Medicines & Healthcare products Regulatory Agency

Regulators Update

QATS Symposium 2023

Christine Gray and Martine Powell

28 September 2023

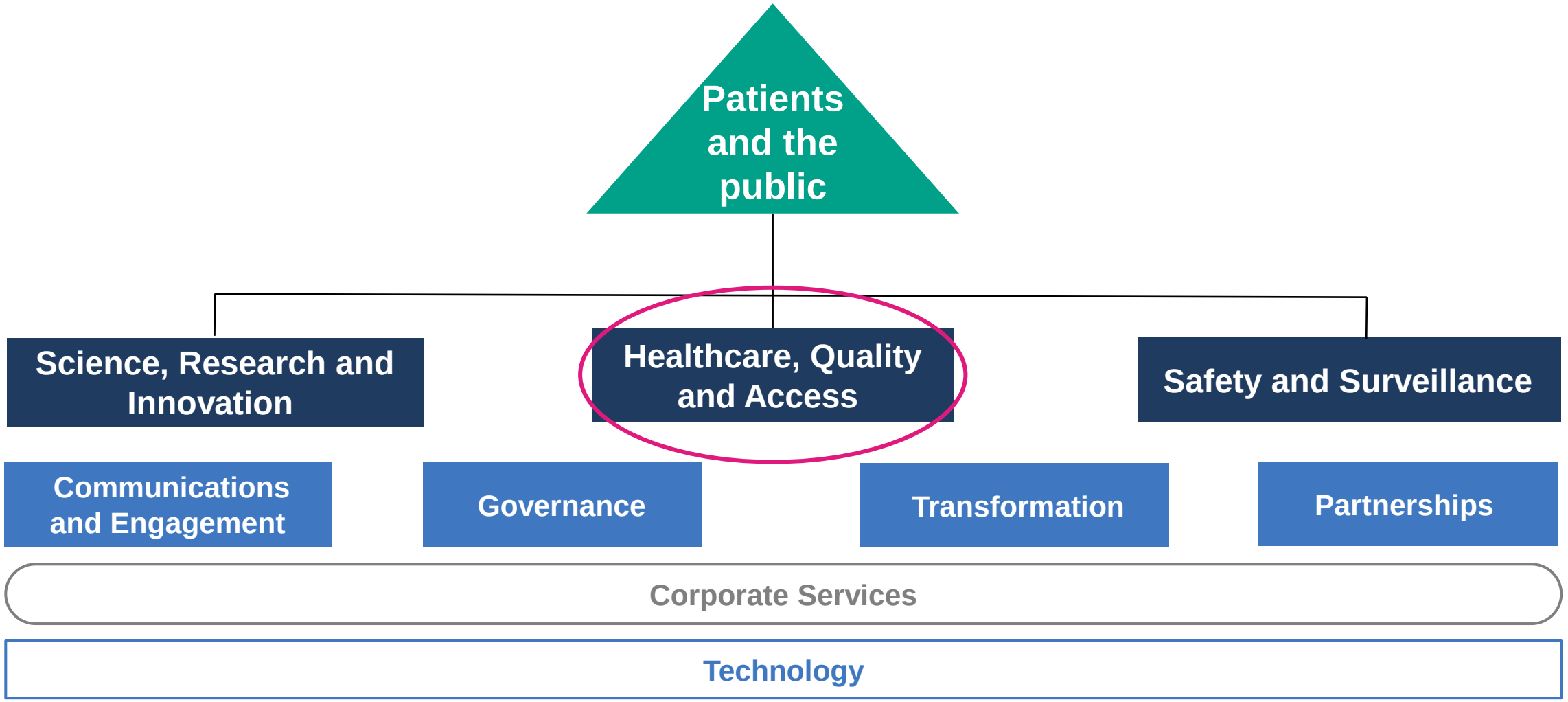
Putting patients first

MHRA Business Plan 2023-24

- Maintain public trust through transparency and proactive communication
- Enable healthcare access to new, 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 2023-24 online

