Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Qualification and validation:
- an inspector's perspective

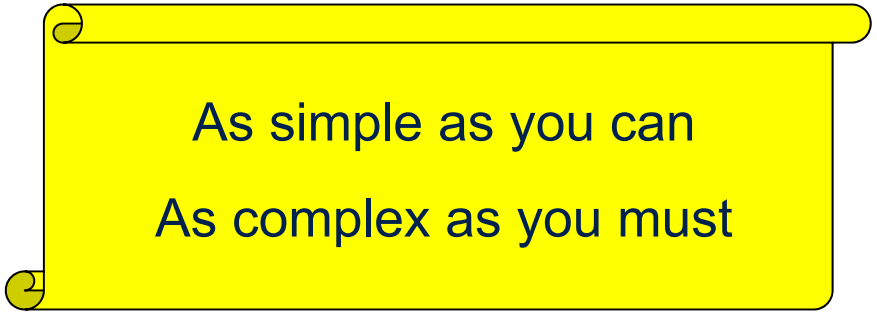
Ian Rees, Unit Manager Inspectorate Strategy

GMP - basics

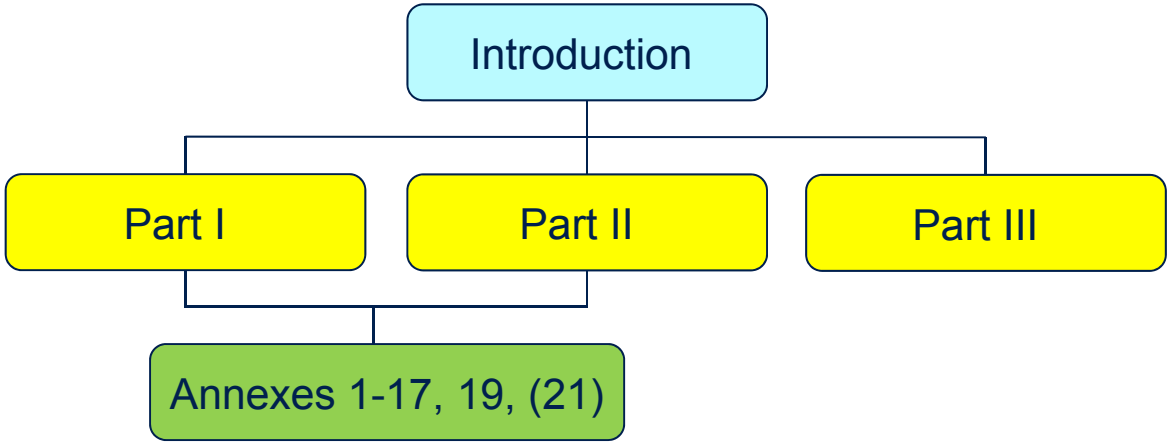
A system within an organisation (or linked organisations) to assure the quality of its products. Qualification and validation is part of that system.

A system, based on QRM principles, to ensure that medicinal products are:

