Overview of GMP Inspections 2018 – 2021

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GMP Inspector

HPRA GMP Information Day

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Radisson Blu Royal Hotel, Dublin

Introduction

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Health Products Regulatory Authority

This presentation provides an overview of summary data for GMP Inspections performed in the period January 2018 – December 2021 inclusive, with the aim of identifying trends and/ or areas for future focus

Two-Phase Approach

1. High level review of inspection volume, nature and findings
2. In depth review and trending of inspection findings, including common deficiencies

Scope

All GMP Inspections performed during the period, including:

- Sites which manufacture active substance, biological active substance, sterile products, & non sterile products; batch certification, packaging, and QC testing sites; and sites of physical importation
- National and foreign inspections
- Routine and non-routine inspections
- On-site and distant assessments

Recommendations

Evaluate the deficiencies referenced in this presentation, along with the information from other presentations shared today to assist in inspection preparation, and consider these when conducting internal audits.

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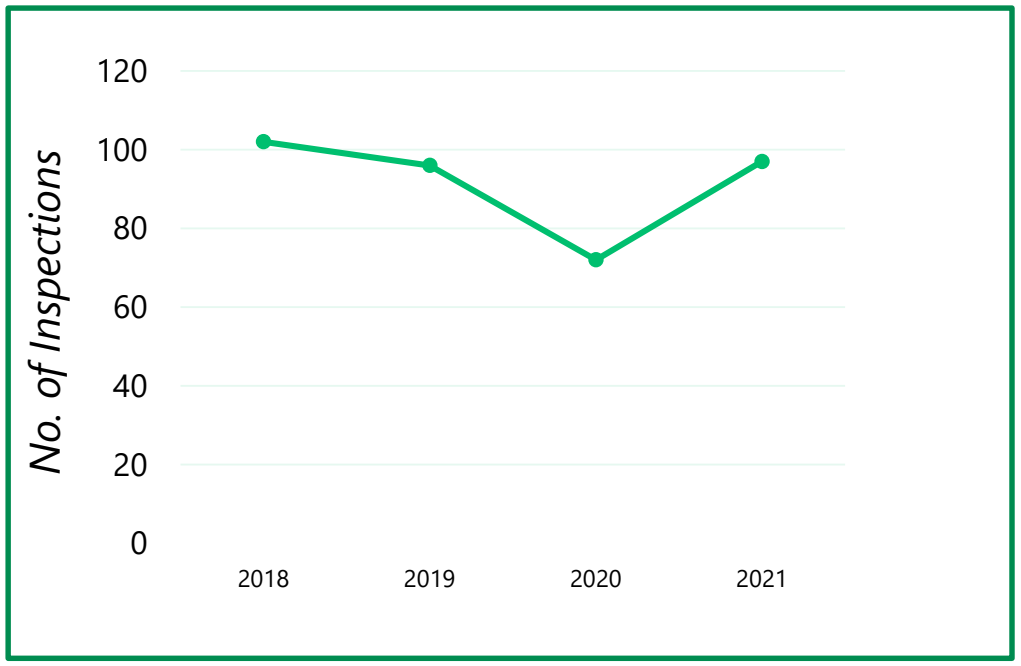
Phase 1: High Level Review of Inspections