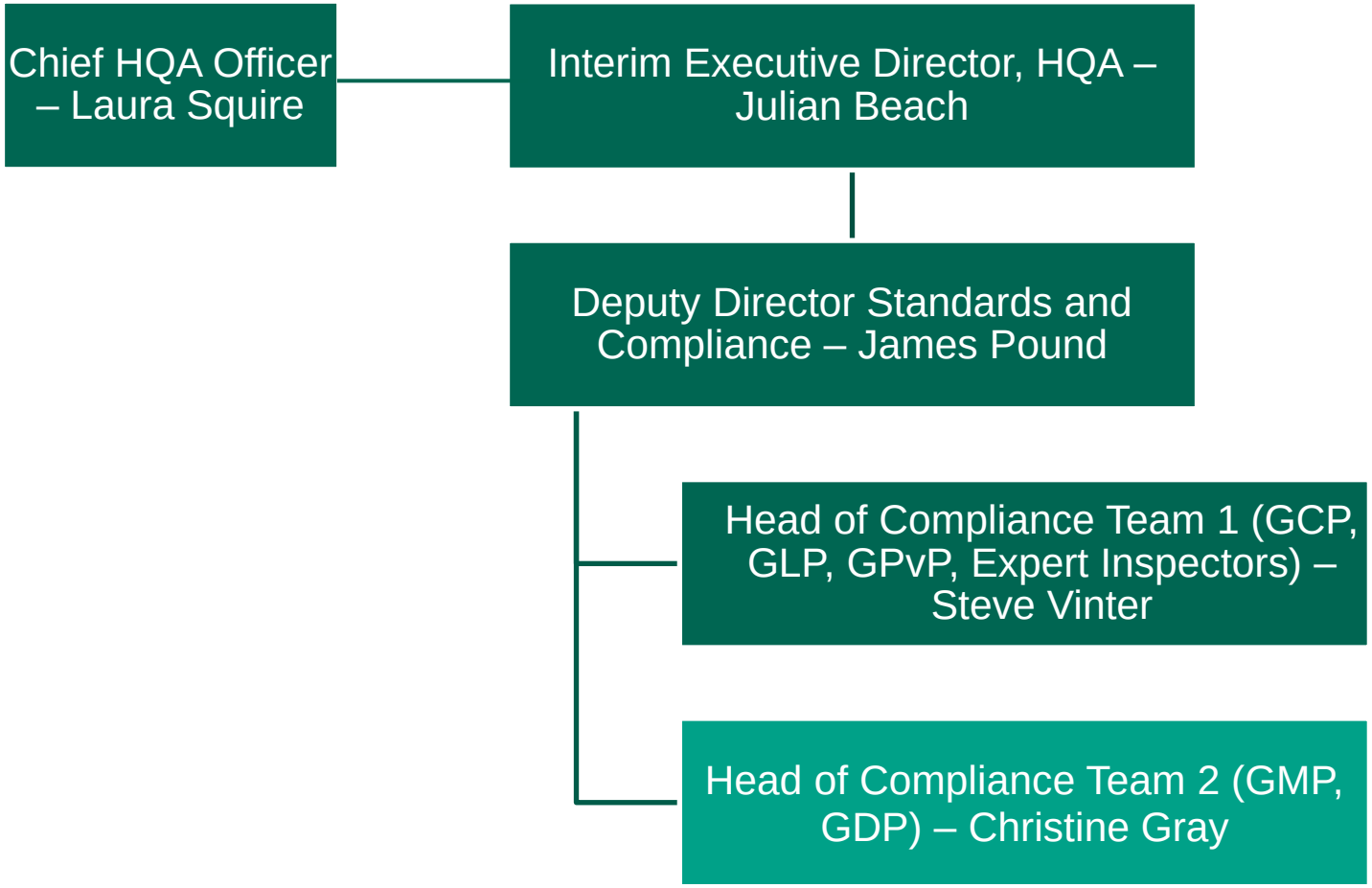
One Agency


Patients and the public
Science, Research and Innovation
Healthcare, Quality and Access
Safety and Surveillance
Communications and Engagement
Governance
Transformation
Partnerships
Corporate Services
Technology

