Medicines & Healthcare products Regulatory Agency

Regulator's Update

QATS Symposium 2024

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October 2024

Putting patients first

MHRA Business Plan 2024-25

- Maintain public trust through transparency and proactive communication
- Enable healthcare access to safe and effective medical products
- Deliver scientific and regulatory excellence through strategic partnerships
- Become an agency where people flourish alongside a responsive customer service

[Read the MHRA Business Plan 2024-25 online]

Outline

GMP Inspectorate

- Inspectorate team for Unlicensed Medicines
- Training programme for Inspectors
- Inspection programme / focus

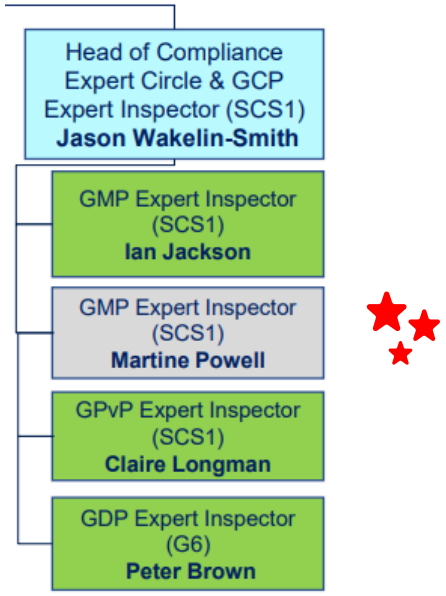
- Collaboration

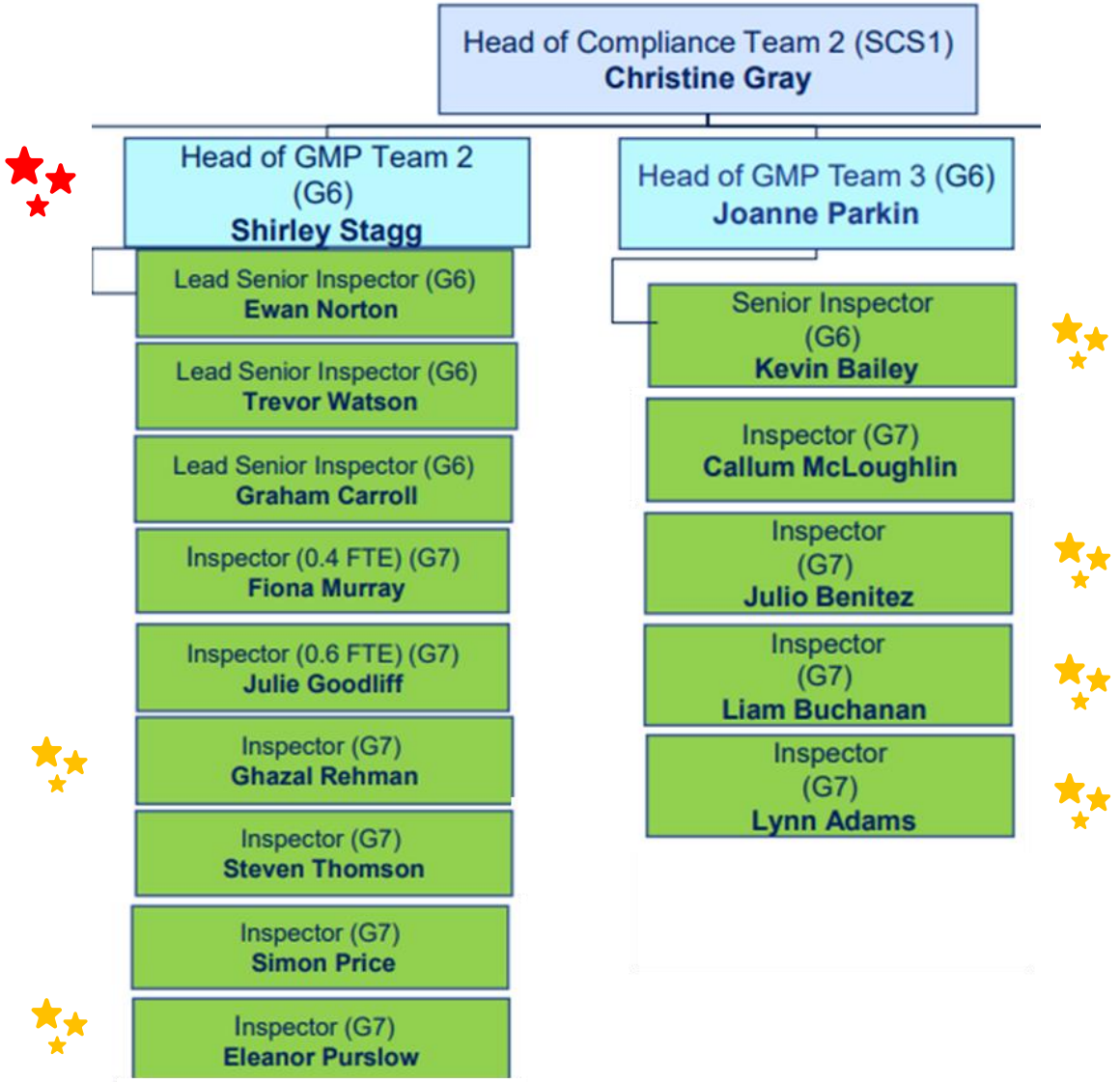
- Inspection Hot Topics

- Decentralised Medicines – Point of Care supply
- Radio-labelling of Clinical Trial materials