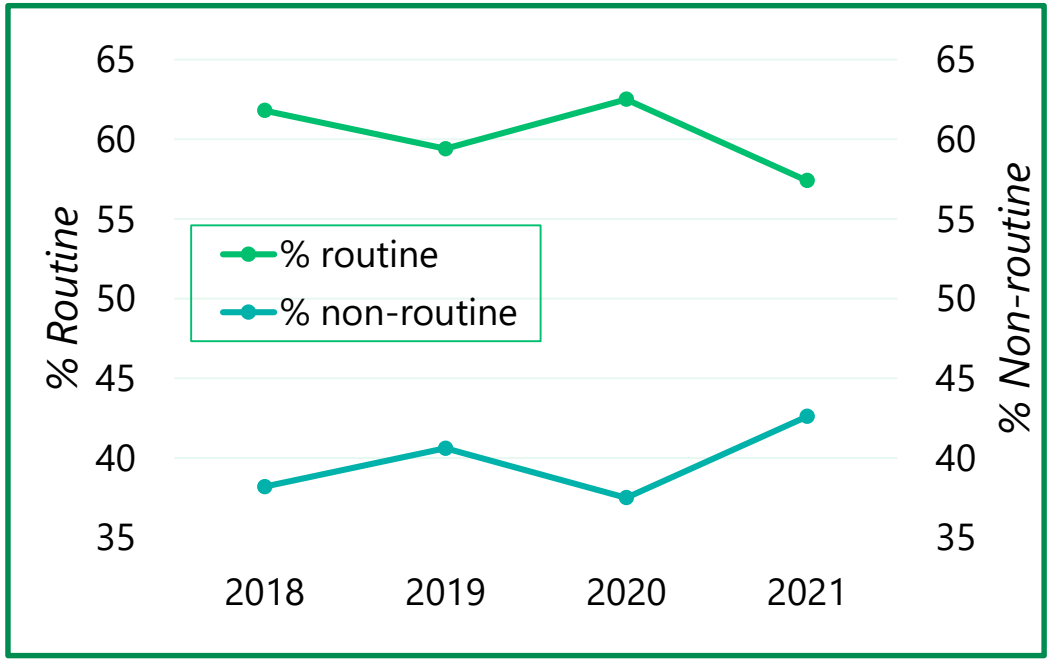
Summary of GMP Inspections - Quantity

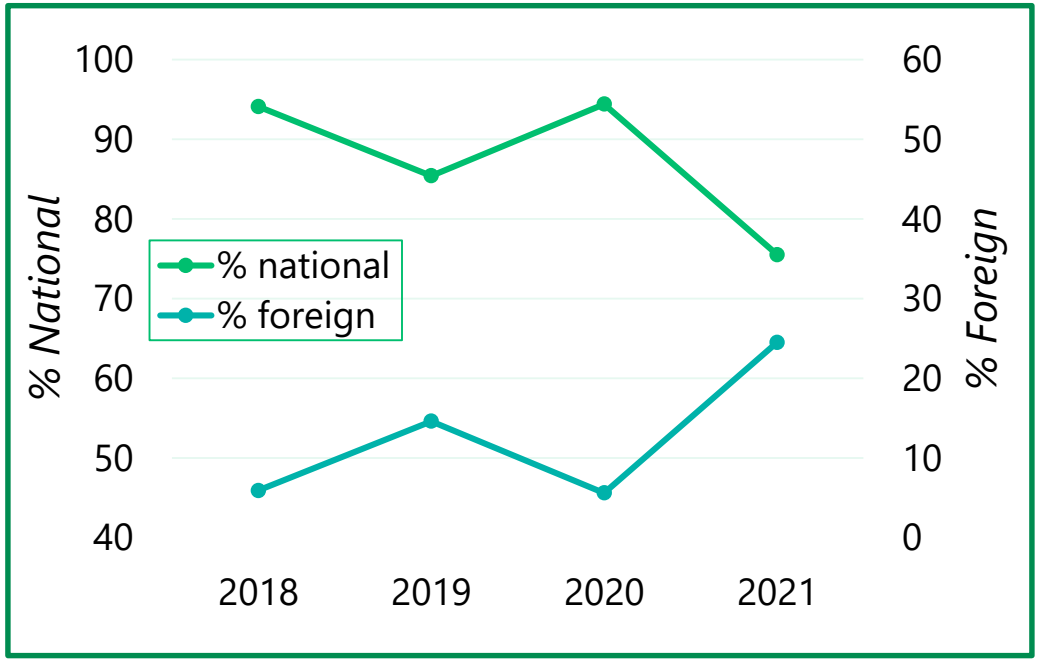
2018	2019	2020	2021
- 102 Inspections	- 96 Inspections	- 72 Inspections	- 97 Inspections