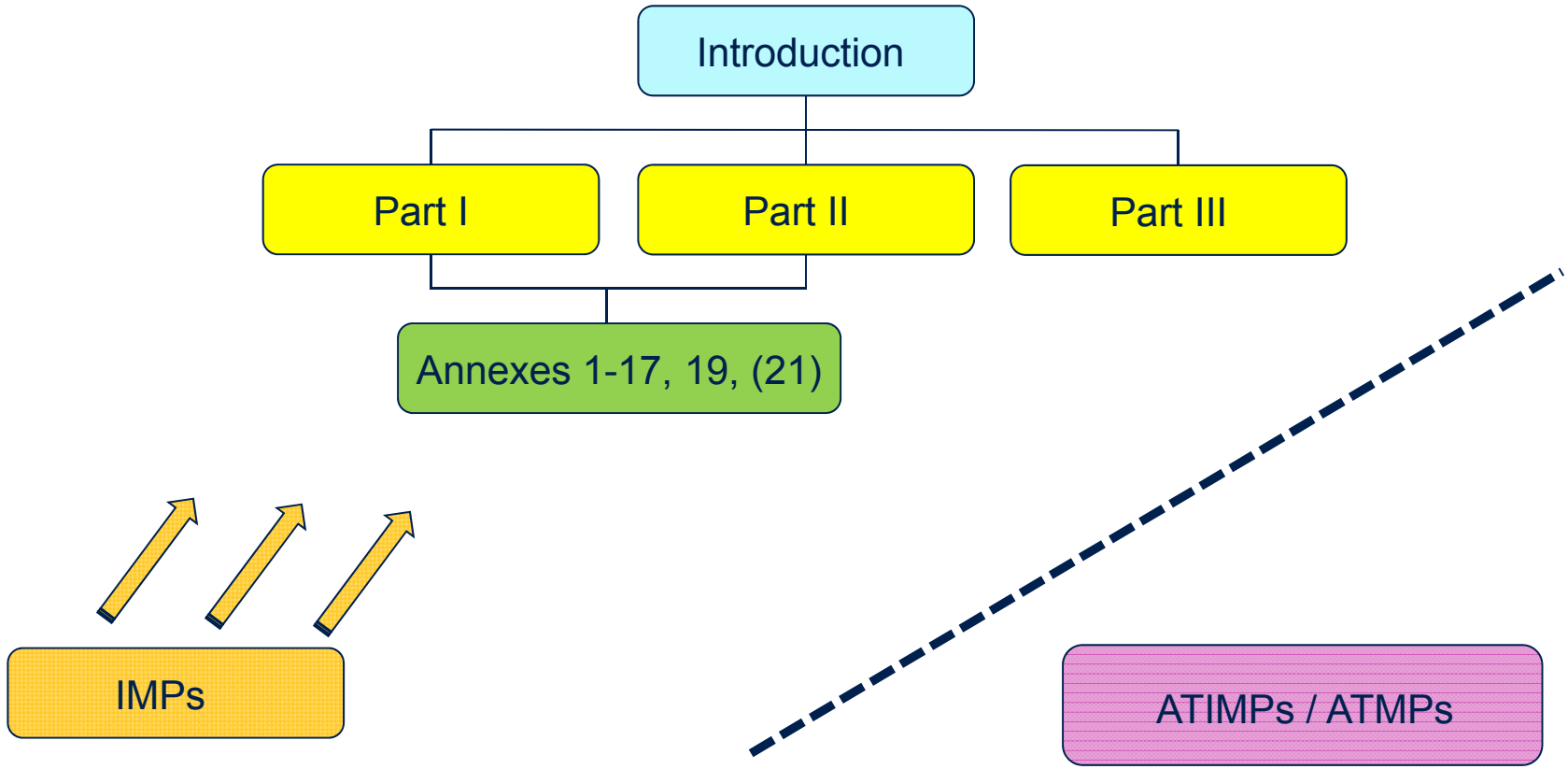
- *consistently manufactured*
- controlled to *quality standards* that are *appropriate* to their intended use (CTA / MA / product specification of MS or HE products)
- *available* when required to avoid shortages



GMP – current structure



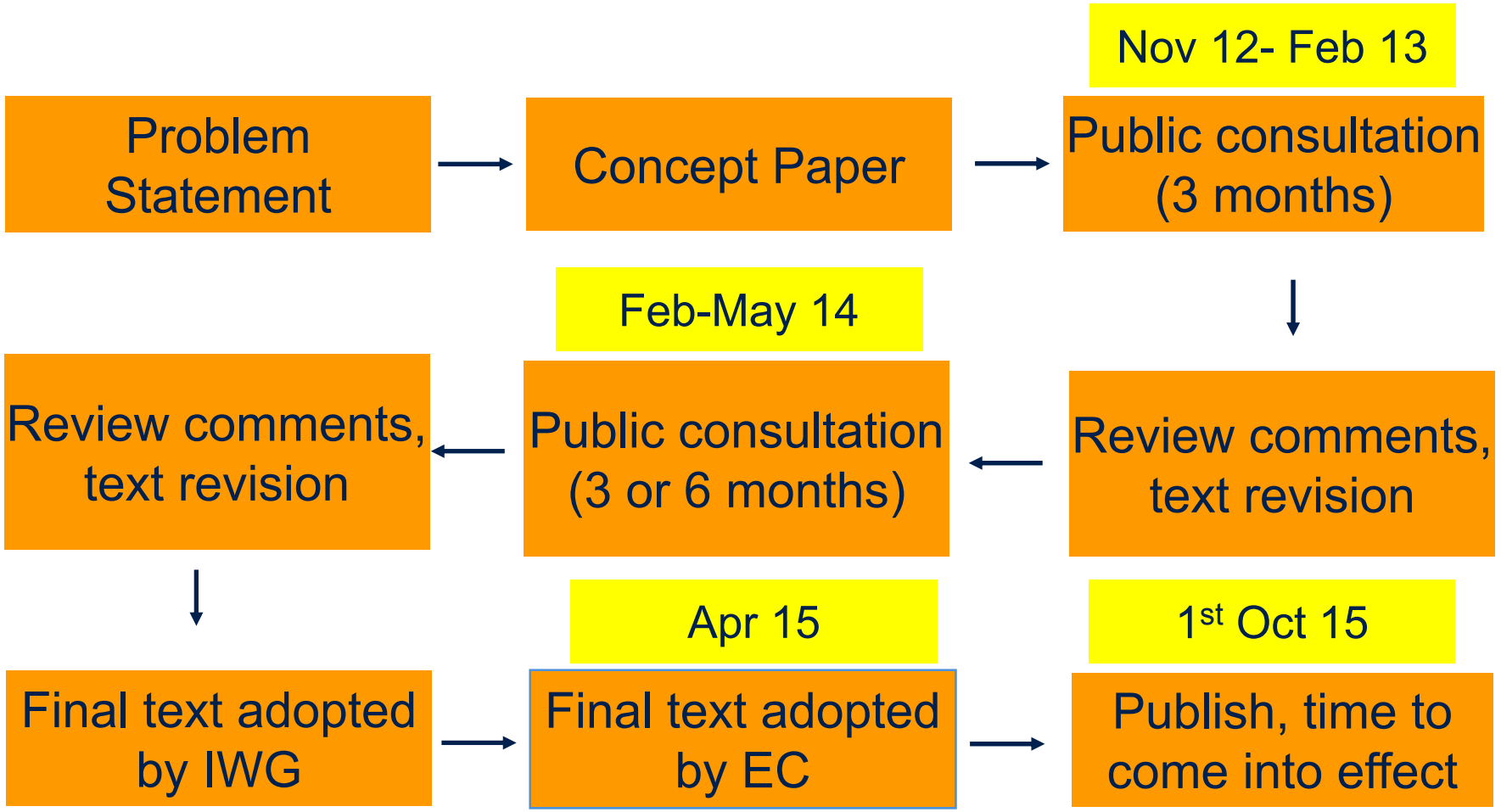
GMP – future structure(?)



