HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Hot topics and your questions answered

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QP Forum

13th May 2025, Trinity College Dublin, Ireland

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An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

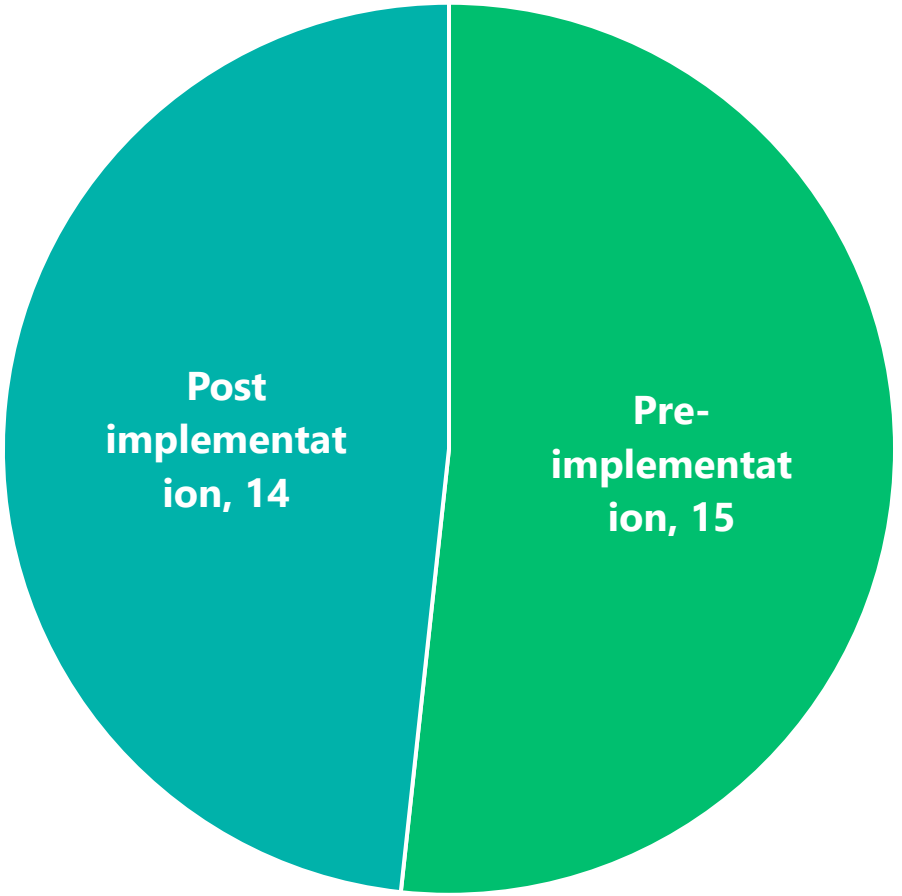
Two years on: Progress and Insights on the Application of Annex 1

What are we looking at?

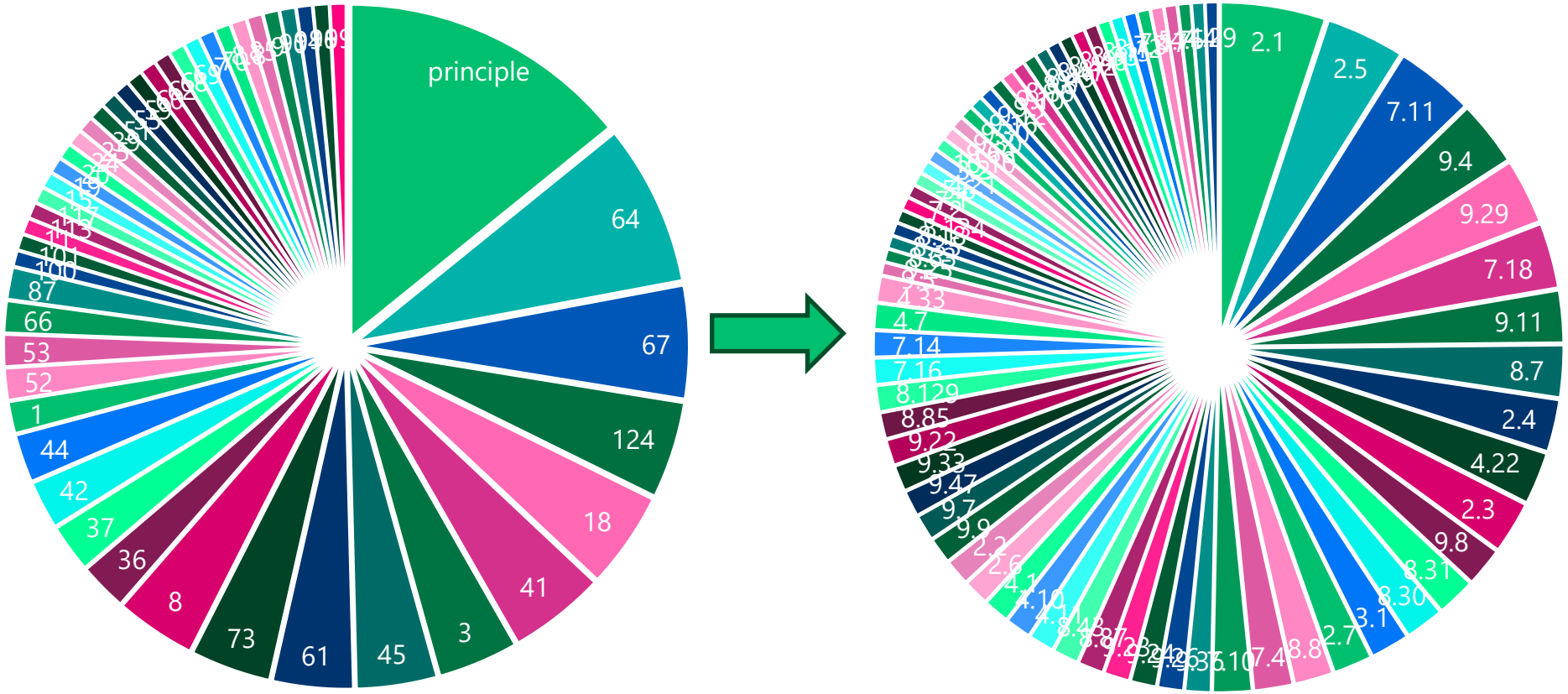
29 inspections in scope i.e. sites primarily governed by Annex 1 inspected between August 2022 and August 2024

15 pre-implementation & 14 post-implementation

Not including ATMP (governed by Part IV) and biological DS (primarily governed by Annex 2) manufacturing sites