Summary of GMP Inspections - Nature

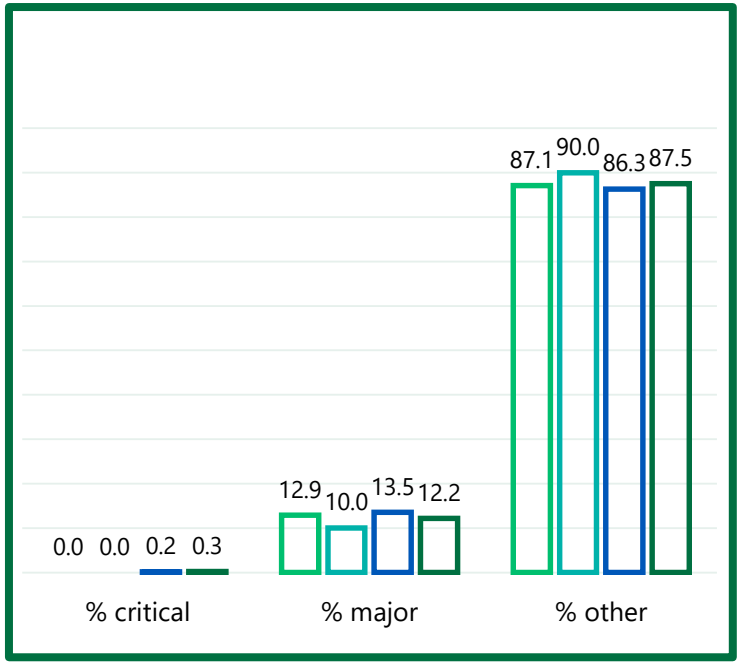
2018	2019	2020	2021
- 63 Routine, 39 Non Routine - 96 National, 6 Foreign	- 57 Routine, 39 Non Routine - 82 National, 14 Foreign	- 45 Routine, 27 Non Routine - 68 National, 4 Foreign	- 54 Routine, 43 Non Routine - 74 National, 23 Foreign