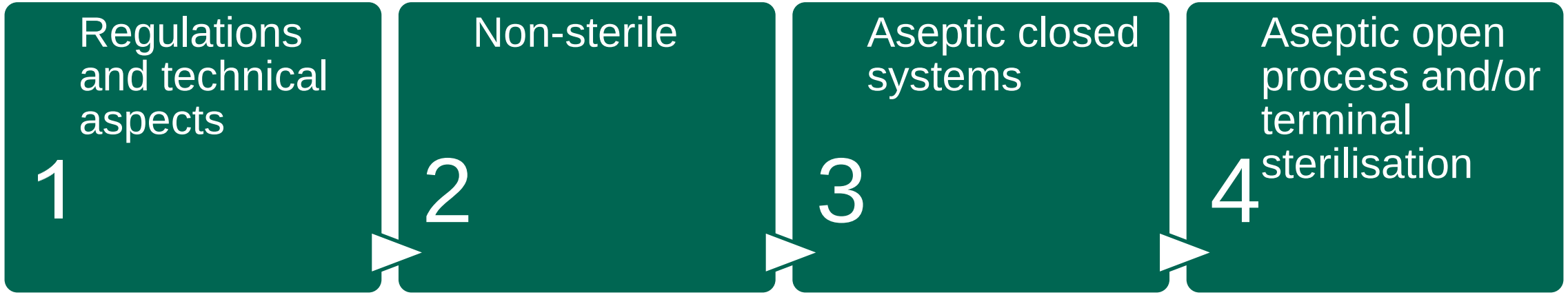
“Specials” inspectors

For sites that manufacture ‘Unlicensed’ Medicines



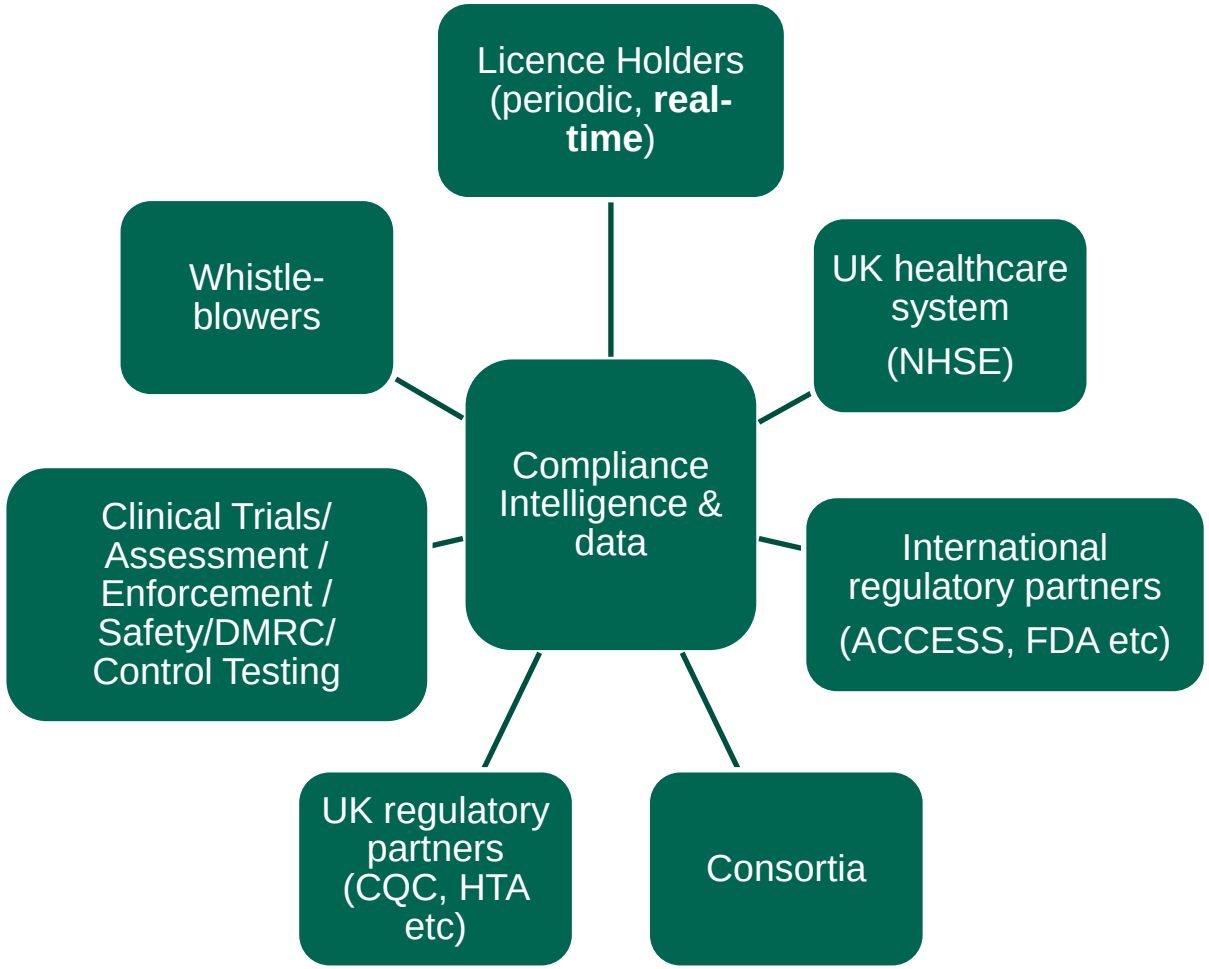


Modular training



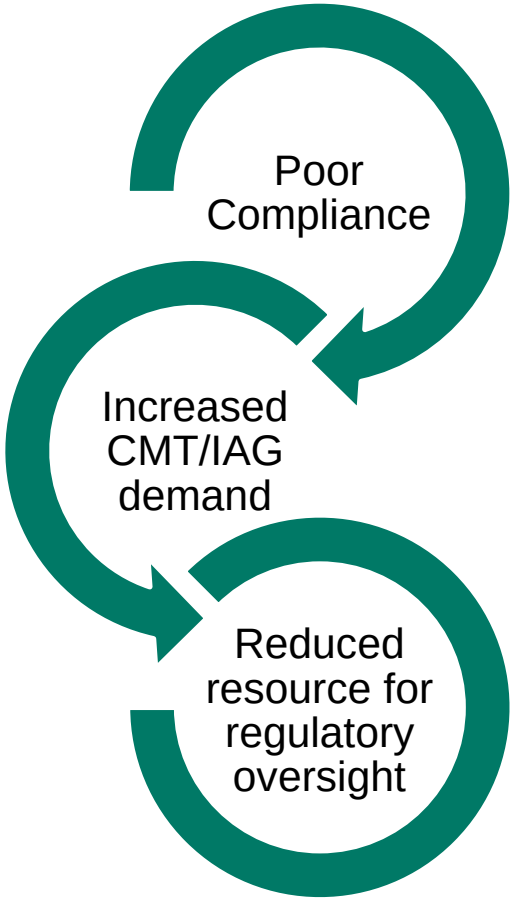
- Required training based on site activities
- Training programme dependent on inspector’s prior experience
- Combination of classroom training and inspection training, including assessment
- Grateful for the offers we have had to support onsite training

Enhanced use of data



Optimal access and use of intelligence and data is critical to our ability to use risk to drive our compliance programme and an OBCR model for regulatory oversight. Better use of data will also better inform inspectors during the conduct of inspections.