Comparison of Citations pre- and post- implementation



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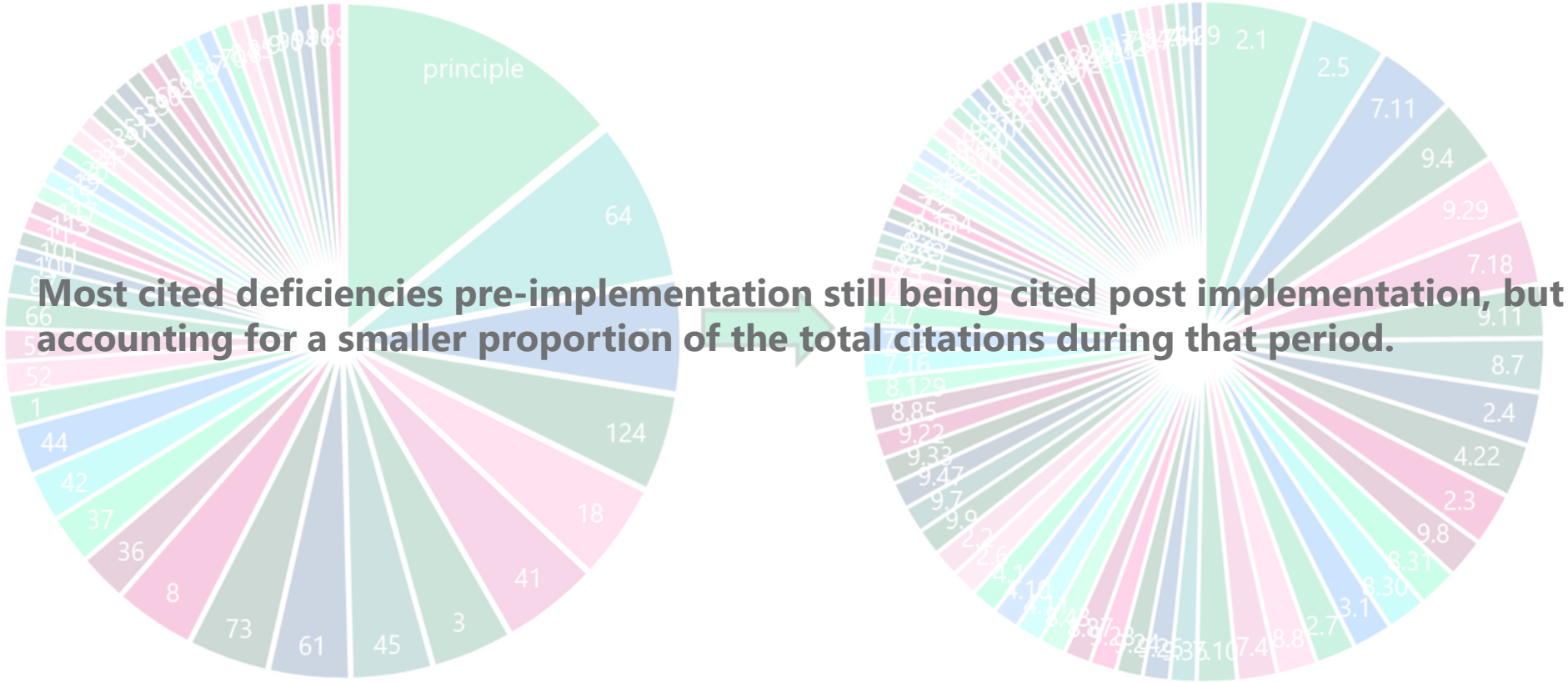
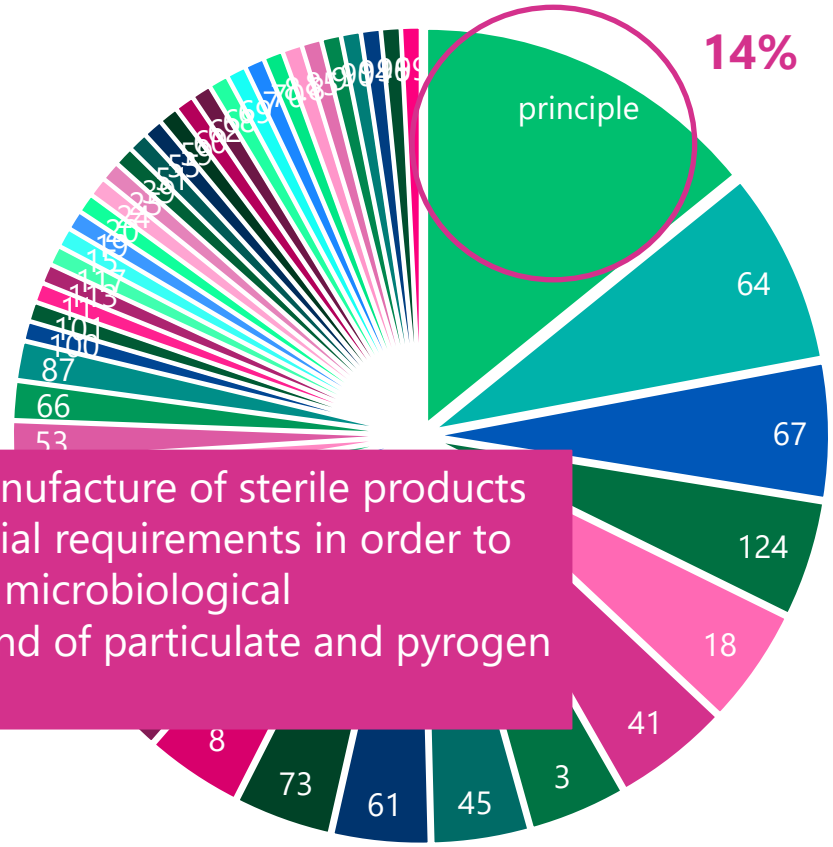
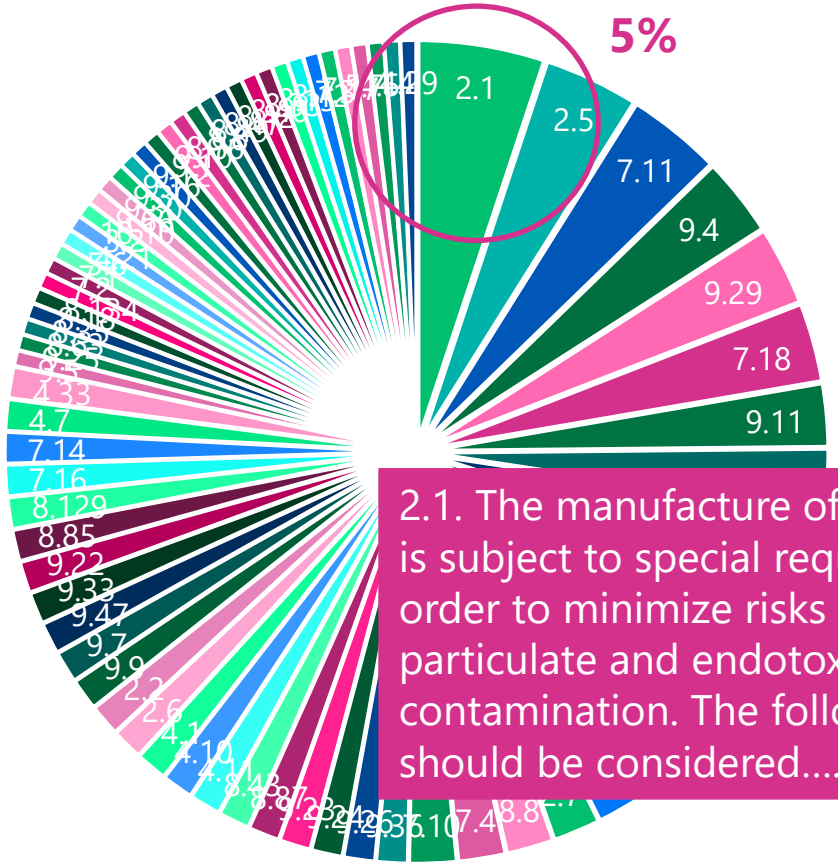


Most cited deficiencies pre-implementation still being cited post implementation, but accounting for a smaller proportion of the total citations during that period.

Most cited pre-implementation



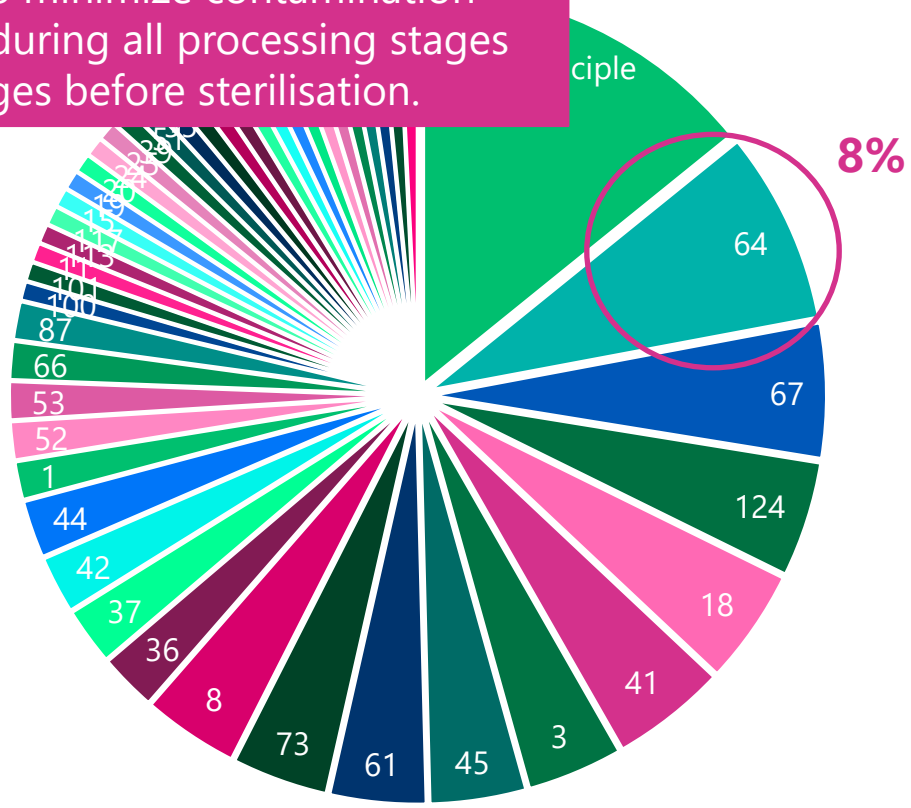
Principle. The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination..