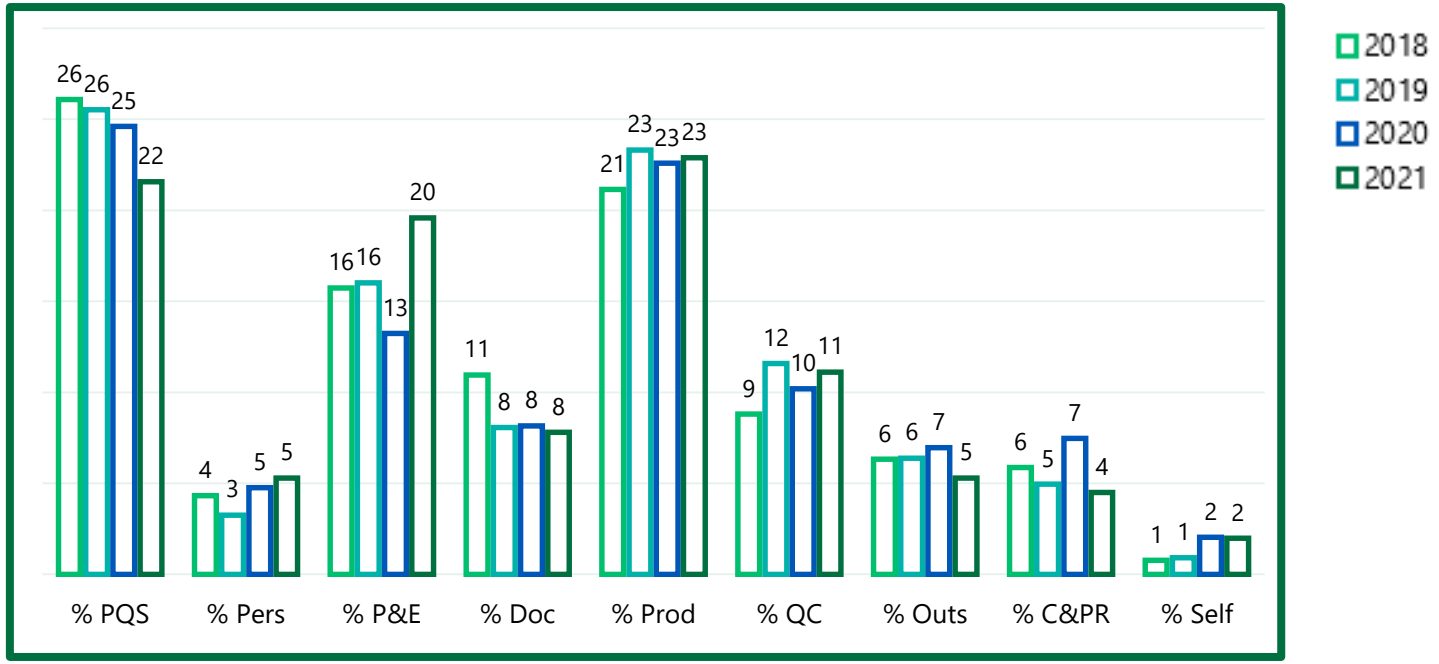




Summary of GMP Inspections - Findings

2018	2019	2020	2021
- 0 critical deficiencies	- 0 critical deficiencies	- 1 critical deficiencies	- 2 critical deficiencies
- 88 major deficiencies	- 77 major deficiencies	- 80 major deficiencies	- 99 major deficiencies
- 595 other deficiencies	- 691 other deficiencies	- 510 other deficiencies	- 716 other deficiencies





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Phase 2: Further Review of Critical Findings

Closer Look at Critical Deficiencies

Pharmaceutical Quality System (1)
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Production (1)
Controls for aseptic operations (1)
Quality Control (1)
Lab activities & Controls (1)

The Pharmaceutical Quality System was not correctly implemented or effective such that GMP controls for the manufacture of aseptically prepared medicinal products were deficient and posed a significant risk of producing a product which could be harmful to the patient:

- The programme for Environmental Monitoring (EM) was deficient.
- Certain behaviours indicated a lack of understanding of basic microbiology principles and good aseptic practices.
- The approach taken to train and qualify production staff was deficient.
- Management of GMP records was deficient.
- The management of identified data integrity breaches at the site was deficient.
- Insufficient qualified personnel were available to carry out all the required tasks at the facility.
- Material management was inadequate including, management of cleaning supplies, autoclaved gowning components, material sanitisation and transfer processes.

CRITICAL

A deficiency which has produced, or leads to a significant risk of producing, either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

Closer Look at Critical Deficiencies

Pharmaceutical Quality System (1)
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Production (1)
Controls for aseptic operations (1)
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Lab activities & Controls (1)

There was a lack of sterility assurance in relation to aseptically processed products, in that:

- Aseptic processing and controls observed during the set up and filling were deficient.
- Deficiencies related to the autoclaving of filling equipment were observed.
- The Environmental Monitoring (EM) and personnel monitoring programme implemented at the site was deficient.
- Management of media fills was deficient.
- The aseptic practices and behaviours observed during sterility testing were deficient.

Appropriate measures had not been taken by the company following identification of issues related to QC data used to support QP certification and release of product to the market. This was evidenced by the following:

- Batches had been released to the market without having the required microbiological testing performed.
- The management of investigation related to a data integrity investigation in the QC laboratory following the recording of spurious test results where testing had not been conducted, was inadequate.
- The company had not taken appropriate action when issues were identified during self-inspection of documentation.
- Handling of deviation which related to the QP certification of batches prior to the required microbiological testing being completed was deficient.

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Phase 2: Further Review of Major Findings

Closer Look at Major Deficiencies

Pharmaceutical Quality System (111)
- *Deviation & complaint investigation (53)*
- *Quality risk management (19)*
- *Batch certification & QP oversight (15)*
- *Outsourced Activities & Supplier Management (14)*
- *CAPA implementation & Management (10)*

Production (105)
- Contamination control & *cleaning validation (32)*
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- *Environmental Monitoring (4)*

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- *OOS/ Lab investigations (13)*
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Premises & Equipment (32)
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Documentation (11)

Other (49)

Most major deficiencies are

MAJOR

A non-critical deficiency:
which has produced or may produce a product, which does not comply with its marketing authorisation;
or
which indicates a major deviation from EU Good Manufacturing Practice;
or
(within EU) which indicates a major deviation from the terms of the manufacturing authorisation;
or
which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;
or
a combination of several 'other' deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Closer Look at Major Deficiencies