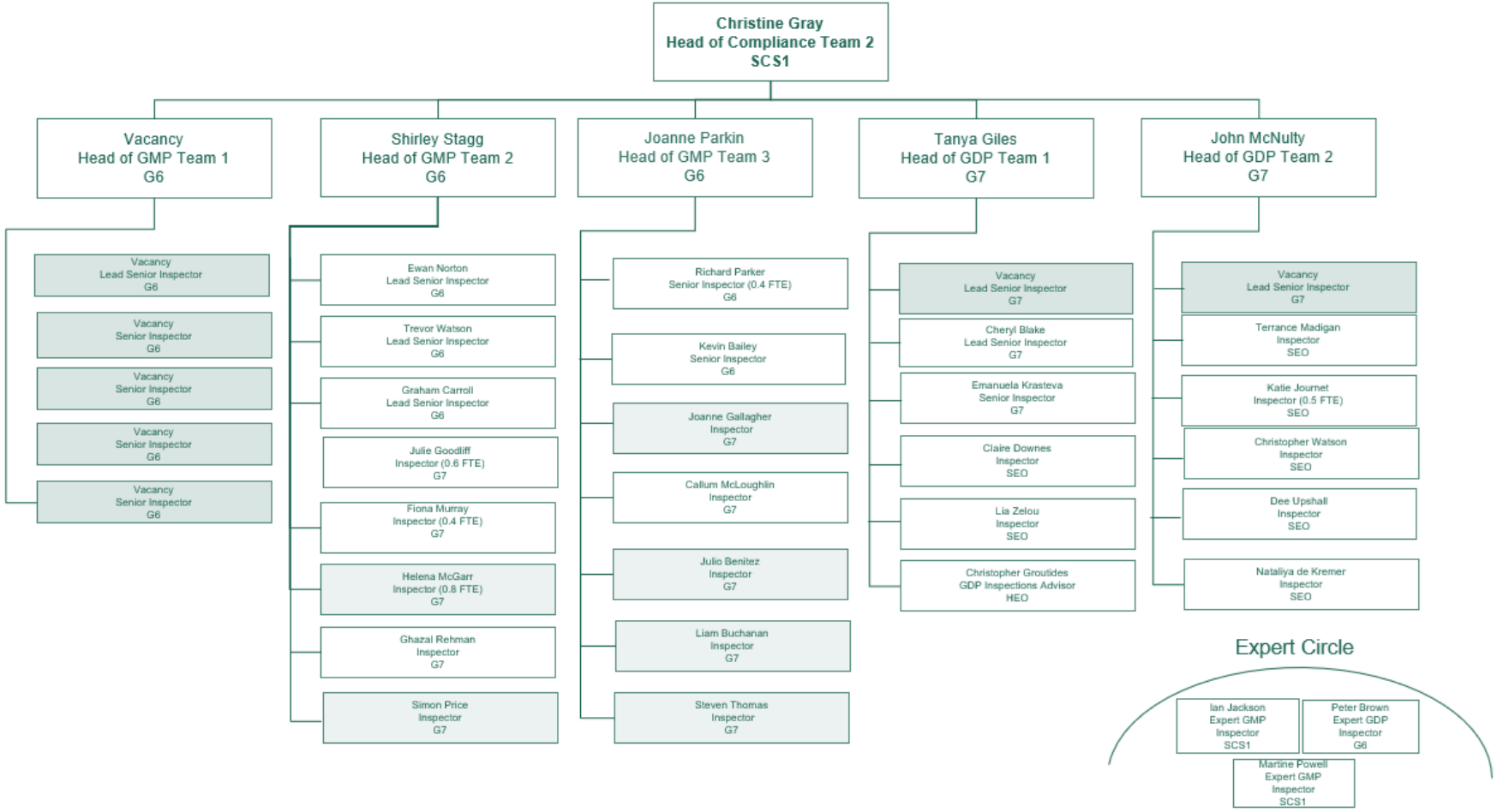
Healthcare, Quality and Access

Innovative Devices	Providing pre-market support and smooth passage to market access for innovative medical devices. This team is also leading the development the new regulatory framework for Medical Devices
Innovative Medicines	Facilitates early access to market for innovative medicines, both through UK accelerated pathways as well as those with International partners
Population Health	Is vital to an affordable healthcare system. supporting early access to market for products that are critical to the health of the wider population and the NHS
Authorisation Lifecycle	Is a centralised function where crosscutting functions are located, such a Borderline, Labels, Leaflets and Advertising and eCigarettes. The ream also delivers essential high-volume, low complexity work is delivered. It includes some data assurance and quality work and will deliver its services across the whole of HQA
Standards and Compliance	Enables innovation and healthcare access across the global product lifecycle by risk proportionate standards development and compliance through the British Pharmacopoeia and MHRA Laboratory, the Inspectorate, the Inspection Action Group and Devices Audit and Compliance