Annex 15 – history

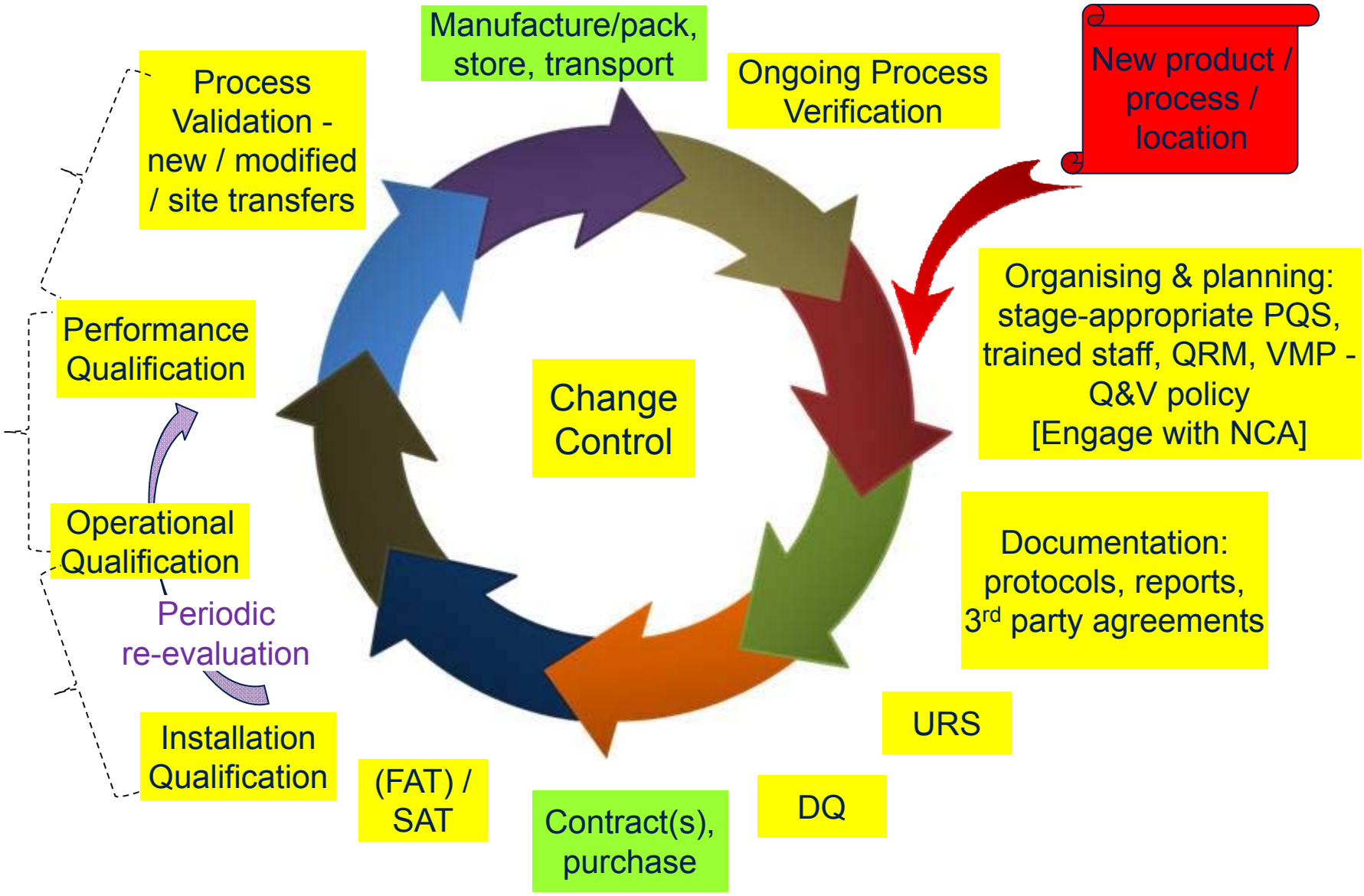
- Main EU guidance document for qualification and validation
- First published in 2001 and revised in 2015 by a group of EU and PIC/S experts and others.
- Revision driven by age of document and need to link to recent QWP guideline on process validation
- Revision team:
  - UK – rapporteur
  - EU member states - Ireland, Germany, Italy and Portugal
  - European Medicines Agency (EMA)
  - PIC/S - Canada, US FDA