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Deviation & complaint investigation: 2018 (14), 2019 (13), 2020 (10), 2021 (16)
- Insufficient procedural guidance for effectiveness checks and checks for previous occurrences; Effectiveness/ reoccurrence checks not performed
- An appropriate level of formal root cause analysis not applied
- Delays in raising, investigating and implementing CAPAs; delays in closing records
- Inadequate level of detail in records; records not reflective of scope of deviation; Critical detail missing from records; missing records
- Level of investigation not commensurate with potential risk; event management not in line with QRM principles
- Human error commonly assigned as root cause without adequate investigation or justification
- No consideration for testing of retain samples during investigation of complaints; inadequate testing of retain/ complaint samples
- No attempts to retrieve complaint samples for analysis

Quality Risk Management: 2018 (6), 2019 (4), 2020 (5), 2021 (4)
- Procedures for implementation of QRM had not been put in place
- Classification of risk profile of supplier/ material not justified
- Suppliers assigned same audit frequencies despite the suppliers presenting different levels of intrinsic risk
- Risk assessment tool used was not scientifically robust. Compliance level and audit frequency outputs were not impacted by whether minor, major or critical GMP deficiencies had been identified during recent audit, and did not take into account the number of deficiencies
- Supplier management allowed for 3 critical observations prior to audit result of unacceptable
- Deviations and change controls not classified based on QRM principles which assessed potential risk to patient and product quality; Complaints classified as critical, major, or minor, but classification of complaints was not based on QRM principles or risk assessment
- Little evidence of QRM principles in investigations
- No risk assessment to determine appropriate level of GMP to be applied to manufacture of excipients

Closer Look at Major Deficiencies

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Management of suppliers/ outsourced activities: 2018 (3), 2019 (2), 2020 (4), 2021 (5)
- No excipient risk assessment, excipient risk assessment did not meet requirements
- Requirements for periodic evaluation of supplier performance not defined
- Inadequate approved supplier list; no approved supplier list
- No system in place for monitoring of performance of all suppliers on ASL
- Non-GMP factors such as pricing formed part of risk based scoring of suppliers
- No quality agreement in place; Quality agreement did not adequately define responsibilities
- Delayed approval of audit reports/ no timelines for approval of audit reports and receipt of CAPA plans
- Not clear how audit frequency was determined and the impact of audit outcome on approval status of company

Batch certification & QP oversight: 2018 (2), 2019 (6), 2020 (4), 2021 (4)
- For testing conducted in external laboratories, there was no process in place to ensure compliance of test methods with the registered MA dossier
- The process for ensuring all required technical agreements were in place for medicinal products manufactured by the company was not defined, and it was not clear how this QP responsibility was being fulfilled
- Not clear how compliance status of a batch with respect to marketing authorisation would be checked in instances where there had been recently approved MA variations; QP access to manufacturing and process controls section of the MA could not be demonstrated during the inspection
- Not evident how the QP would determine the MA compliance status of batch artwork; access to current version of approved artwork could not be demonstrated
- Supply chain maps were not controlled documents, and in some cases were inaccurate or incomplete
- Template document for recording batch certification was deficient as it did not require any statement that batch was in compliance with its marketing authorisation
- Batch release register was not a controlled document, was an uncontrolled spreadsheet

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CAPA Implementation & Management: 2018 (3), 2019 (2), 2020 (3), 2021 (2)
- CAPAs not implemented/ lack of progress in taking action for major deficiencies, aspects of CAPAs defined in post inspection correspondence to HPRA not completed
- CAPAs not implemented in line with communicated timelines, without notification of delay to HPRA/ non-adherence to CAPA plan
- No system in place to track CAPAs to completion
- Deficiencies from regulatory inspections managed outside the formal CAPA system

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Contamination control & Cleaning validation: 2018 (7), 2019 (10), 2020 (3), 2021 (12)