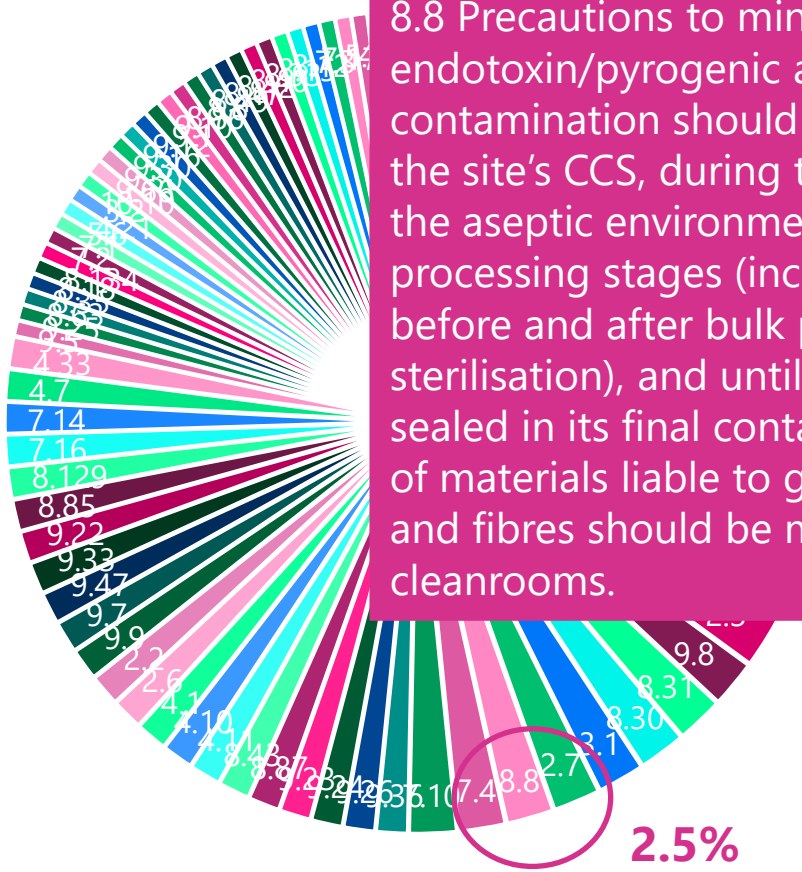
2.1. The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered....

Most cited pre-implementation

64. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilisation.

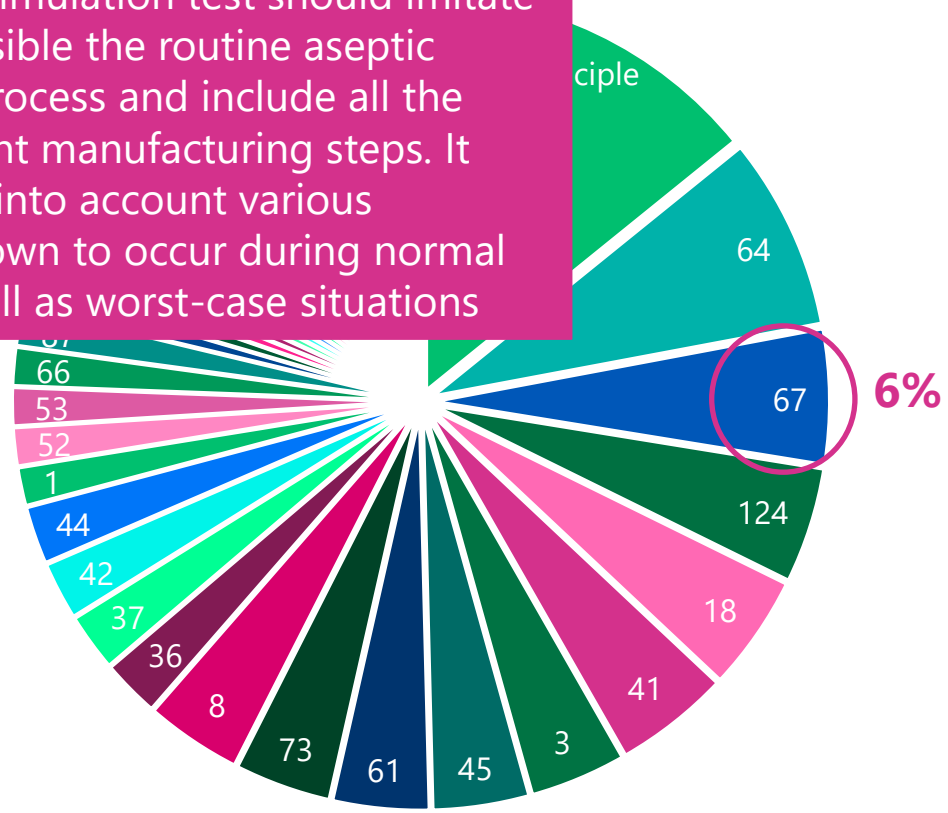


8.8 Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilisation), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres should be minimized in cleanrooms.