Upstream intervention



Poor compliance results in significant downstream impact on patients, the supply chain and the resources of the regulator (CMT, IAG). By increasing our upstream engagement across the product lifecycle with stakeholders we can inform and educate and reduce the cost of poor compliance

Collaboration

“If you want to go fast, go alone…

…but if you want to go far, go together”

Global Collaboration

The MHRA collaborate with other agencies worldwide, for example:

- Mutual Recognition Agreements: Australia, Canada, Israel, Japan, New Zealand, Switzerland, United States

https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-manufacturing-practice/mutual-recognition-agreements-mra

- Trade and Co-operation Agreement between the UK and EU
  - Rolls over pre-EU Exit recognition of GMP inspections between UK and EU.

https://www.gov.uk/government/publications/ukeu-and-eaec-trade-and-cooperation-agreement-ts-no82021

So why not consider the approach inside the United Kingdom

- What is the future collaboration between the MHRA and NHS QA for example?

UK Collaboration – The future?

Information sharing on sites within the UK

- NHS QA Regional Assurance – Section 10 Facilities
- MHRA Inspectorate – MS licenced facilities

- ➢ Common systems?
- ➢ Common findings?
- ➢ Impact onto alternative Services?

Nothing is fixed, however conversations are ongoing

- ❖ Focus for 2025

GMP Inspections of MS licenced facilities – hot topics

- Understanding Staffing requirements and proactive monitoring of Capacity
- Compliance with Pharmaceutical Quality System requirements
- Sterility Assurance controls
  - Awareness and application of Annex 1 and Contamination Control Strategies
  - Release processes

Top deficiency type breakdown MS sites over the past year

	Total	PQS	Aseptic & Contamination Control	Management oversight & Capacity
Critical	7	2	2	3
Major	29	9	11	3
Other	49	6	4	2

Understanding Staffing requirements

Critical Findings:

- **The manufacturer had not ensured that there was an adequate number of personnel with the necessary qualifications and practical experience to implement and maintain the quality management system and continually improve its effectiveness**
- **Senior management had not provided adequate oversight, support and resource to ensure the effective implementation and operation of the Pharmaceutical Quality System in support of product manufacturing and testing and therefore had failed to ensure the quality and safety of medicinal products**

Capacity Detail – but not the only focus of these critical findings

- The capacity plan did not ensure adequate resourcing for the expected demand and did not include the QA/QC functions
- The Capacity SOP did not clarify the basis for capacity oversight and resource required
- The Capacity utilisation for Production did not account for all activities such as management tasks, training, equipment management or support for QMS.

Pharmaceutical Quality System requirements - Deviations

- An appropriate level of root cause analysis was not applied during investigation of deviations
- Risk assessments lacked detail and did not adhere to GMP quality risk management principles with regards to scientific knowledge or focus on patient protection
- Not all deviations required to be investigated with those incidents scoring “low” not requiring investigation, yet the site scoring system was inappropriate leading to significant issues that could impact product quality and harm patients being marked as “low” risk
- Only approximately 20% of all raised non-conformances had associated CAPA.
- Several errors raised noted “distraction” as contributing factor, with no further analysis or actions relating to human caused errors.
- Approximately 50% of records raised in the past 2 years remained open past their due date.
- The site was consistently unable to meet the 30-day target date for closure of deviations
- Deviation tracking tools did not contain sufficient detail to allow trending, for example missing criticality, root cause, target closure date

Pharmaceutical Quality System requirements – Change Control

- Quality risk management was not used to evaluate the planned change and determine the potential impact on systems such as documentation, training, capacity planning, process validation.
- There was no prospective evaluation of planned changes via quality approval of changes before implementation
- The FMEA did not ensure that all risk mitigation activities were appropriate or implemented

- The CC process did not ensure that a regulatory or capacity assessment was included.