Structure for Standards and Compliance



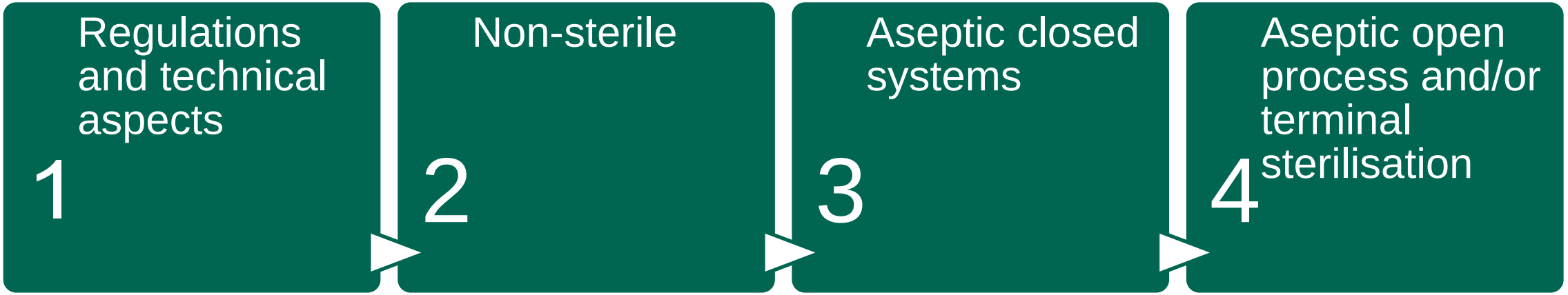
Structure of Compliance Team 2



Inspections

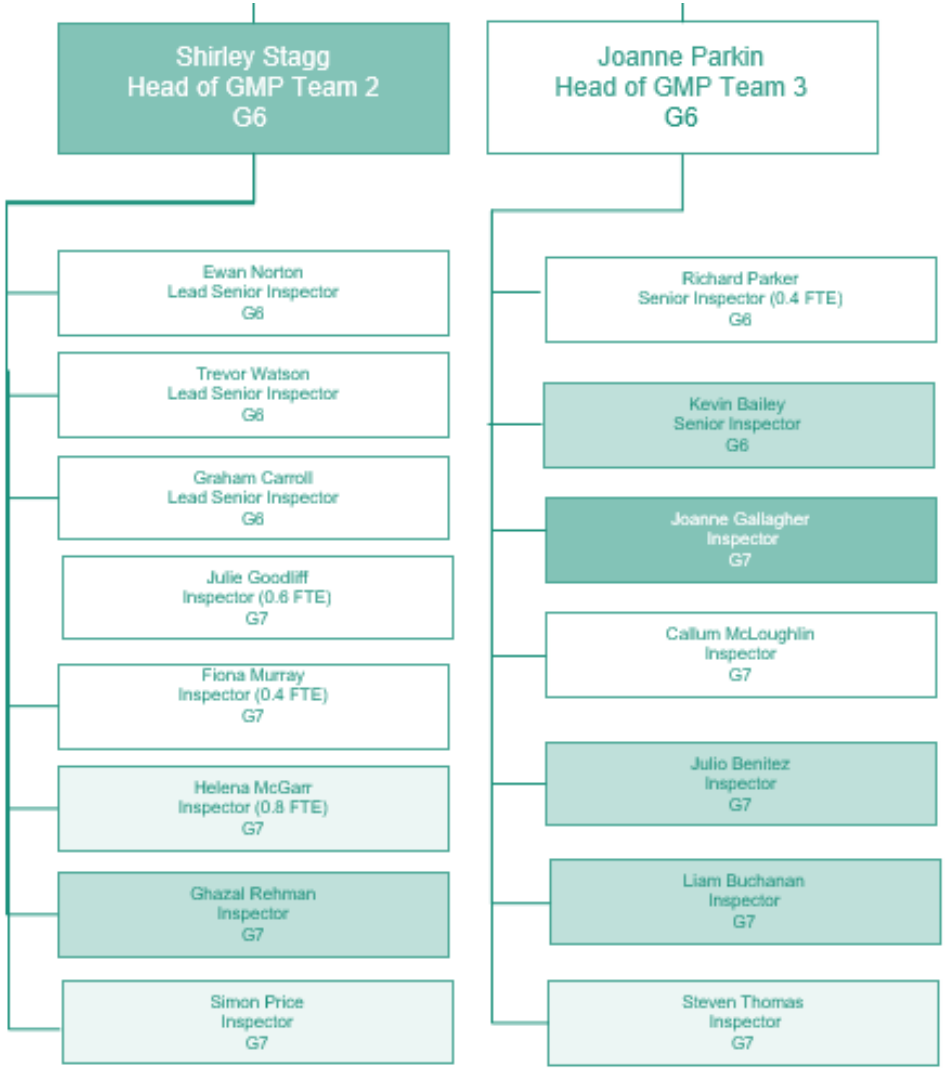
- Aware of delays with routine inspections
- Aware of need to engage
- Working to improve on both

Modular training



- Required training based on site activities
- Training programme dependent on inspector’s prior experience
- May require an existing accreditation to inspect sterile manufacture
- Combination of classroom training and inspection training
- Grateful for the offers we have had to support onsite training

