Safeguarding public health

EMEA SME Workshop
Biological GMP Issues

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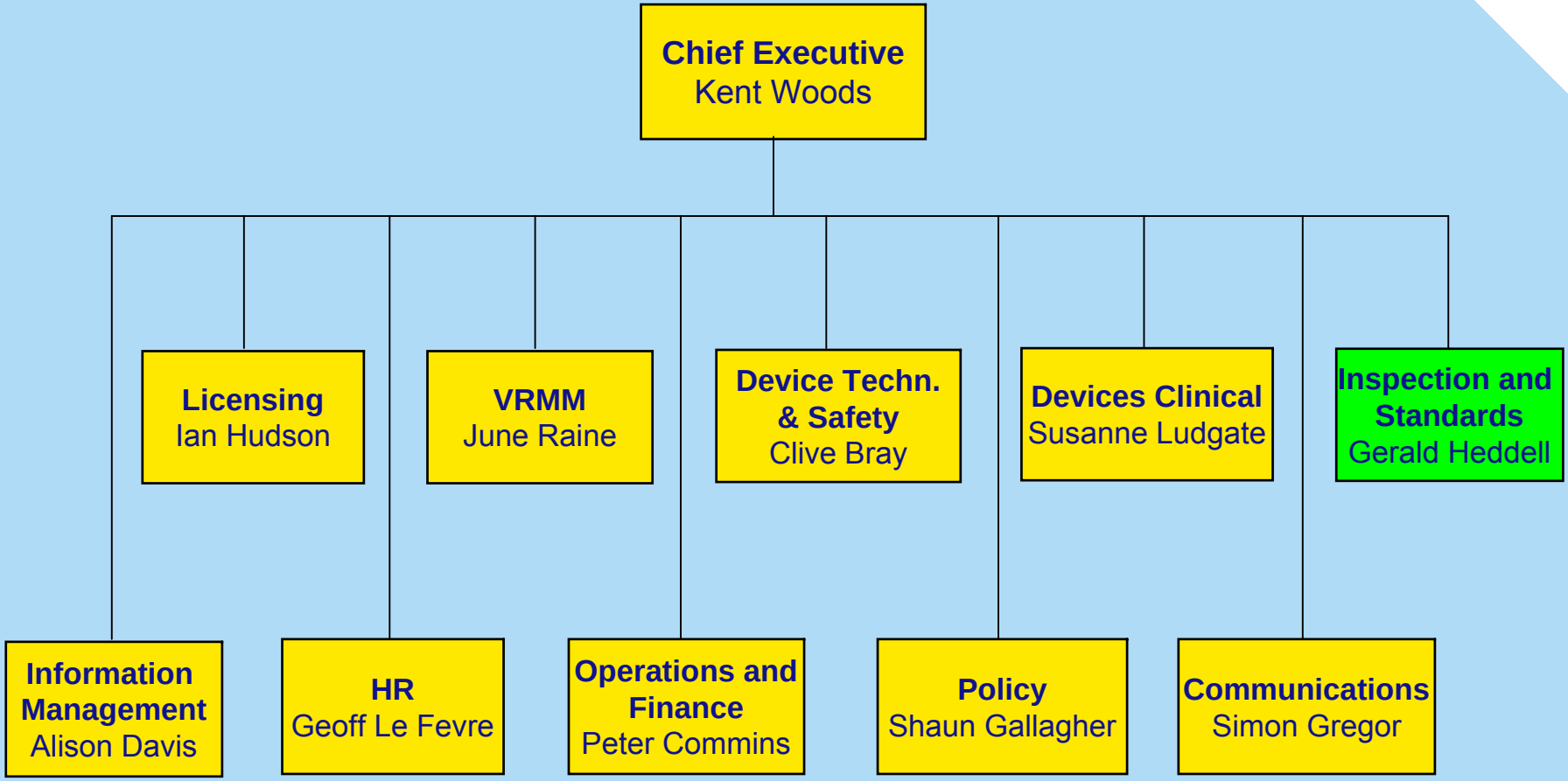
Presentation Outline