- There was no assessment of the impact of delayed changes
- Effectiveness check criteria were not correctly assigned to ensure quality objectives were achieved and there was no unintended deleterious impact on product quality

Sterility Assurance – overarching controls

Critical Findings:

- **A quality risk management approach was not taken to protect products and patients from the risks of cross-contamination**
- **Collective measures to ensure product quality, including sterility were not ensured and therefore patients were at risk of receiving contaminated products**

Details:

- Compliance with EU GMP Annex 1 was not assured. A risk assessment to address the gaps with Annex 1 requirements did not describe suitable actions or mitigations
- The Annex 1 gap assessment had no evidence of actions with target dates or steps taken to assess and mitigate the currently identified risks within it.
- The site had no active contamination control strategy (CCS)
- The contamination control strategy (CCS) did not adequately address the effectiveness of controls and monitoring measures to establish a robust assurance of contamination prevention.

Sterility Assurance - Practical controls

- A sanitisation step including a sporicidal agent designed to inactivate bacterial and fungal spores was not carried
- Sanitisation did not ensure adequate and complete coverage of materials and components
- Double and tripled wrapped materials were not handled in a manner to minimise cross micro-contamination
- Material transfer qualification was not representative of the range of materials and components as the standard transfer processes
- Material transfer qualification activities did not ensure that there was a reasonable bioburden on the preclean samples to confirm effectiveness of the transfer sanitisation process
- The manufacturing areas could not be shown to consistently achieve the required level of microbial cleanliness
- There was no documented procedure for actions to take in the event of an incorrect volume withdraw or the requirement to record actual actions taken

Order management and Release processes

- Orders were accepted via telephone communications, without subsequent written records.
- There were no formal instructions to ensure that product formulation and stability matrixes were securely controlled and that there was no access to uncontrolled copies.

- There was no current list of individuals authorised to perform batch release
- Training records for releasing officers did not align with the site or regulatory requirements
- There was no requirement to ensure that product was released against a named patient order or specification in place of this for batch manufacturing to stock.
- Release activities did not ensure that the facility and all systems were in place and operating correctly to support the daily release activities
- The inspectors noted frequent interruptions for the releasing officer

- Specials labelling did not conform the BP requirement

Decentralised Manufacture

A new Statutory Instrument detailing a new regulatory framework is being laid in Parliament this week

The Goal – to support and enable the safe development of innovative products with a very short shelf life and may be highly personalised, requiring them to be manufactured and supplied at the point of care for patients in hospitals or at home

- This will be a new regulatory framework for medicinal products manufactured at the Point of Care and Modular Manufacture
- This will be supported by new guidance on the requirements

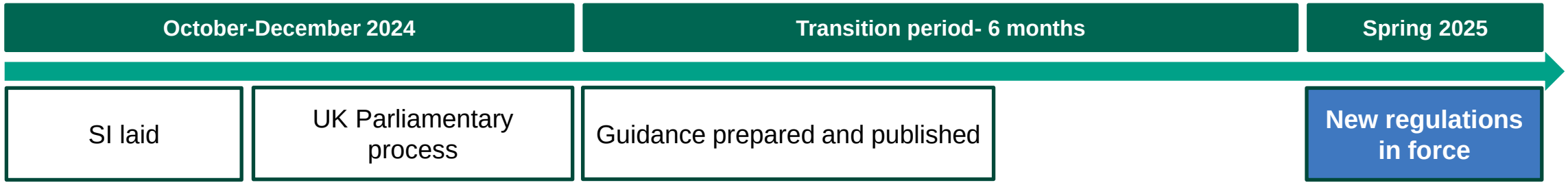
<u>Applicable to:</u>

Pharmaceutical innovators, Patients & their carers, Healthcare professionals (in particular NHS Specialist Pharmacy Service teams), Health system partners across the UK: DHSC, NICE, NHS England, Devolved Administrations and health partners in Scotland, Wales, N.Ireland & Others

New framework - where we are today

- Proposals and legislative drafting have been finalised
- Legislation is set to be laid 17 Oct 2024 – pending parliamentary processes
- Implementation will begin following a 6-month period to ensure stakeholder and sector readiness