- Approach to determining worst case products not clear or not documented
- Maximum carryover limit not based on scientific rationale
- MACO calculated based on 'worst case' surface area of largest vessel, rather than the entire shared equipment train, which resulted in over estimated MACO
- PDE assessments used a weight adjustment not appropriate or in line with EMA guidance. The relevant MACO calculations were therefore overestimated
- PDE values not calculated by qualified toxicologist
- Acceptance criteria defined for rinse samples did not take into account rinse volume and surface area of equipment rinsed
- No assessment of levels of recovery achieved during sampling or need to apply recovery factor to the analysis to account for losses
- Threshold at which residues were visually detected not established
- Policy for campaign manufacturing and how this affected cleaning validation not adequately defined
- No data to support dirty and clean equipment hold times
- Potency and toxicological evaluation had not been performed for products produced in shared manufacturing facility
- Disinfectant efficacy validation had not been completed.
- It was not known if analytical methods used to detect active ingredients and detergent residues had been validated
- No risk assessment associated with sterilisation of fill parts off site and no instruction to check integrity of packaging on autoclaved parts at receipt
- Validation of autoclave cycles deficient
- Residue observed on equipment / extract grill of sampling booth despite it being cleaned, inspected and ready for use
- Tanks which had clean status were observed to be visibly unclean
- Cleaning activities not documented
- Pest control system ineffective, many insects observed in various production areas at the site including sampling/ dispensing room and production rooms

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Manufacturing processes & Controls: 2018 (4), 2019 (5), 2020 (7), 2021 (7)
- Lack of control of manufacturing recipes
- Manufacturing process not in line with registered process
- Manufacturing processes not validated
- No CPPs identified for steps which had documented impact on final product attributes / specifications
- Inadequate assessment/ assurance of homogeneity of finished product
- No consideration for placing reprocessed batches on stability or taking additional QC samples
- Inadequate batch traceability / pooling of batches where this process has not been registered
- No record of mixing/ hold times where minimum/ maximum mixing/ hold time are defined process parameters
- No action required if Individual tablet weights were outside IPC, if average across sampled tablets was within IPC

Process Validation: 2018 (1), 2019 (5), 2020 (4), 2021 (7)
- Not clear how CQAs and CPPs had been determined/ identified, No robust control strategy for the process, no documented assessment of the process to define and justify which parameters were critical to ensure validated state
- CPPs/ CQAs to be assessed not included in protocol or equivalent document, Acceptance criteria not defined in pre-approved protocol
- Batch size validated not representative of commercial batch size, not justified
- Appropriate statistical process control tools not specified
- No demonstration of homogeneity during filling
- No critical review of deviations/ OOS in validation report
- Acceptance criteria amended during validation activities
- Process parameters optimised during validation activities
- Three consecutive batches had not met acceptance criteria, no root cause extrinsic to the manufacturing process found for failing batches

Closer Look at Major Deficiencies

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Material Management: 2018 (6), 2019 (5), 2020 (2), 2021 (2)

- No requirement to verify approved status of supplier of incoming materials against approved supplier list
- ASL deficient: part number/ item codes not stipulated, did not distinguish location of different entities and activities for which they were approved
- No system for traceability of goods post receipt and prior to use in production
- Goods receipt checks not documented
- Inadequate labelling/ not clear what contents were or how long items had been in inventory
- No guidance on handling of temperature recording devices at receipt
- No sampling process defined/ established at the site
- The contents of drums which failed to meet in-process specification for water content were permitted to be mixed with contents of other drums known to be within specification such that overall content was within allowable specification
- Areas/ controls for storage of rejected/ Recalled/ returned material not established
- No system in place for internal labelling and identification of each delivery of materials with unique identifier

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Controls for aseptic operations: 2018 (4), 2019 (1), 2020 (5), 2021 (4)
- Layout and orientation of line made it necessary for operators to lean across line to position stopper hopper, potentially shedding particles over line
- Vial conveyor exiting sterilising tunnel had no protective surrounding guard and exposed vials were at risk of contamination from technicians in surrounding grade B areas
- Movement of personnel not controlled and methodical
- Personnel behaviours: Gloves not regularly disinfected, rested hands on base of BSC during waiting periods, personnel leaned over and rested arms on grade B benches
- Sanitisation of materials into BSC not performed in consistent unidirectional manner
- Glove integrity checks not performed or required (sterile gloves donned by personnel and RAB gloves)
- Removal of needle sheath not deferred until end of aseptic set-up to minimise potential contamination risk
- Inadequate gowning process - No integrity checks of packaged items prior to removal from packaging, no check to ensure goggles had been exposed to gamma irradiation prior to donning, no check of integrity of cleanroom garments prior to exit from cleanrooms
- Material transfer sanitisation process not qualified
- Donning of grade C/ D plant uniform in general office areas including toilets

