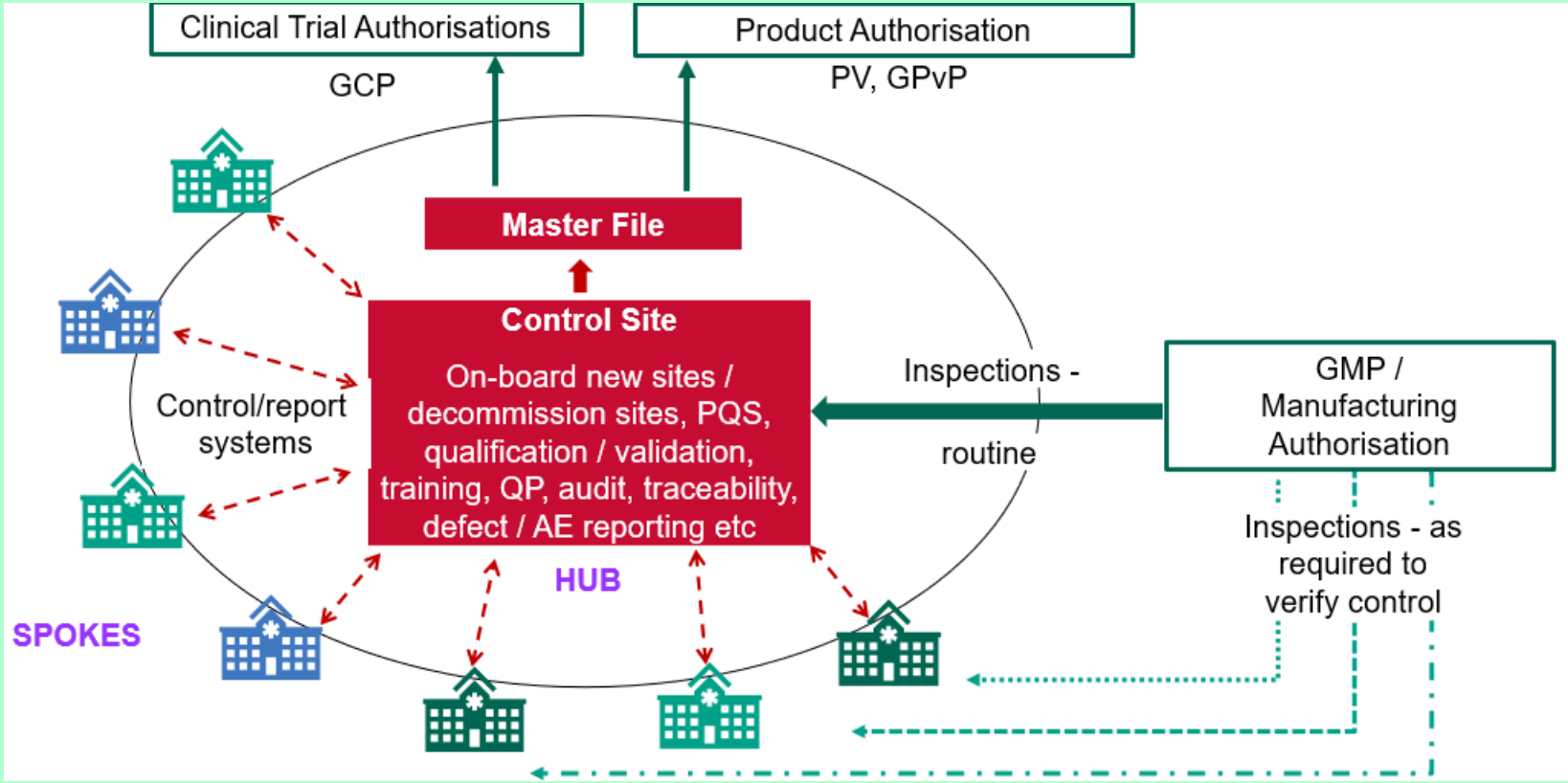
Typically to address public health needs or deliver significant clinical advantages

Legal Test = Product qualifies where, for reasons relating to method of manufacture, shelf life, constituents or method or route of administration – it can only be manufactured at or near the point of administration.

Convenience or cost is not an acceptable reason

ENABLING AND ENDURING LEGISLATION

Regulation – Hub and Spoke



- Control sites will be required to submit a master file. New requirement for MS holders.
- Spokes will nominate a named individual at each site with key responsibilities for product quality.
- The MHRA will inspect the hub and a selection of spoke sites

MHRA. Oct 2024

Back to the amended CTR….Practical things to know:

New Definitions:

Non – Investigational Medicinal Product (NIMP)

used in a clinical trial, as described in the protocol, but not as an investigational medicinal product.