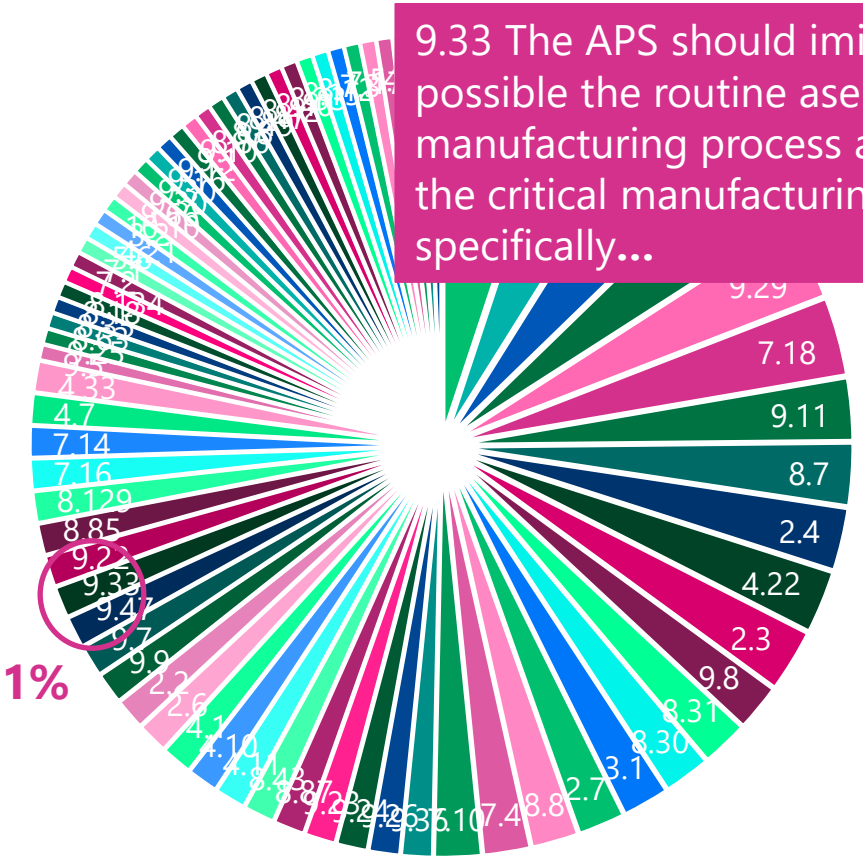


Most cited pre-implementation

67. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations

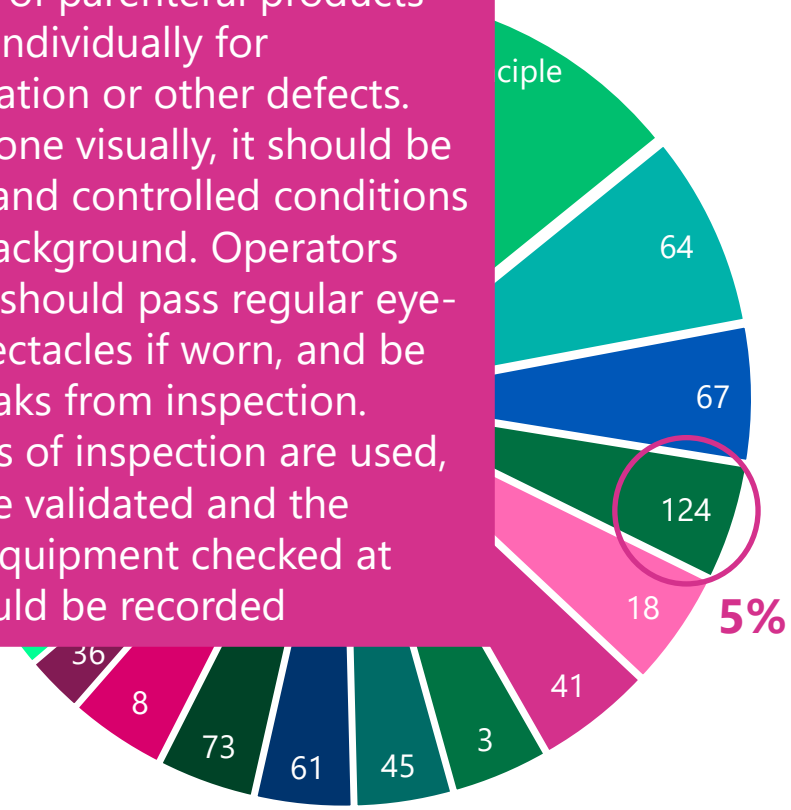


9.33 The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically…



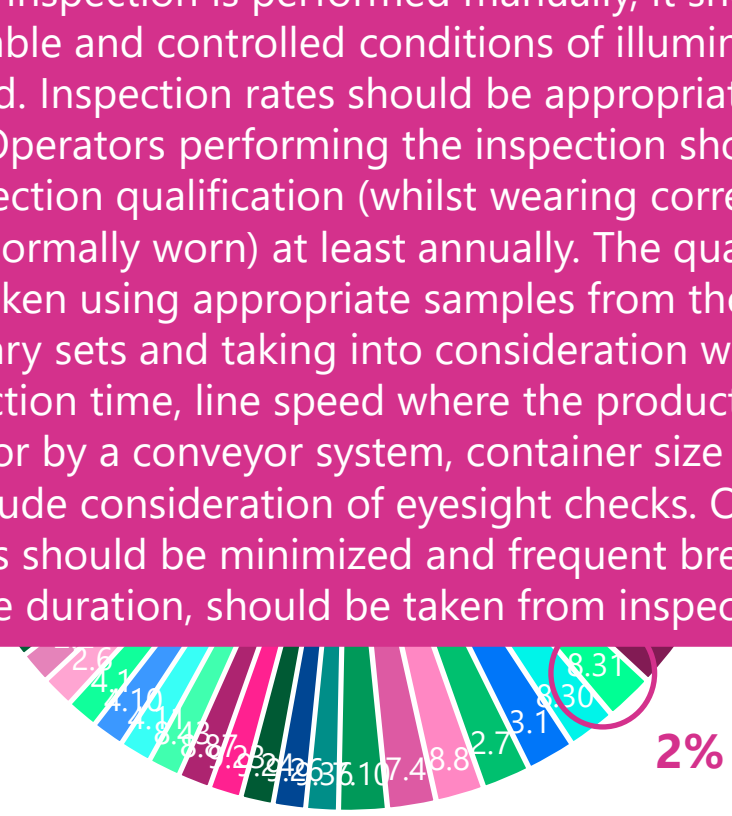
Most cited pre-implementation

124. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded



5%

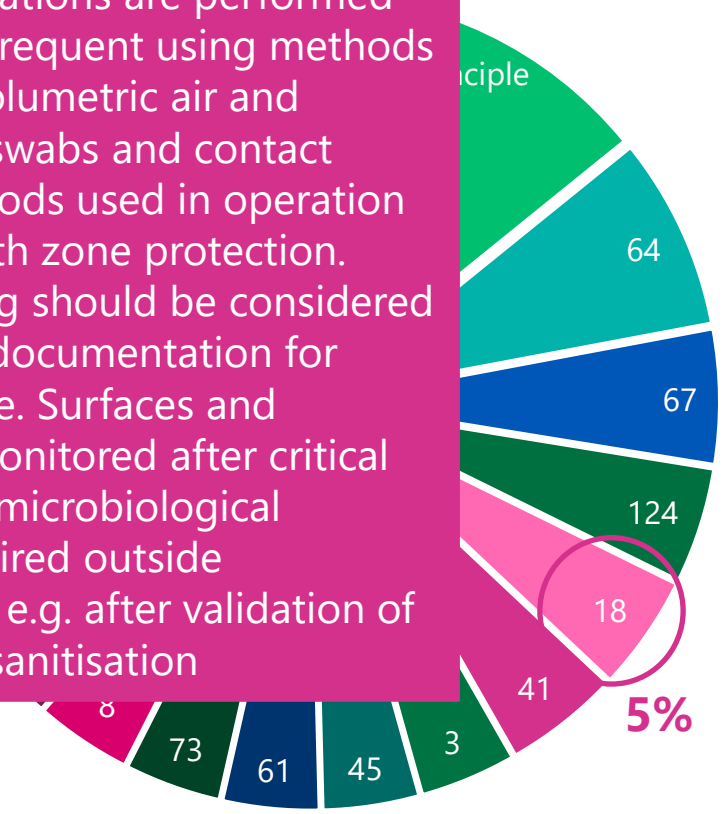
8.31 When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, should be taken from inspection.



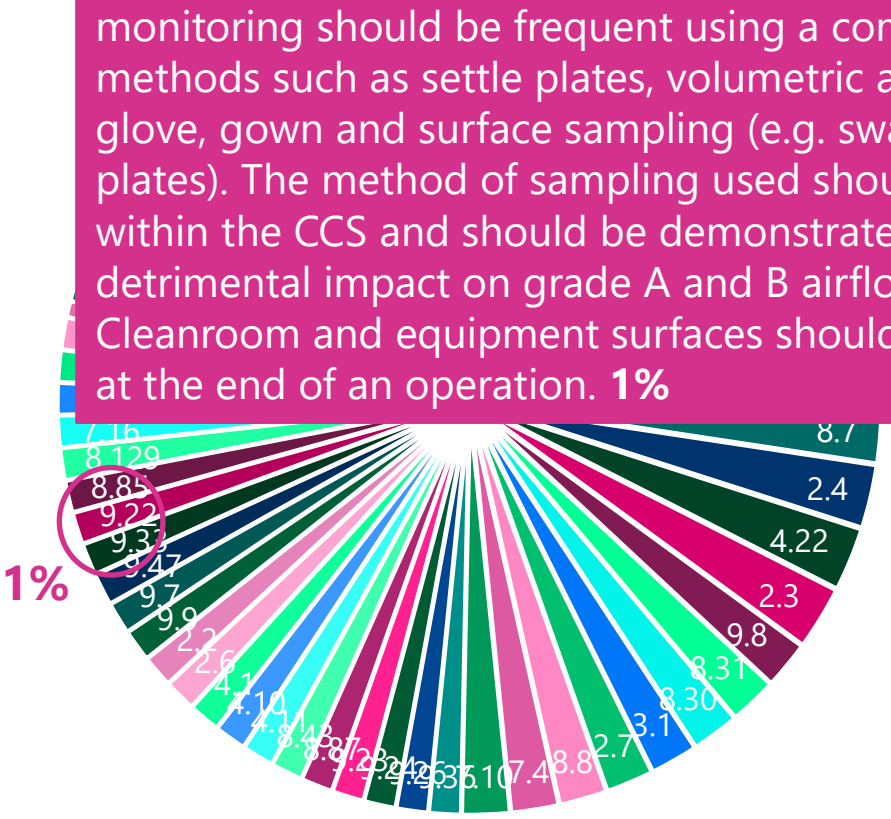
2%

Most cited pre-implementation

18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation

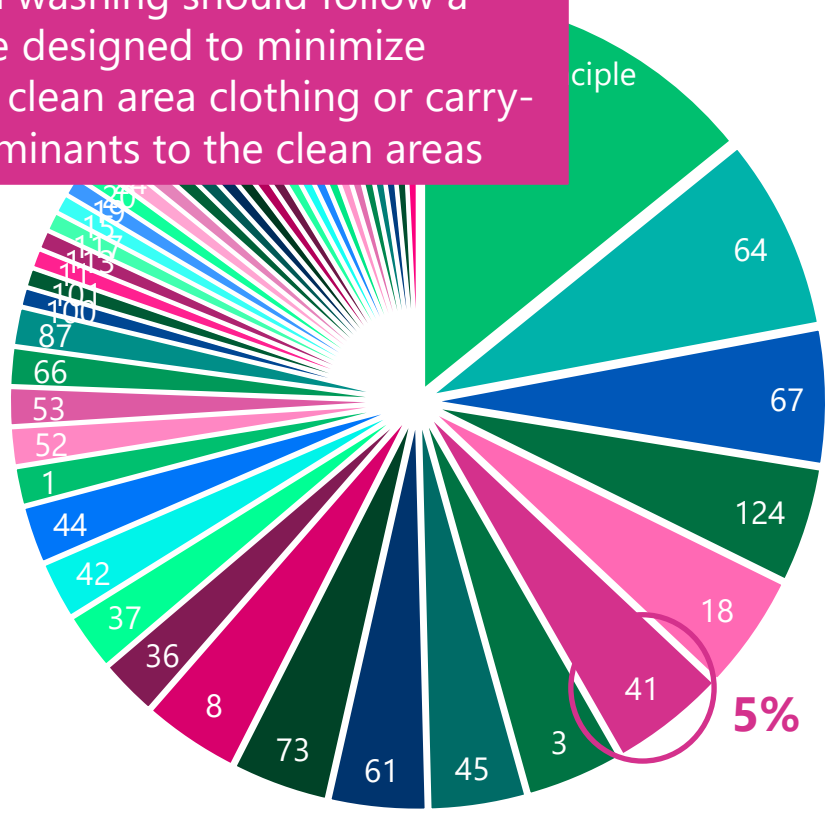


9.22 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B airflow patterns. Cleanroom and equipment surfaces should be monitored at the end of an operation. **1%**