Environmental Monitoring: 2018 (1), 2019 (1), 2020 (1), 2021 (1)
- Settle plates not used during EMPQ or routine EM at the site
- Media released prior to growth promotion testing
- SDA for selective cultivation of yeasts and moulds not utilised at the site, without justification or sufficient data to support use of single growth media TSA
- No active air samples in grade A or grade B areas
- No viable or non-viable monitoring in grade B areas
- Sanitisation of surfaces with IPA prior to surface monitoring/ sanitisation of gloved hands with IPA prior to finger dabs
- No system for reconciliation of plates

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Lab Activities & Controls: 2018 (2), 2019 (7), 2020 (3), 2021 (8)
- Testing not in accordance with European pharmacopoeia
- Inadequate control (issuance, review and reconciliation) of logbooks and analytical data sheets
- Limits of quantitation not known/ not established
- With regards to HPLC:
  - No guidance with respect to inhibition of integration of peaks during HPLC
  - Standard and sample runs performed with different processing parameters/ initial testing and re-testing performed with different parameters with no justification
- No in-use/ open shelf life established for reference standards

OOS/ Lab Investigations: 2018 (3), 2019 (5), 2020 (1), 2021 (4)
- Resampling was permitted as part of preliminary laboratory investigation
- No requirement to perform hypothesis testing as part of lab investigations to confirm proposed root case prior to invalidation of initial results and retesting
- No requirement for retest plan to be approved by Quality management
- Retesting not required to be pre-defined or documented prior to approval to proceed being granted
- Inconsistent approach to OOS investigation with regard to use of second analyst, number of retests performed and recording of hypothesis testing
- No requirement to document root cause and appropriate CAPAs where a laboratory error was identified
- OOS results obtained during stability testing at first timepoint were not notified to registration holder or relevant health authority
- Batch with confirmed OOS released to market without prior variation in relevant marketing authorisation
- No formal manufacturing investigation following confirmed OOS result

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Computerised Systems: 2018 (2), 2019 (0), 2020 (0), 2021 (2)
- No requirement/ no procedural guidance regarding review of electronic data and audit trails during review
- Risk assessment of laboratory computerised systems not available. In particular an assessment of integrity and security of laboratory data throughout its acquisition, transfer and storage and identification of risk mitigating actions
- Security of data acquisition systems inadequately assessed/ no justification for assigned user privileged and permissions
- Access rights not documented or understood
- Data recovery study to assess the ability to restore laboratory data and the integrity of restored laboratory data was not performed prior to implementation of the laboratory systems
- URS for HPLC software system not generated
- No supplier/ service provider qualification or technical/ quality agreement with vendors who provided services for computerised systems which impacted critical laboratory data
- Physical location of the server was not known
- No system or plan in place for maintenance of records in trackwise system, or their potential transition to MasterControl

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Premise & Equipment: 2018 (7), 2019 (3), 2020 (4), 2021 (3)
- Insufficient segregation between grade A and grade B zones
- No controls/ data to support laminar air flow to grade A zone
- No environmental controls to prevent air from grade B entering grade A zone
- Discolouration/ rusting/ flaking observed on ceiling/ walls
- Vessel discoloured/ stained
- Scratches/ Rust on manufacturing equipment
- Baffles in vessel/ flexible pipework worn, such that there was risk of material shedding into a batch
- Grease observed leaking from vessel agitator
- Staining/ damage to mixing paddles
- Inadequate temperature control In ambient areas
- Dents/ cracks present in tanks
- Blocked drains/ lack of drain sanitisation
- Inadequate facility sanitisation
- Holes in partition walls/ doors

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Documentation (11)

Other (49)

Equipment Qualification: 2018 (4), 2019 (1), 2020 (5), 2021 (5)
- No URS or equivalent functional specification
- Requirements listed in URS not verified during qualification
- No pre-approved protocol
- Rationale for acceptance criteria not clearly documented
- Lack of detail in protocol with regards to how tests were performed
- No confirmation/ verification that previous stages of qualification had been completed prior to execution of subsequent stages, Approvals incomplete prior to moving to next phase of qualification
- IOQ leveraged from FAT without documentation or justification for the suitability of this approach
- No summary report which addressed failures during qualification and changes to approach
- Operation of particle counter not tested or verified
- No rationale for user privileges assigned
- Positions of CIs and BIs not risk assessed