Notifiable Trial

trial with no significant safety concerns relating to any of the investigational medicinal products (IMPs), as far as the sponsor is aware having made reasonable enquiries

- automatic approval after submission review for eligibility

Public Registry

Updated Definitions:

Authorised Health Care Professional will become **Health Care Professional**.
(HCP can be a Chief investigator)

Health Care Professional - List of professions who are eligible.

Chief Investigator: Single centre is also the PI and multicentre does not need to be an investigator at any particular location.

Investigator – new reg does not use PI but investigator means lead investigator

Participant now replaces the term “Subject”

Trial Location now replaces the term “Trial site”

Modifications replace Amendments.

Modifications replaces the term Amendments. (international alignment)

Substantial Modifications can be approved by Route A or Route B

Route B is for substantial modifications that do not bring any new safety concerns, It is a risk proportionate review rather than a full assessment.

Automatic approval if conditions are met:

Condition A Not FIH and holds a MA in EU EEA or USA

Condition B Ltd to a specific set of changes to trial protocol

Condition C Let to a specific change to the IB or SMPC (eg safety update, ADR frequency etc)

Labelling

Amended UK CTR (effective April 26) Reg 46(1)
For clinical trial use only
“Keep out of reach and sight of children”
Sponsor and investigator details
Trial identifier (e.g. reference code or acronym)
Participant identifier (e.g. name or ID)
Product identification (active substance, strength, form, contents, batch number)
Instructions for use or administration (can x ref PIL)
Route of Administration
Expiry date
Any special Storage conditions

Reg 46(1) applies if IMP is not authorised or being used outside the terms of its SmPC or has been modified.
Flexibility: If administration in hospital or health centre then KOORSOC not required.

If IMP holds UK authorisation then Part 13 HMR 2012 applies (ie normal dispensing label) with where possible items in red OR as per 46(3)

Reg 46(3) = Reg 46(1) - KOORSOC

If IMP holds EU or ICH region authorisation (but not UK) – default is 46(1) but reduced can be applied for if:

- imp Unmodified and used as per EU/ICH authorisation in a hospital or health centre then apply for use of 46(3)
- As above **AND in English** (also PIL) then Part 13 HMR 2012 applies (ie normal dispensing label) with where possible items in red

Labelling Contd.

Small Containers: 46(1) or 46(3) is primary package expectation but for blister packs or other small containers then secondary packaging can hold full particulars and small container should have:

- Trial sponsor and Investigator ID
- Participant ID
- Route of admin (unless oral solid dose)
- Product identification (active substance, strength, form, contents, batch number)

Or as per Part 13 HMR 2012 if applicable

Blinded Trials – name of comparator or placebo should be alongside the IMP

Decentralised Manufacture: No labelling required for True POCM (pre-identify primary pack advised).

Post QP Certification Labelling

Reasons include:

- **application of an identifier to ensure that a reconstituted IMP in its final container is administered to the correct subject**
- application of expiry date labelling (or revised expiry date labelling)
- application of an investigator name
- application of a protocol number

MIA(IMP) required unless risk to product quality is elevated unacceptably by transportation to the admin area. If it is not possible then a risk assessment should define mitigations including:

- a clear formalised procedure for the activity (including any sample labels and documentation to be completed)
- documented training and delegation of the activity to appropriate trial staff
- The level of assurance of the quality of the final product should not be less than if this labelling were performed prior to QP certification