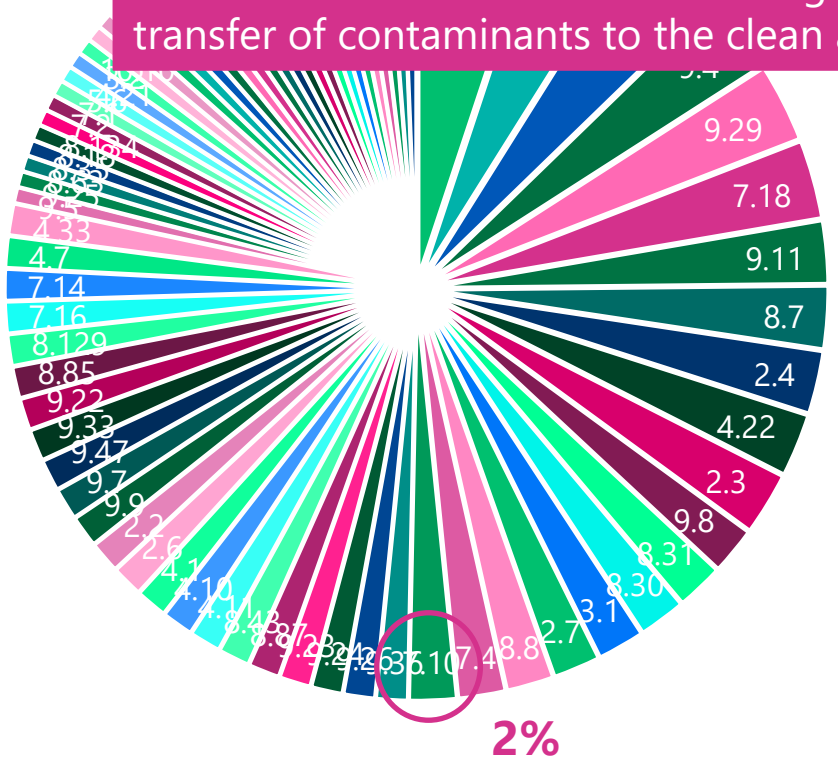


Most cited pre-implementation

41. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas



7.10 Cleanroom gowning and hand washing should follow a written procedure designed to minimize contamination of cleanroom clothing and/or the transfer of contaminants to the clean areas. (2%)



Most cited post-implementation

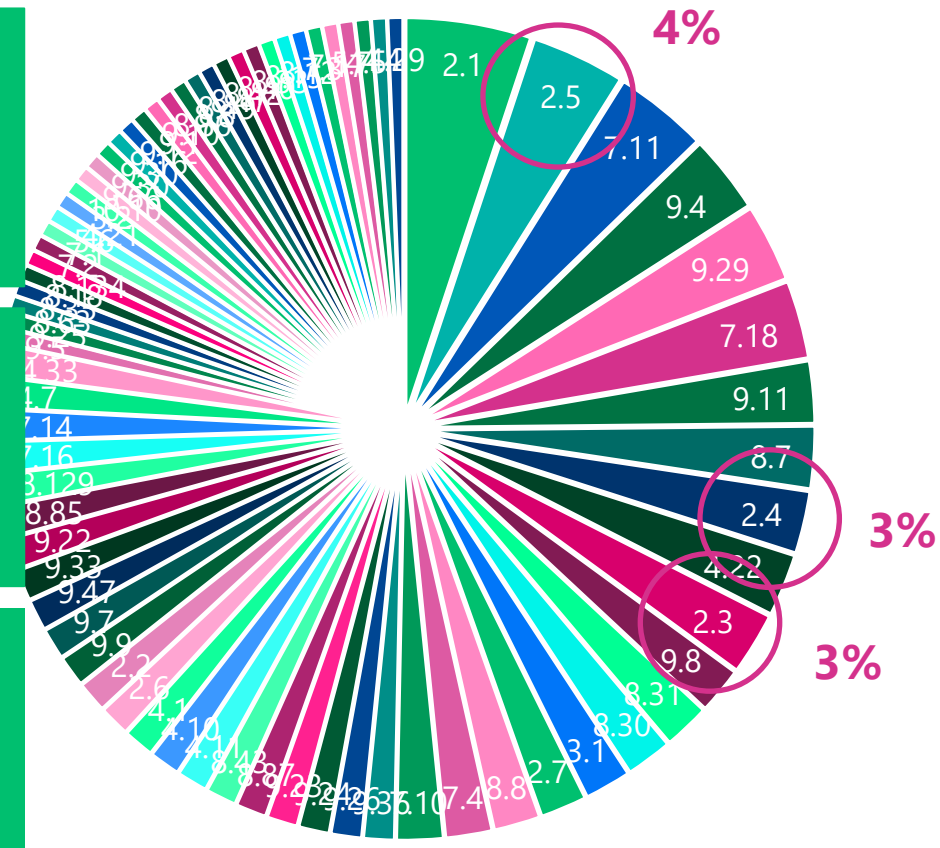
Most cited deficiencies post-implementation relate to CCS (10%), environmental monitoring (9%), personnel (7%), APS (3%), & decontamination methods (3%). These paragraphs are more detailed than previous and include some new requirements, although in some cases e.g personnel, citations don't represent 'new' common citations/ gaps.

Most cited post-implementation

2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety…

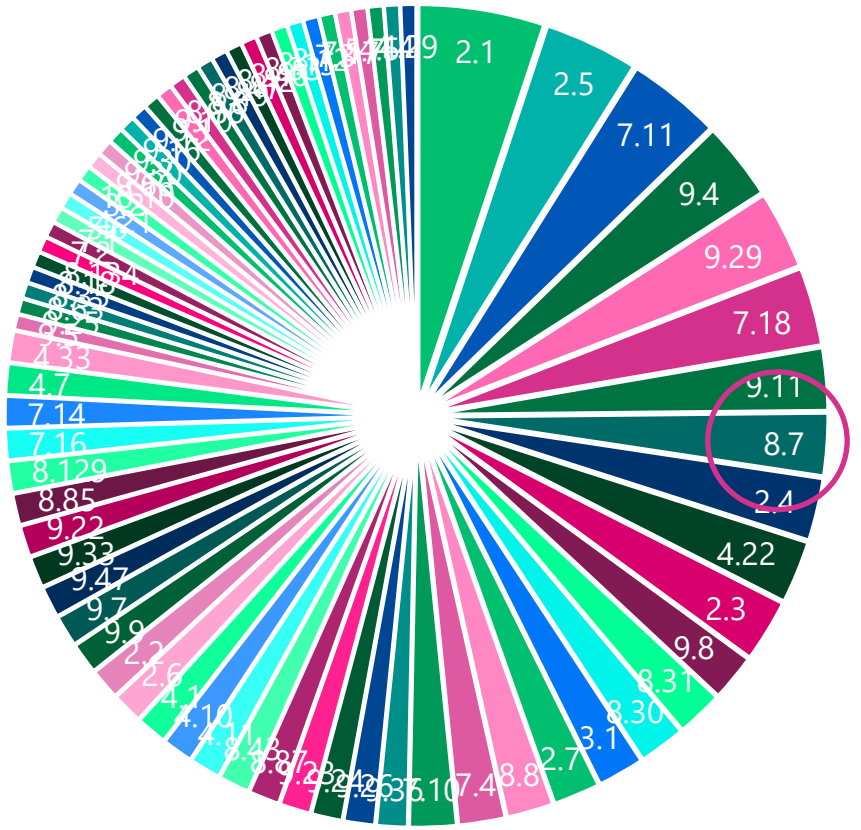
2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.