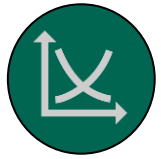
“Specials” inspectors



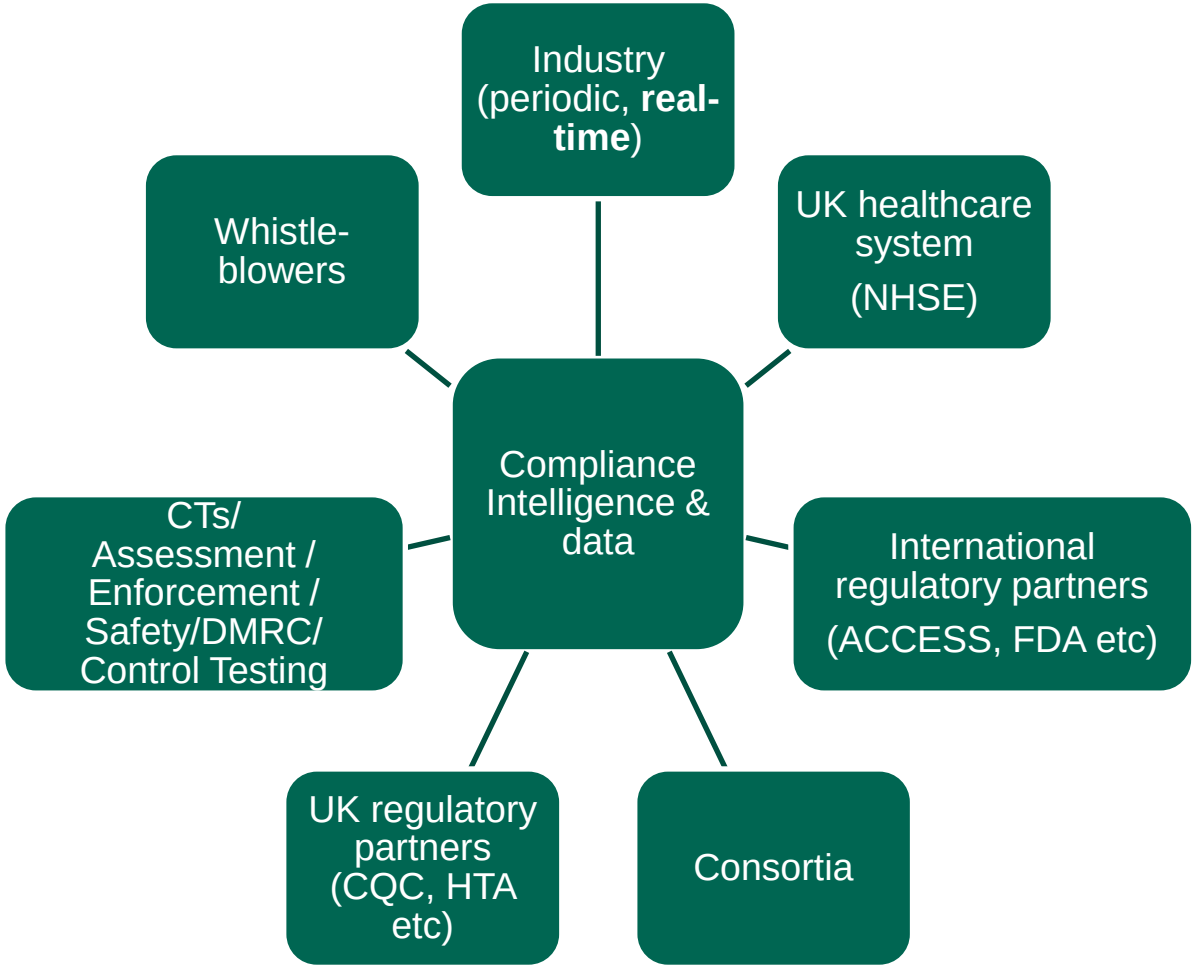
Transforming our work

- To truly focus regulatory oversight on risk and incentivise compliance by pioneering an outcome based cooperative regulation approach that means compliant and trusted organisations would be subject to a different regulatory regime
- Enabling lifecycle management in line with ICH Q12 for post approval changes
- Prevent non-compliance occurring in the first place by being an enabler to compliance-by-design for both existing and new innovative products
- To use new and innovative technology to radically improve regulatory oversight