Regulation 37 exemption still applies too- Ongoing MHRA query

Labelling

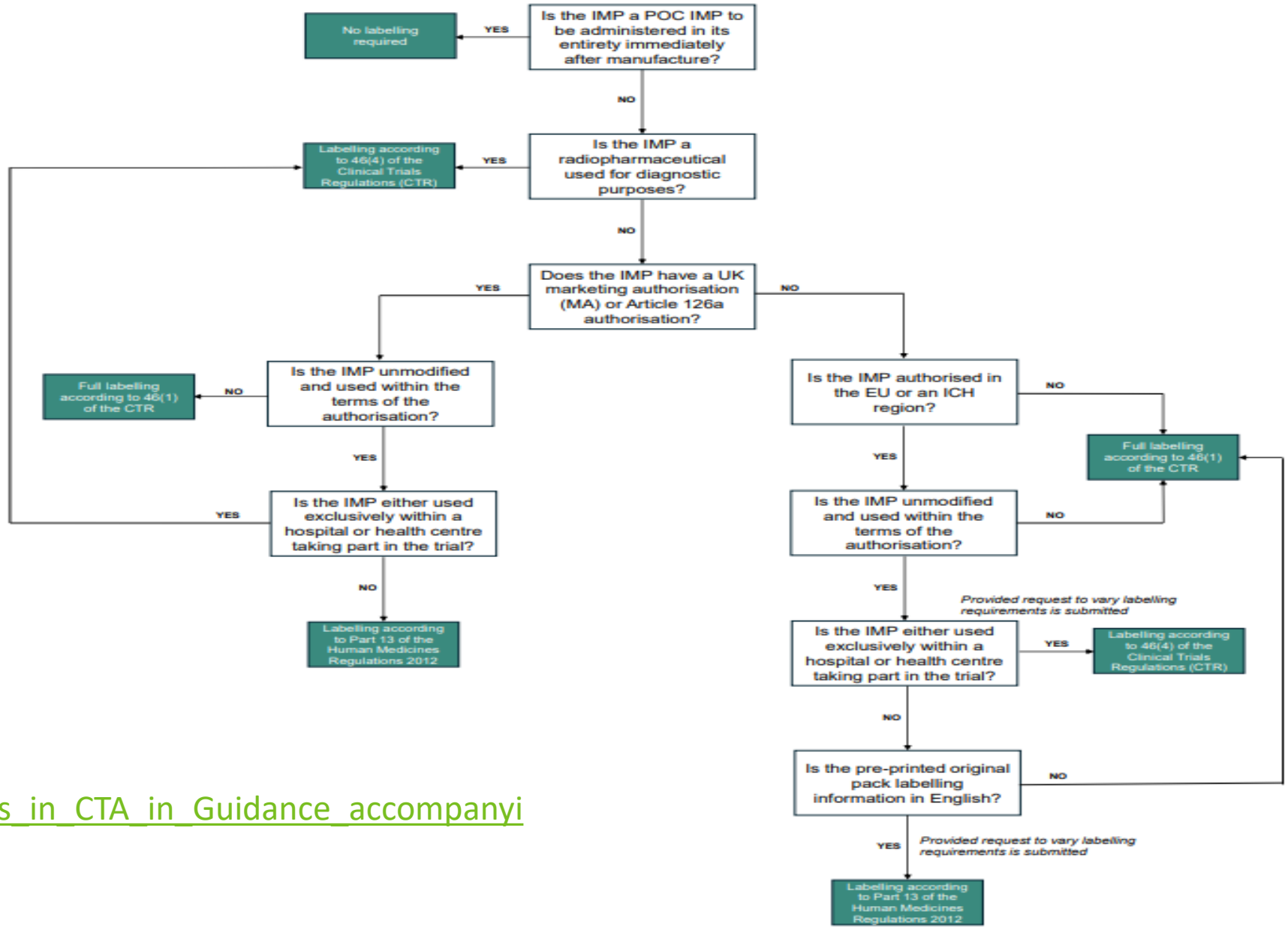


Fig3._Labelling_requirements_in_CTA_in_Guidance_accompanying_MfHU_CT_R.pdf

NIMPS – can be licensed or ULM

Rescue medicines:

- when the IMP does not have satisfactory efficacy
- when the effect of the IMP is too great and is likely to cause an adverse reaction in the patient
- to manage an emergency situation

Challenge Agents:

- NIMPs used to assess endpoints eg PET radiopharmaceuticals to measure function of organ, effectiveness, or assessing disfunction of organs.
- Background Treatment.

CTA submission will require:

- NIMPS to be listed in the cover letter
- Submission of a dossier containing details re the Quality of any NIMPs in use in the trial. ie a n-IMPD. (Simplified version acceptable for authorised and unmodified NIMPs)
- NIMPs should be manufactured according to GMP –if MS then manufacturer's authorisation will be included

Labelling:

Same labelling requirements as IMPs (Reg 46) but most NIMPs will be licensed so exemptions will apply.

How do we get Ready in Pharmacy?

Sponsor Pharmacy Role and Location pharmacy Role wi and Aseptics Team will need different actions.

Aseptics and Locations Role:

Undertake Gap analysis of new legislation

Undertake Controlled Change Process:

- Identify impact of the amended CTR and put in place actions.

  e.g. Expect faster operational changes (e.g., label, comparator updates)

Identify Actions required

e.g. Review terminology in SOPs / documentation, tighten change control & version management

Identify Risks

Prioritise actions to mitigate risks: e.g. New SOP for notified trials, low risk modifications may be priority over amended SOPs for new terminology

Collaborate and communicate:

- SPEAK TO R & D,
- Collaborate with Clinical Trials team – ensure roles and responsibilities are clear.
- Don’t leave it until April 2026.