2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles). Elements to be considered within a CCS should include (but are not limited to)…



Most cited post-implementation

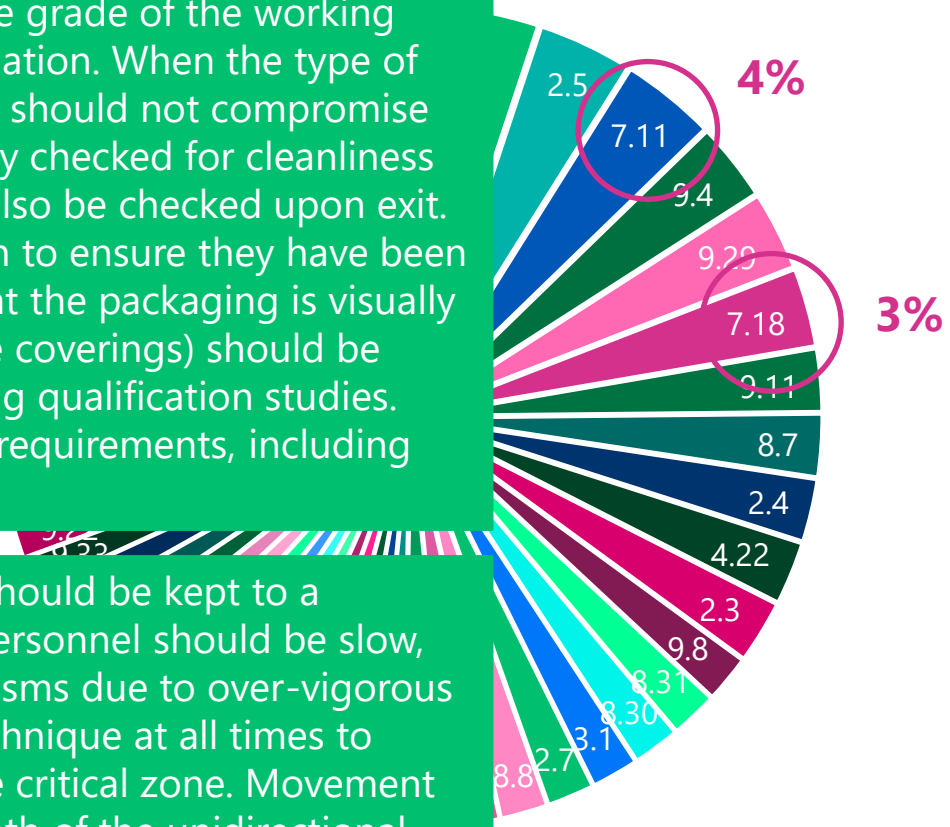
8.7 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.



Most cited post-implementation

7.11 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to and after gowning. Gown integrity should also be checked upon exit. For sterilised garments and eye coverings, particular attention should be taken to ensure they have been subject to the sterilisation process, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced if damage is identified, or at a set frequency that is determined during qualification studies. The qualification of garments should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.

7.18 Activities in clean areas that are not critical to the production processes should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity. Operators performing aseptic operations should adhere to aseptic technique at all times to prevent changes in air currents that may introduce air of lower quality into the critical zone. Movement adjacent to the critical zone should be restricted and the obstruction of the path of the unidirectional (first air) airflow should be avoided. A review of airflow visualisation studies should be considered as part of the training programme



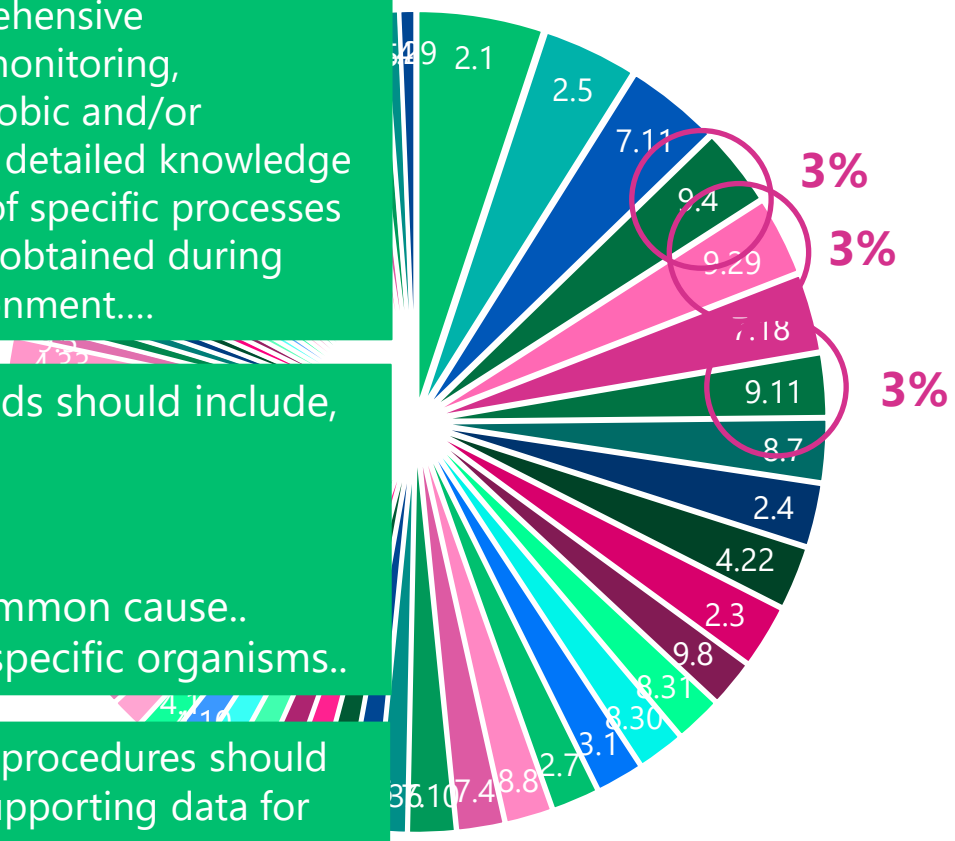
Most cited post-implementation

9.4 '….Risk assessments should be performed in order to establish this comprehensive environmental monitoring programme, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions). These risk assessments should be conducted based on detailed knowledge of the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment….

9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:

i. Increasing numbers of excursions from action limits or alert levels.
ii. Consecutive excursions from alert levels.
iii. Regular but isolated excursion from action limits that may have a common cause..
iv. Changes in microbial flora type and numbers and predominance of specific organisms..

9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available

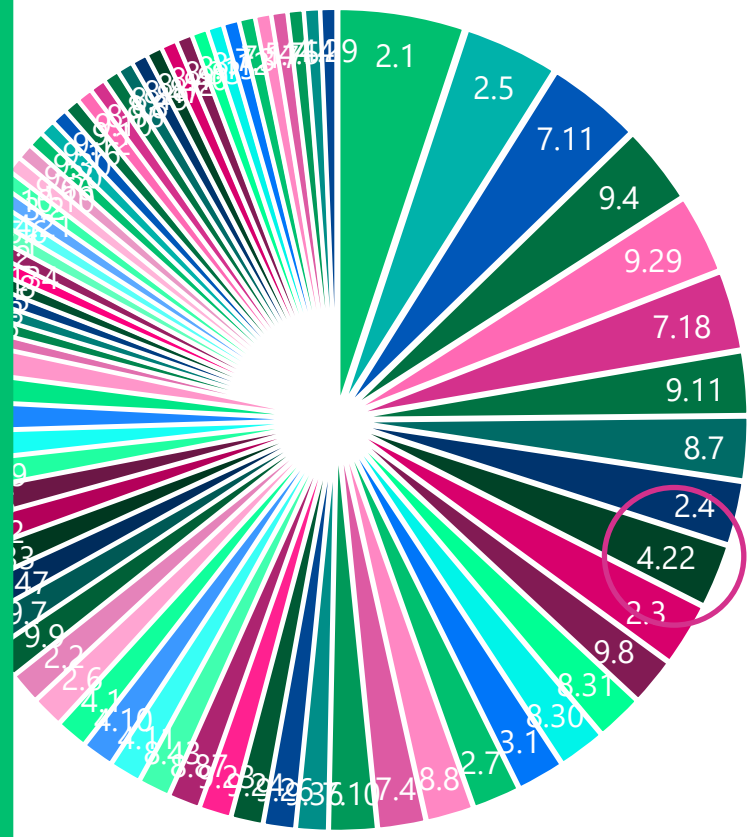


Most cited post-implementation

4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and biodecontamination agents used do not have adverse impact on the product produced within the RABS or isolator.

i. For isolators The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.

ii. For RABS The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly include all areas of the interior surfaces and ensure a suitable environment for aseptic processing.



Summary & Conclusions

Summary

Greater spread of citations across different paragraphs post implementation of new Annex 1 to be expected due to a greater number of paragraphs with more detail than previous revision

Many of the common citations pre-implementation remain post implementation, albeit accounting for a smaller proportion of overall citations.