- Background
  - Focus on start-up of organisations and/or products
- GMP changes - biological
- GMP issues
- Common findings

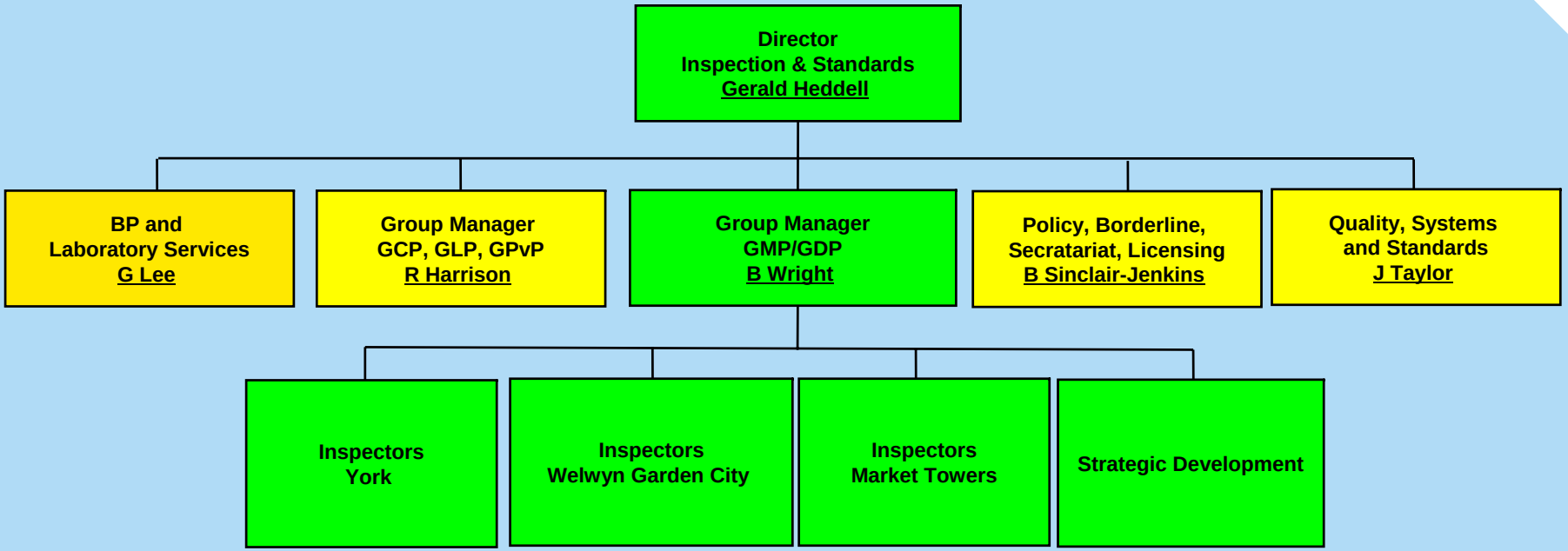
Abbreviation Glossay

- SCT - Somatic Cell Therapy
- GT - Gene Therapy
- TEP - Tissue Engineered Product
- ATP - Advanced Therapy Products (SCT + GT + TEP)
- GLP - Good Laboratory Practice
- GCP - Good Clinical Practice
- GMP - Good Manufacturing Practice
- GPvP - Good Pharmacovigillance Practice
- GDP - Good Distribution Practice
- EUTCD - EU Tissue and Cells Directive
- IMP - Investigational Medicinal products
- QRM - Quality Risk Management (ICH Q9)