Compliance strategy on a page

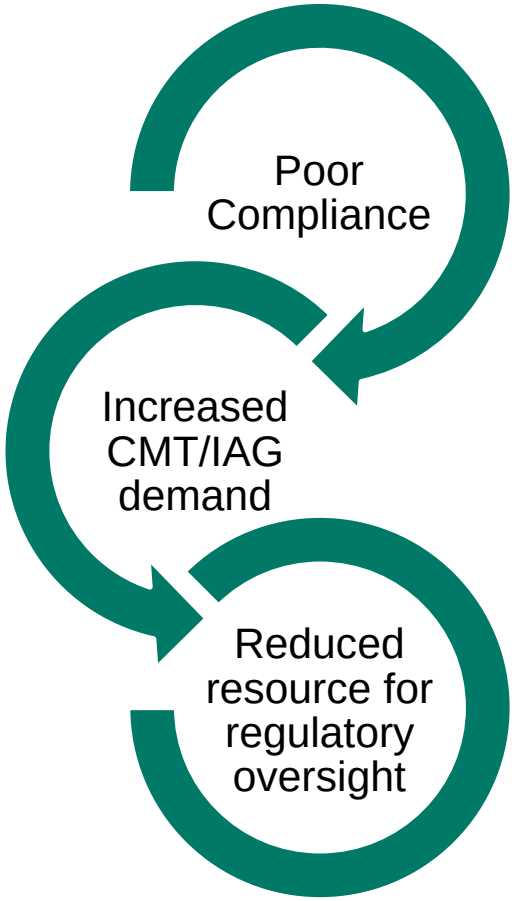
Enhanced use of Intelligence and Data	Upstream Intervention	Technology as an enabler	Drive and Incentivise Good Compliance	Collaborate and Partner	Capability and Capacity
					
Making optimal use of data and intelligence (both ours and those of our peers and stakeholders) to inform our work and decisions	Preventing non-compliance and enabling innovation by upstream engagement with our stakeholders through a variety of mechanisms.	Using technology as an enabler to our work. Improving efficiency and effectiveness of our compliance activities.	Further developing our existing risk-based compliance model in line with Outcome Based Cooperative Regulation (OBCR) concepts.	It is only by collaborating with partners both domestically and internationally we can spearhead innovative regulation.	Industry require a workforce with new skills and a pipeline of talent that we can both grow/develop and recruit/retain.

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

Capability and capacity

Compliance is a knowledge-based activity that requires teams of highly skilled and motivated Inspectors across the GxPs

- Retention
- Training
- Recruitment

Inspection processes

Inspections are assigned to the inspectorate team on a quarterly basis.

For inspections of “Specials” sites holding an MS licence, we will be typically contacting sites 1 to 2 weeks prior to the dates that each inspector has allocated for that site.

For a site involved in any Sterile operation, the inspection will typically be around 1.5 days

- Where a site holds more licences (such as an MIA(IMP) for clinical trial products), this may be extended
- If the site is larger, has undergone significant changes, processes complex products or has a poor compliance history, this may also be extended
- Where a site does not undertake sterile processes, this may be reduced to 1 day

Inspection preparation

When we send notification of inspection, you will be asked to complete a “Pre-Inspection Compliance report” found here: Link to pre-inspection compliance report

We may also ask you to send us information from your Quality system, such as spreadsheets for Deviations, Change Controls, Complaints and other records.

- Please only send these if requested, and only if you use electronic tracking systems.

Be prepared to give a summary of the site for the introductory opening meeting

- This should be an overview presentation of the company/site/products would be appreciated, highlighting current processes, systems and structures

Inspection hot topics → CAPACITY

From the 2021MHRA Guidance for Specials Manufacturers document :

3.1.3 Capacity planning.

A capacity plan should be in place, to ensure adequate resourcing for the expected demand. Note: The expected utilisation in a manufacturing facility is around 70 - 80% to allow adequate resource for the associated ancillary tasks outlined below. Utilisations greater than this will be viewed as increasing the risk profile of the site.

There should be a thorough understanding of production demand and supply constraints, and appropriate strategies to highlight imbalances in a timely manner to ensure appropriate action is taken.

Capacity plans should also address associated essential tasks such as maintenance of the quality management system, order entry, surface sanitisation, preparation activities, and product release and any other relevant activities so that a company clearly understands any bottlenecks in its process.

A unit's defined capacity should only be exceeded infrequently. If it is exceeded, approval from QA must be sought through the use of the planned deviation system.

Compliance with the capacity plan should be assessed at a minimum monthly during management review and reviewed at least annually. Any changes should be evaluated through the change control system.

Guidance for 'specials' manufacturers - GOV.UK (www.gov.uk)

Inspection hot topics → Capacity concerns

Inspection deficiencies are routinely raised related to capacity.