Annex 15 – history/GMP revision



6

Qualification and validation lifecycle



Key changes to Annex 15

Principle and General sections

- Include the concept of the validation life cycle
- The use of risk assessments is a general expectation in the document and during the lifecycle of a medicinal product

Organising and Planning section

- Validation is performed by suitably trained personnel but quality oversight is required
- The use of risk assessments for validation should be defined in detail, they are dynamic and change.

Key changes to Annex 15

Documentation including VMP section

- Links documentation to knowledge management
- Emphasises the role of deviations
- Need well founded, justified conclusions against pre-defined acceptance criteria in reports

Qualification stages for equipment, facilities, utilities and systems section

- Clarifies what qualification applies to
- includes guidance on URS, FAT/SAT

Key changes to Annex 15

Process Validation – General

"documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes"

- Concurrent validation - allowed in exceptional circumstances, strong risk benefit to the patient, make visible in VMP
- Retrospective validation - removed
- Scope includes all dosage forms, new, modified processes and site transfers
- Includes 'traditional' and 'Continuous verification approach' to process validation

Key changes to Annex 15

Process Validation – General

- Promotes involvement of production staff in validation work
- Requires knowledge from product development to be available for commercial manufacturing sites
- Where validation batches are to be released - define up front as part of a planned process.

Key changes to Annex 15

Process Validation – Traditional approach

- A series of batches are made to confirm reproducibility.
- The number of batches required should be based on QRM principles and should be justified.
- However, the guide still quotes the number 3, without prejudice, to avoid too much confusion
- In general - more variability / uncertainty / complexity in the process the greater the number of validation batches required

Key changes to Annex 15

Continuous process verification (CPV)

"An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)"

- Based on:
  - an enhanced approach to development or
  - a substantial amount of product and process knowledge and understanding, gained through historical data and manufacturing experience

Key changes to Annex 15

Hybrid approach

A hybrid approach could be used for products which were validated using the traditional approach but where a lot of process knowledge has been built up over many years allowing a CPV approach.

Key changes to Annex 15

Ongoing process verification

"Documented evidence that the process remains in a state of control during commercial manufacture"

- Replaced 'continued' to 'ongoing' process verification to avoid confusion.
- Applies to all (traditional, CPV, hybrid) approaches.
- A monitoring process to:
  - confirm control is maintained across the product's lifecycle
  - detect unplanned departures or unintended process variability from the process as designed

Key changes to Annex 15

Ongoing process verification

- Could be performed:
  - in conjunction with the annual Product Quality Review (PQR)
  - according to a protocol and a report, e.g. for a new product where a PQR has not yet been written or after changes to products where trends are noted.
- Should be more frequent for new products where process knowledge is limited.
- The extent and frequency should be reviewed periodically

Where can it go wrong?

- Links not made between documents in complex projects
- Forget the basic elements of any experiment: objective, method, acceptance criteria, results, conclusion
- Changing acceptance criteria during execution of the protocol with no / insufficient justification
- No checks of data in the report against the raw data resulting in anomalies which question the report's integrity

Where can it go wrong?

- Confusion between PQ of equipment / utilities / systems and process validation.
- Risk assessments:
  - start with preconceived ideas of the end result
  - not reviewed / updated on frequent basis
- Validation protocols don’t include additional sampling other than normal IPC checks.
- Deviations only recorded in protocols and not in the formal deviation system so cannot be used in future investigations

Proportionate approach to risk?

Early engagement with MHRA!

Thanks for your attention

Questions?

© Crown copyright 2014

21