- This is in part due to an increased number of citations in the post implementation period,
- Also may be a consequence of a more detailed Annex which permits deficiencies better attributed to a different paragraphs

Most common citations post implementation relate to contamination control strategy and environmental monitoring paragraphs, which include more detail regarding specific requirements.

Conclusions

Inspections have found that in general, gap assessments have been effectively completed and any gaps appropriately mitigated against resulting in compliance with the revised annex.

However, there have been a small number of sites at which non-compliance were identified during inspection.

Do you have assurance of Compliance?

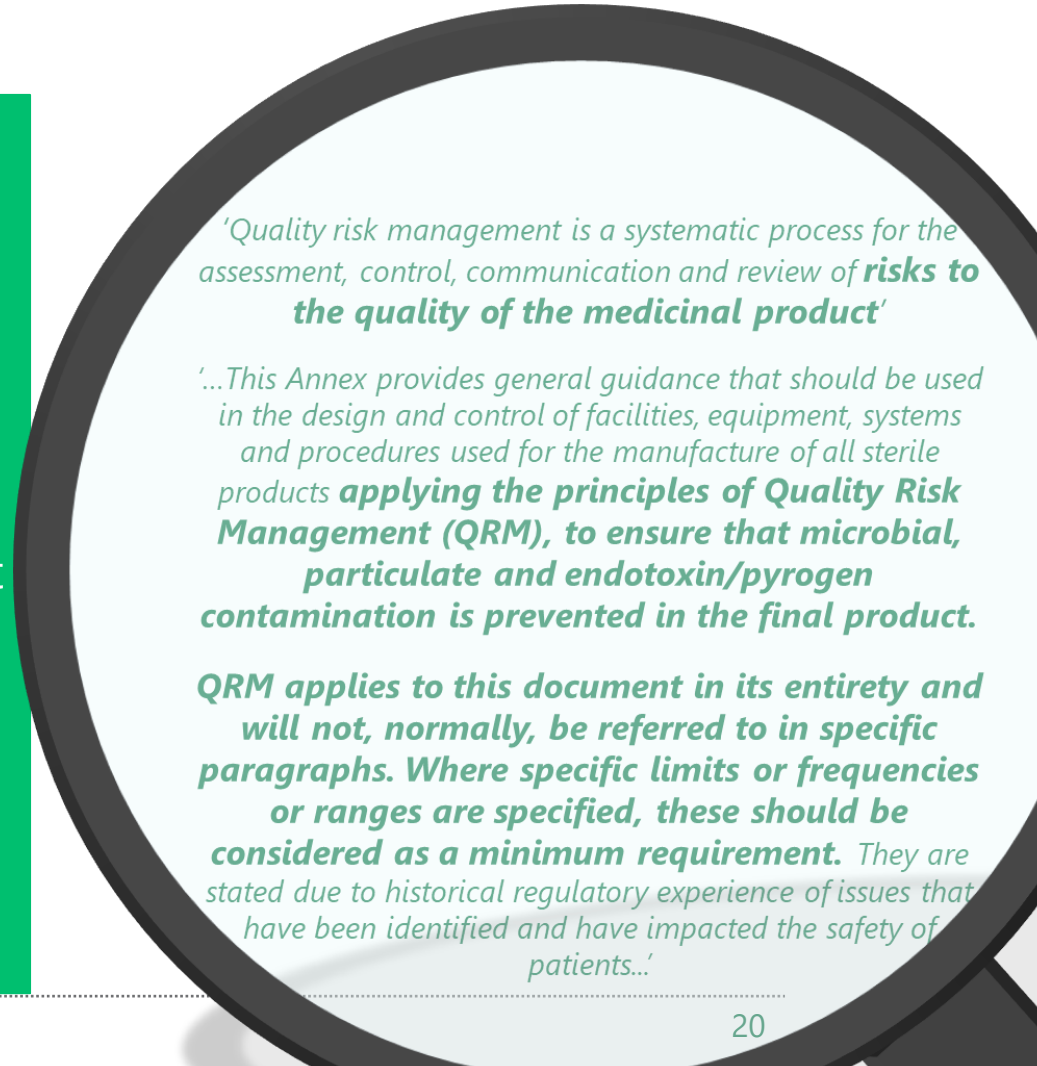
Inspectors have come across significant non-compliance with the Annex at a small number of sites due to following issues:

	Recommendations
Misinterpretation of the technology in use at the site and therefore assessing compliance against incorrect requirements	Assurance of compliance is only as good as the gap analysis process. Ensure involvement from all relevant personnel/ functions
CAPAs raised to address identified gaps subsequently closed/ cancelled without CAPAs being implemented, supported by risk assessment	Risk assessments should not be used to justify non-compliance with the Annex, compliance with the Annex is required.
Non-compliance in practice. E.g. despite the policies/ procedures detailing requirements these not happening on the floor	Challenge activities against the Annex e.g. through self-inspection. Many parts of the Annex are prescriptive enough to do so with ease Assess compliance with the annex in practice rather than sole reliance on what is detailed in policies/ procedures.

Final thoughts

Data limited to 29 inspections during the period
- Not all sites will utilise all technologies
- There will be greater insights into Annex 1 application as time goes on

QRM is implicit in the Annex
- Personnel should understand the objective of QRM.
- Risk assessments should not be used to justify non-compliance with GMP
- Risk assessments should not be used to justify acceptance of a risk that has already been pre-determined.
- An element of subjectivity is expected in risk assessments. However, risk assessments should be able to withstand scrutiny during inspection and the company should be able to provide rationale and justification in support of the process employed.
- QRM is focused on protection of the patient and rightly so, but Annex 1 compliance is good for everyone (more compliance = less inspections)



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Questions and Answers

Question

Is there any prospect of a Mutual recognition agreement with UK any time soon

No update at this time

Provision in the trade agreement for recognition of GMP certificates issued by VMD and MHRA by EU Supervisory Authority

Question

When IMPs are imported into the EU a certificate of importation is issued by the CMO responsible of the physical importation of the IMP, this certificate of importation is used by the QP responsible of the QP Certification and responsibilities are layout in the Technical Quality Agreement. Is there any concern from the HPRA regarding this process?

No reason for concern if the sites are appropriately authorised for the activities carried out and there are clear agreements between the sites. Should we have concerns??

The QP performing batch certification must be satisfied that appropriate arrangements have been put in place to ensure that the batch meets all GMP and legal requirements. The QP may only share responsibilities in relation to the batch with another QP and this must be described in a written agreement.

Question

Are there greater expectations recently around controls and checks required regarding procurement, import and the use of commercial product for use in clinical trial studies?

A commercial product used in a clinical trial is an IMP. CTR applies for any modification to the commercial product e.g. labelling / packaging

WDA not required for IMPs, but commercial entities (WDA holders) do supply to organisations that use these products in clinical trials. Operational requirements such as bone fide checks apply.

Question

Are there any recent updates or clarifications from HPRA regarding expectations for QP oversight during outsourced manufacturing and testing activities, especially with remote or hybrid work models becoming more common?

Expectations for QP oversight have not changed with remote working – refer to HPRA MIA application guidance on remote certification

Question

Is there any updated guidance on handling data integrity issues found post-batch certification, and what would HPRA expect a QP's role to be in such scenarios?

Reference previous HPRA newsletter (issue 57) on responding to a data integrity failure. If issue is found post batch certification, impact assessment on product on the market is required. If product released has been impacted this may be a quality defect / recall and require reporting – refer to HPRA website

Question

As a CMO that manufacture and package (primary and secondary) medicinal product, should the CoA be for a specific finished product batch released against a specific marketing authorisation, contain only the tests on the marketing authorisation of the batch being released?

The CoA is generated on the bulk product. The bulk product can go into finished product batches for different MA/markets. The COA contains all tests that may be required for packed product of the bulk. (ie. all markets).

CoA should contain at least registered tests for a specific market and comply with specification. Assume in the scenario listed above that difference in tests would only apply to packaged product? Refer to next question..

Question

A problem for the QP is that they cannot verify all data on the COA, only the data of the tests that are contained in the MA of the batch being released, and not the data/spec of the test that is not in the specific MA for the batch being released.

The QP should be able to certify compliance with the terms in the MA. If the additional test results indicate something additional e.g. apparent out of trend results for a test which is not in the MA …then this could be additional information that the QP may need to consider.