RECAP of IMP Reconstitution (now)

- Reconstitution does not require an MIA(IMP)
- Uses QP certified IMP according to Pharmacy manual (under GCP)
- Annex 13 Labelling is good practice and is an assembly activity.
- Exemption from MIA(IMP) under Reg 37 exemption (pharmacist supervision)

- Reconstitution often occurs in unlicensed aseptic units but not under S10 exemption
- SPS audits scope under EL97(52) - S10 units.

QAAPs 5

5.3.5 The Chief Pharmacist is responsible for regulatory compliance. For example, in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004, manufacture of an investigation medicinal product requires an MIA (IMP)

Other mentions of up-to-date protocol required

NHSE POLICY – March 2023

Assurance of aseptic preparation of medicines

< Publication

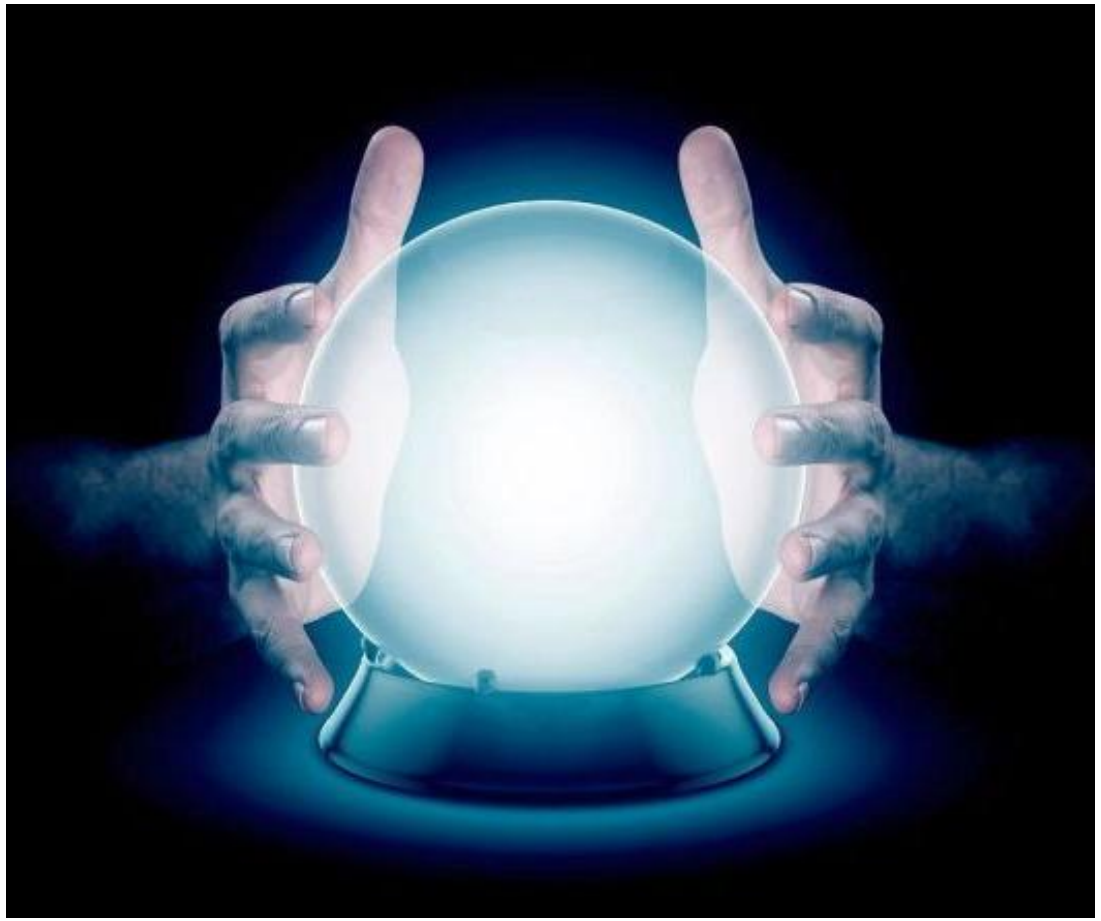
Content

NHS Infusions and Special Medicines Programme: Guidance to replace EL(97)52 in England

The guidance applies to:

- Aseptic reconstitution of any medicinal products or IMPs, where this is performed in a pharmacy aseptic facility.

QAAPS 6



- Standards will apply to IMP

- Expect some dedicated standards for IMPs
  - ❖ Roles and Responsibilities
  - ❖ Onboarding IMP SOP
  - ❖ Labelling
  - ❖ Version Control
  - ❖ NIMPs

- Anything Else? What would help?

The Future

Government encouraging UK research excellence

Regulation facilitating UK trial access and delivery.

Innovative Complex Medicines

Increased Clinical Trials needing aseptic capacity

Pharmacy teams upskilled to expedite (not delay) safe, compliant implementation

more robust data

more patient benefit


Any
Questions