Background – MHRA structure

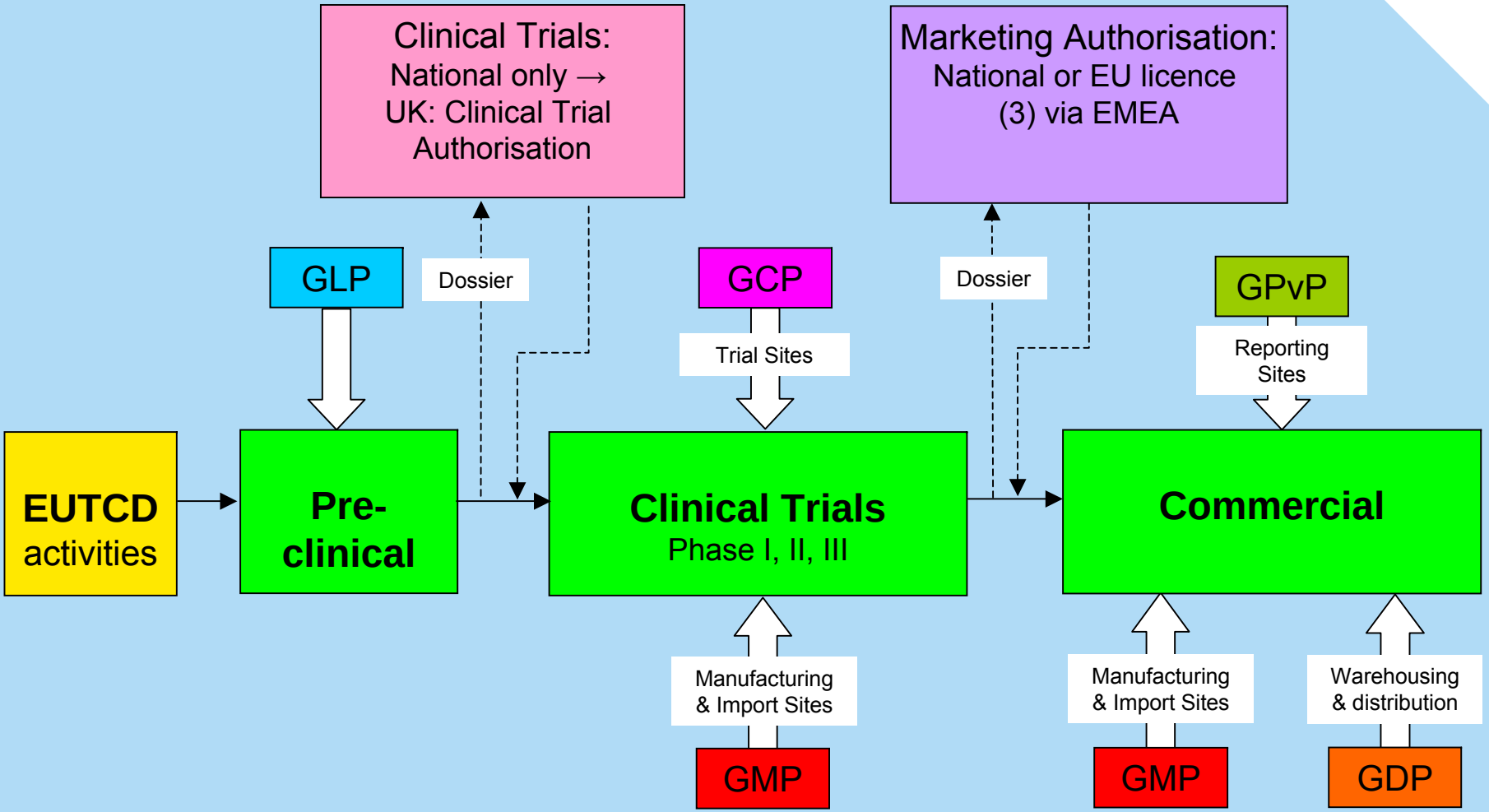


Background – I&S Division



- 60 inspectors across GXPs, 28 in GMP, 5 specialise in biologicals.

Background – linking the GXPs



GMP changes – Annex 2 Revision

- Current Annex dates from early 1990's
- At public consultation until 14th March
- Please submit comments!
- Review comments and incorporate where appropriate
- Further Advanced Therapy Products (ATPs) input
- Proposed changes:
  - Part A – general biol guidance
  - Part B – 10 specific biological product types: allergens, animal immunosera, vaccines, recombinant, monoclonals, GT, SCT and xenogeneic, transgenic animals and plants, TEPs