Question

What gaps are you seeing in QP knowledge?“

ANNEX 5 QUALIFIED PERSON(S)

Applicants **must** submit the following details:

- A copy of relevant qualifications as issued by a relevant third level institution to support educational requirements for a QP.
- A copy of the proposed QP's CV. This should include evidence of QP status if the applicant has acted as a QP in another EU jurisdiction.
- The current email address for each proposed QP.
- A summary of training, relevant to the role of QP, performed at the manufacturing site concerned. This should be in the form of a training programme for the role of QP at the site rather than simply a printout of training in various standard operating procedures (SOPs), for example as might be obtained from a learning management system. This should be signed by the proposed QP and, if applicable, their relevant superior.
    - Details of product specific training should also be included in cases when the product types are new to a site.

Question

Guidelines for Cell Bank manufacture testing - update please.

International Conference on Harmonisation (ICH) Q5

Quality of Biotechnological Products: Derivation and Characterisation of Cell

Substrates Used for Production of Biotechnological/Biological Products

Question

In the concept of Europe and a possible integration and harmonisation of all member states, was the topic on having common requirements for being certified as QP ever discussed so far?

There are minimum common criteria across the member states and this is defined in EU legislation. Individual countries e.g. France has specific legislation on Pharmacien Responsable

There have been areas of ongoing discussion on harmonisation of specific aspects of QP role. These do not always result in all countries having the exact same requirements and provision is made for some national requirements. .....e.g. remote QP certification

Education is a national competence.

Question

How is the HPRA adjusting its strategies to tackle the challenges and leverage the opportunities arising from the growing implementation of new technologies, particularly artificial intelligence, in pharmaceutical manufacturing?

Mission, Vision and Values

Our Mission - We regulate medicines and devices for the benefits of people and animals

Our Vision – Excellence in health product regulation through science, collaboration and **innovation.**

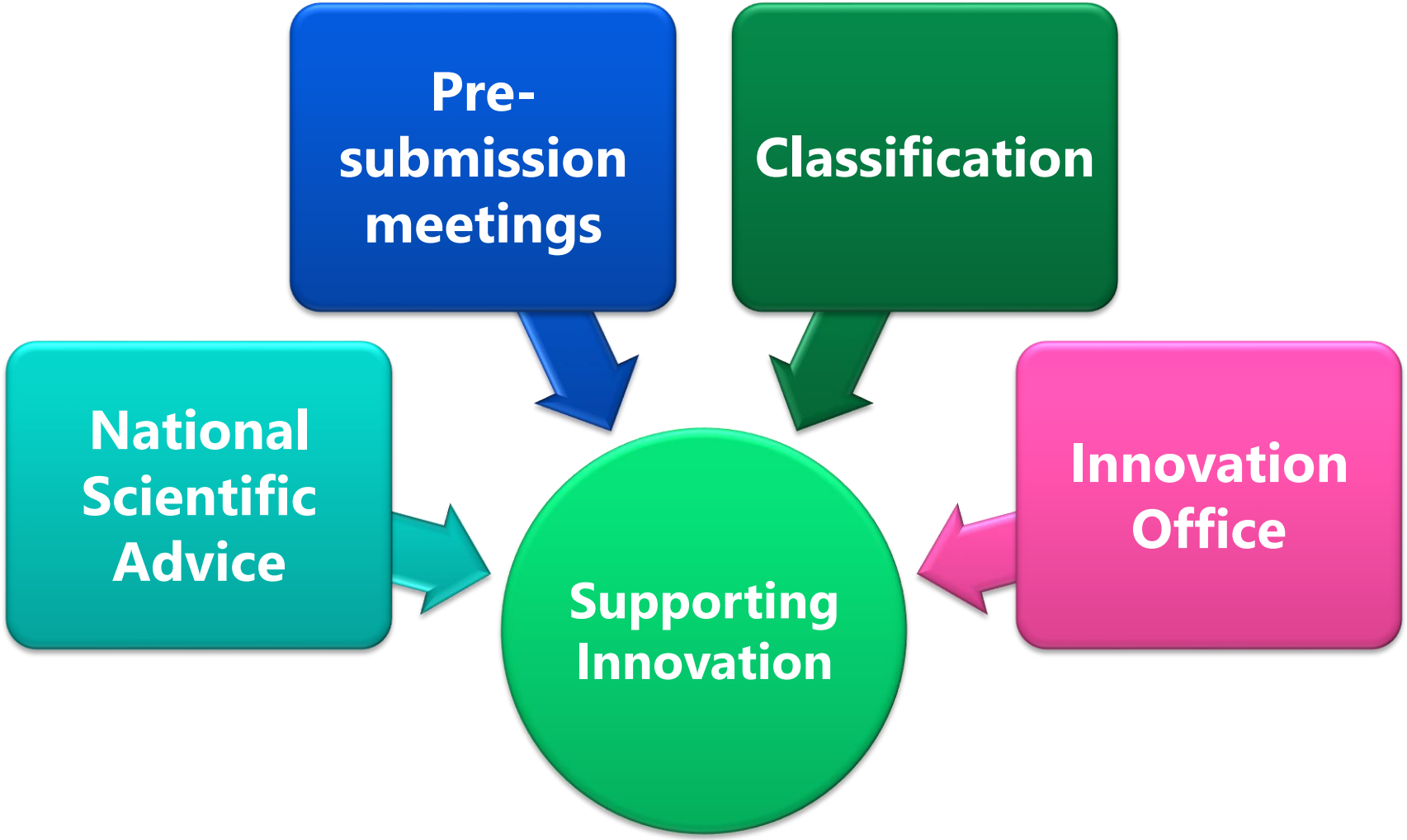
Our first value: Patient Focused – We put the interests of those who use health products first.

Strategic Goals

- Enabling Innovation – engage with stakeholders to drive improvements in regulatory activities

HPRA Innovation Office

Some HPRA Mechanisms to Support Innovation



European Medicines Agency (EMA)

- EMA's Innovation Task Force (ITF)
- HPRA Co Chair of EU-Innovation Network

Question

What are the emerging concerns about AI in the regulated pharmaceutical industry and what to be aware of as a QP?

Consideration - Application of a risk based approach

Question

Aseptic Process Simulations - starting points for lyophilized products i..e where should the APS start when using low bioburden products that are subjected to sterile filtration.

Annex 1, paragraph 9.33

- i. The APS should assess all aseptic operations performed subsequent to the sterilisation and decontamination cycles of materials utilised in the process to the point where the container is sealed
- vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters.

Question

Role of QP after Brexit [EU QP and UK QP (GB QP, NI QP)] and importation of product into EU, GB, NI from third countries, product testing and QP release

Role of the QP has not changed specifically as a result of Brexit.

MAHs could apply for certain derogations in certain markets (ROI, Cyprus, Malta) up to Dec 2024

Third country importation rules apply (apart from NI)

Release of product manufactured in or imported into NI for supply to EU markets permitted where site of batch release in NI is named on the MA / IMPD

Importation into GB from third countries – refer to MHRA / VMD for requirement

UK QP—not legally equivalent to the EU QP with respect to imported products.

Question

How does a start up company (in the process of applying for an MIA) go about obtaining a QP declaration for the active substance to be used for MA submission? They can't sign the QP declaration as they don't yet have MIA.

Site of batch release must be named in the application for a product MA. This site will have to hold an MIA at the time of submission or else this will be identified as an issue at the time of application. QP at site of batch release would be the QP who submits the QP declaration for the API

Question

- Our company is the Marketing Authorization Holder (MAH) for a Biological Drug Product. The DS, DP manufacturing, and QC testing activities are all outsourced by our company.
- The DS is manufactured in the EU and each batch is QP released by us, also undergoes full panel testing for each release, and is integrated into a stability program, with one lot set down per year for ongoing monitoring. Additionally, the Drug Product manufacturer complies with Annex 8 requirements, performing identification on each DS shipment they receive.
- Citing Chapter 5 (5.36 v in particular), the Drug Product manufacturer is of the opinion that they need to carry out independent testing on one batch annually of the Drug Substance, even though our company, as the MAH, oversees the sourcing and supply of the DS and oversees/monitors the QC testing of the DS in line with Quality Risk Management principles.
- **Does the responsibility for oversight of QC testing laboratories performing Drug Substance release testing lie with the MAH, irrespective of the CMO's role as the Drug Product manufacturer?**

Considerations

- Ch 5, 5.36 v. The medicinal product manufacturer should also perform (or via a separately approved contract laboratory) a full analysis at appropriate intervals based on risk and compare the results with the material manufacturer or supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier should be discontinued until these measures are completed.

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Other questions

- Tariffs
- Impact of FDA restructure
- What is the most common issues experienced by New QP's?
- Update on pending regulation up dates and what is the focus for the next few years
- Veterinary Regulation 2019/6 implementation acts on manufacture of veterinary medicines - What are any significant differences from GMP requirements for Human medicines

Acknowledgements

With thanks to

Aedin Hogan, HPRA GMP Inspector

Paul Sexton, HPRA Policy Manager

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Thank you