Target timelines, pending parliamentary process



Decentralised Manufacture – the next 12 months

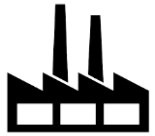
- Stakeholders to be involved to collaboratively develop detailed supporting guidance
  - Technical workshops on guidance development
  - Potential webinars to socialise guidance once finalised (April/May tbc) for industry and healthcare professionals
- Guidance to be in place in good time – this will support organisations to implement local policies and procedures ahead of the regulations applying
- Regulatory framework to launch from Spring 2025
- International collaboration to harmonise approaches internationally via the International Coalition of Medicines Regulatory Agencies (ICMRA)

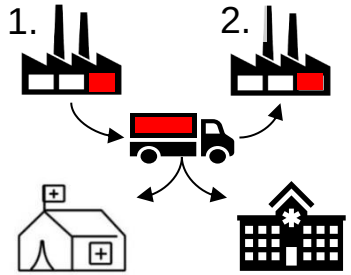
DM - Broadened spectrum of manufacture

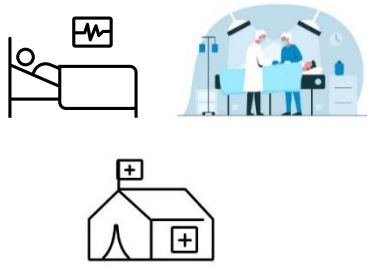
Mass market
Global

Personalised
Local

Factory | **Modular (POD)** | **Mobile** | **POC** | **Home**







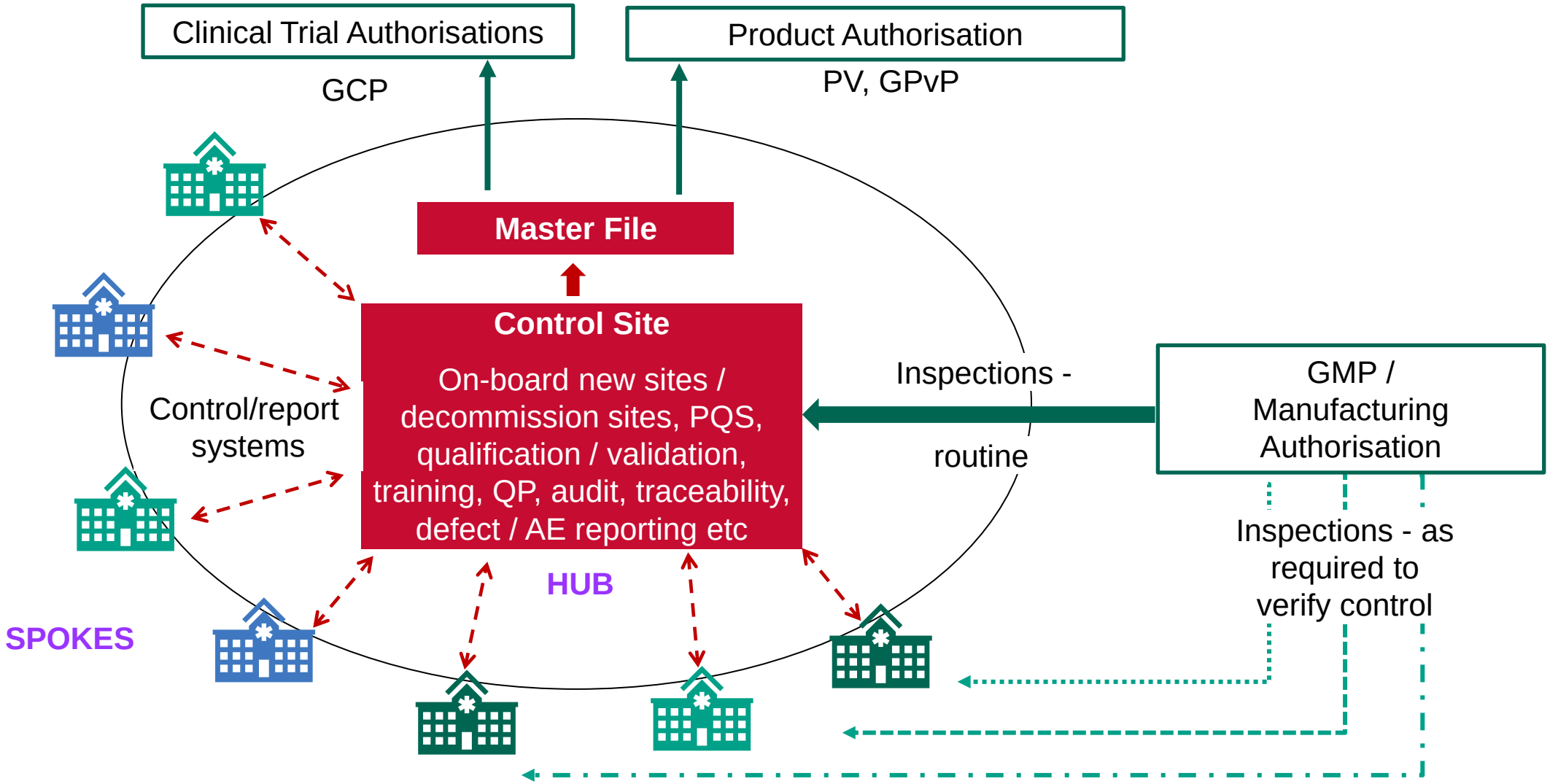
Large scale
Stable batches
Small number of manufacturing sites