GMP changes – biological

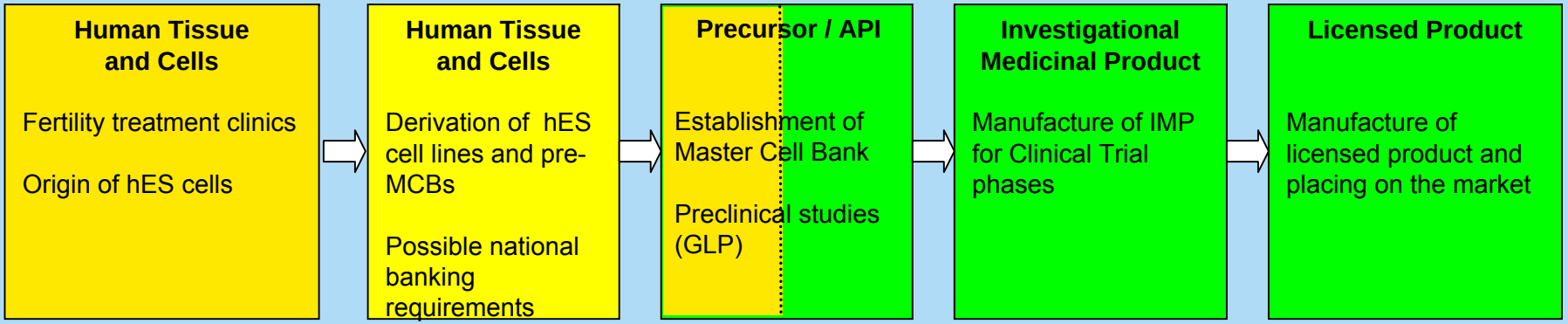
- Indirect changes but significant effect:
  - Better regulation
  - Quality Risk Management, ICH Q9, principles (Chapter 1)
    - evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient
    - the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk
  - Dedicated facilities (Chapter 3 and 5)
    - Work in progress to agree text
    - Annex 2 revision text changes on certain products, e.g. BCG, Bacillus anthracis, of *C.botulinum* and of *C.tetani*

GMP issues - general

- Changes from R&D to IMP/GMP:
  - EU Tissue and Cells Directive (2004/23/EC)
  - Active substance (API) start point
  - History of product: consent, facilities approvals, records
- Facilities – focus due to capital and running costs
- Quality Systems – may be overlooked
- Annex 13 requirements:
  - Product Specification File
  - Validation requirements, process validation relaxation

GMP issues - derivation

- Human embryonic stem cells:



  - Long derivation sequence – time and facilities
  - Cut-over between Directives: EU Tissue and Cells (initial stages, yellow) Medicines (later stages, green)
  - Possible cut-over between Competent Authorities in some Member States

GMP issues – cell lines

- Consent for research/therapeutic use (EUTCD)
- Regulatory coverage of manufacturing and storage sites
  - ‘Good Practice’ (EUTCD) – donation, procurement, testing
  - Good Manufacturing Practice (medicinal products)
- Manufacturing and storage activities:
  - TSE and other adventitious agent risks
  - Contamination and cross-contamination risks
  - Suitability of in-contact materials, solutions, media
  - Issues affecting stability of cell lines

GMP issues - cell lines

- Establishing Master and Working Cell Banks
  - Authenticating cellular starting materials
  - Prove that cells are what is stated
  - Which tests and how many?
    - Area of interest to inspectors and assessors
    - QRM principles apply – science base, effort vs. risks and consequences
    - How much more than visual/morphology?
    - At what stages – in-process controls, release tests

Common Findings

- Quality System issues:
  - 'Simple as you can, complex as you must'
  - Missing procedures or linkages between procedures
  - Change controls weak
  - Lack of investigation into issues

- Potential for contamination:
  - Bioburden monitoring
  - Surface sanitisation procedures weak / not followed
  - No media simulation studies to show process capability

Common Findings

- Potential for cross-contamination and mix up:
  - Weak controls on labeling
  - Concurrent working on different products / cell lines
  - Storage of materials of different status in same container
  - No documented justification / risk-assessment

Useful Sites

- The Rules Governing Medicinal Products in the EU :
  - http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm
- What's new in legislation:
  - http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new.htm

Questions?