Closer Look at Major Deficiencies

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Pharmaceutical Quality System (111)
- *Deviation & complaint investigation (53)*
- *Quality risk management (19)*
- *Batch certification & QP oversight (15)*
- *Outsourced Activities & Supplier Management (14)*
- *CAPA implementation & Management (10)*

Production (105)
- Contamination control & *cleaning validation (32)*
- Manufacturing processes & controls (23)
- Process validation (17)
- *Material Management (15)*
- Controls for aseptic operations (14)
- *Environmental Monitoring (4)*

Quality Control (37)
- *Lab activities & Controls (20)*
- *OOS/ Lab investigations (13)*
- *Computerised systems (4)*

Premises & Equipment (32)
- *Premise & equipment (17)*
- *Equipment Qualification (15)*

Documentation (11)

Other (49)

Documentation: 2018 (2), 2019 (1), 2020 (7), 2021 (1)
- Procedures were not easy to follow and adequately tailored to activities at the site (procedures written to cover several manufacturing and supply models, not reflective of arrangements for release/ recall of product to/ from EU markets)
- Procedures in draft and not yet effective
- Procedures not current and reflective of operations at the site
- Procedures lacked critical detail
- Responsibilities not clearly defined within procedures
- Procedures did not include appropriate use of QRM and did not demonstrate a functional risk management system was in place
- Second person checks were not being performed at time of operations as was required and signatures were being applied to batch records retrospectively
- Controls for issuing manufacturing documentation deficient: records photocopied from controlled copies of master records issued to production; IPC sheets loose with no control over number of times they could be photocopied
- Personnel signatures applied for tasks which they had not completed, lack of traceability
- Records completed retrospectively

Major deficiencies also cited in relation to:

- Marketing authorisation
- New product introduction
- Analytical tech transfer
- Training
- Packaging
- Shipping
- Data integrity
- Manufacturing computerised systems
- Compliance with authorisation holder requirements
- Independence of Quality & Production functions
- Cell bank manufacture
- PQR
- Change management
- Quality defects
- Self inspection
- Marketing authorisation
- Personnel
- Sample management

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Summary & Recommendations

Summary

Across 4 year period examined:

- The number of GMP inspections has been consistent, other than the period at the start of the Covid-19 pandemic during which time the HPRA, together with EU partners, worked to develop, define and implement a distant assessment process.
- The introduction of distant assessment in Q3 2020 has not resulted in significant difference in the overall number or nature of significant deficiencies

- 56-63% of inspections were performed on a routine basis, and 37 – 44% on a non-routine bases
- 75 – 95% of inspections were performed for sites in Ireland, and 5 – 25% were performed for sites in third countries.
- Critical deficiencies account for less than 1% of the total deficiencies cited, major deficiencies for approximately 12%, and other deficiencies make up the remainder, at approximately 87%.

- Majority of major deficiencies cited are 'a combination of several 'other' deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such'
- Critical deficiencies cited where there has been 'a significant risk of producing a product which is harmful to the human or veterinary patient'

- Pharmaceutical Quality System (Chapter 1) has the largest number of deficiencies across the period, and leads the way for major deficiencies with over a third of majors being cited against this chapter. Chapter 5 (Production) is a close second. Critical deficiencies have been cited against both of these chapters, in addition to chapter 6 (Quality Control).

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Conclusion

When considering the top chapters cited, the issue of investigations and root cause analysis appears frequently.

This is similar to the findings previously cited by other regulatory agencies, and is considered to highlight the importance of quality systems and the quality unit, investigations and assignment of root cause, and the continued focus on these areas.

Companies would be well served to evaluate the deficiencies referenced in this presentation, along with other presentations shared today (related to batch certification & outsourced activities, OOS Investigations, and Cleaning Validation, all of which are areas commonly cited for major findings) to assist in inspection preparation, and to consider these when conducting internal audits.

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Thank you