Single person ‘batch’
Short shelf life
Large No. of manufacturing sites

Centralised | Decentralised / distributed

UK: same basic structure for all DM types based on ‘hub’ (Control Site) and ‘spoke’ (POC/MM) Model and a Master File

Decentralised Manufacture Oversight - Control Site & Master File



Controls for Radiopharmaceutical labelling – the review

- There have been a cluster of enquires around the management of radiopharmaceutical products, especially linked to clinical trials.
- The review of the clinical trials legislation and the associated public consultation in 2022 considered this, via the following question:

  Do you agree that it is appropriate for radio pharmaceuticals used in a trial to be able to be exempted from the need to hold a Manufacturers Authorisation for Investigational Medicinal Products (IMPs)?

- The consultation aim was to streamline clinical trials approvals, enable innovation, enhance clinical trials transparency, enable greater risk proportionality, and promote patient and public involvement in clinical trials.
  - The comments received supported the exemption for radiodiagnostics but not for radiotherapeutics

Controls for Radiopharmaceutical labelling – the outcome

Additional detail on the Radiolabelling of IMPs has been included into the upcoming update to the Clinical Trials legislation.

- This applies an exemption from the need to hold an MIA(IMP) to carry out the radio-labelling of cold kit clinical trial materials that have been previously certified by a Qualified Person at a site holding an MIA(IMP) licence
- This will apply for radiopharmaceuticals used for diagnostic purposes, where the radiopharmaceutical is exclusively for use in a hospital or health centre which is a trial location for the clinical trial in which the product is to be used; or taking part in the clinical trial
- The Site carrying out the radiolabelling of IMPs must however hold an MS licence
  - Note that the radiolabelled IMP is NOT a Specials or Unlicenced medicine and should not be labelled with the MS licence number; Guidance is included and will be provided.

The new regulatory framework is expected to be laid in Parliament before the end of the year with a 1-year implementation timeline

Controls for Radiopharmaceutical labelling – the Interim

The MHRA has taken a considered approach to support on-going and imminent trials, as few Radiopharmacy sites hold an MIA(IMP) licence.

So – what is the process today?

- The MHRA GMP inspectorate and Clinical Trial Assessment units have agreed a process to allow labelling of cold kit IMPs today under an MS licence operation, with input from Policy and Regulatory colleagues.
- The Sponsor must state in the CTA application the use of MS licenced sites in the radiolabelling process.
  - The Sponsor must indicate which IMPs this applies to within the trial
  - The Sponsor must confirm that radiolabelling on this basis applies where the primary objective or mode of action for that product is diagnostic scanning / imaging; either for trial eligibility or detection of take up, localisation or characterisation of the defined and QP certified IMP

This is to support UK trials and to align with the EU where there is no requirement related to radiolabelling under an MIA(IMP) licence.

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Thank you

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