Examples noted:

- The recent average utilisation was approx. 150% across four months, with spikes up to 200%.
- No strategies to address the imbalances in a timely manner had been put in place, to ensure appropriate action was taken.
- Compliance with the capacity plan could not be robustly assessed because the data and formatting contained withing the excel workbook was seen to be unreliable. For example, a capacity of >200% was showing as “green”
- Capacity was only reported as a stated number of batches produced per month (rather than a %) and did not address any comparison to maximum output levels
- Capacity plans did not address associated essential tasks such as maintenance of the quality management system, order entry, surface sanitisation, preparation activities, and product release and any other relevant activities
- There was no formal assessment required and no escalation process in the event of exceeding capacity.

Inspection hot topics → Capacity focus

Ensure that your operations have or carry out the following:

- Assessed how you manage compliance with the guidance requirements
- Capacity oversight SOPs that include all required activities, not just those related to the daily morning dispensing activities
- Routine assessment to Future proof capacity – Prospective analyses to check if you can fulfil demand
- Escalation of Capacity issues – to senior Management, to Executive management and MHRA where needed

Key to this:

- Knowledge of how much time different tasks take – both manufacturing, quality and management
- Assessment of any significant changes – personnel, products, support for other units with respect to how these impact your capacity
- Routine assessment of actual process - Retrospective checks to see if you kept to plan

Inspection hot topics → Sterile operations

The MHRA Specials Guidance states that “all aseptically prepared products where open systems are used, should be manufactured in accordance with the standards outlined in the EU Guide, specifically Annex 1”.

Annex 1 was updated in August 2022 and came into force on the 25th August 2023.

Please make sure that your site, if handling Sterile products, has read this updated Annex. The revised document was written to remove ambiguity and inconsistencies, whilst taking account of advances in technologies.

ACTION:

- Carry out a gap analysis of this document and operations on site
- Look to perform a risk assessment of identified gaps and resolve matters.

Inspection hot topics → Sterile operations: Transfer concerns

The transfer of materials and products using Surface sanitisation into a controlled Grade A area for manufacturing continues to be identified as a key inspection finding.

This is accepted provided that there is evidence that the process is controlled within the boundaries of capability (as per the MHRA Specials Guidance).

We still continue to see poor practise using spray and wipe as a result of inadequate training, time pressures and difficulty in ensuring proper surface coverage, and also lack of consistent use or application of sporicidal agent designed to inactivate bacterial and fungal spores.

Ensure appropriate approaches for verification of surface sanitisation processes

- Ensure duplicate sets are used, such that pre-sanitisation levels are known with an acceptable bioburden
- Ensure challenge carried out via a robust method, on a rolling basis for all involved staff.

Inspection hot topics → Environmental monitoring concerns

Where growth promotion tests are carried out for EM plates or the check of fertility is performed, ensure that your local environmental isolates from the manufacturing area are used.

Ensure that plates are stored appropriately:

- Prior to Use
- In known temperate storage areas, typically in triple wrapped bags
- Segregate or clearly identify plates under quarantine versus those available for use
  - During exposure
  - In a representative area, fully open
    - Post Exposure
    - In controlled incubators
    - Uniformly stacked

Inspection hot topics → General

Across all licence holders, the highest frequency of deficiencies remains those for Chapter 1:
the Pharmaceutical Quality System

Do not overlook the importance of ensuring what should be the corner stones of your operations and involve of all departments, not just Quality.

- Ensure that deviation and issue investigations are robust and address the root cause to ensure prevention of recurrences
- Ensure Changes are well defined and measurable, with robust actions and effectiveness checks
- Ensure recalls are correctly defined (anything that has left the licenced unit / your control) and notify the applicable parties including the MHRA Defective Medicines Reporting Centre

Maintain an awareness of the “health” of your quality systems via good metrics and key performance indicators.

Thank you

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