Llywodraeth Cymru
Welsh Government

Assurance of aseptic preparation of medicines in NHS Wales

Governance and regulatory arrangements for aseptic preparation of medicines by health boards and NHS trusts in Wales

February 2024

Purpose

This guidance sets out the governance and regulatory arrangements for aseptic preparation of medicines for NHS patients in Wales and replaces NHS DGM(97)5 entitled Aseptic Dispensing in NHS Hospitals issued in 1997.

It defines the roles and responsibilities of:

- NHS organisations in meeting quality standards, responding to audits and inspections, and reporting quality indicators when performing aseptic preparation activities. This includes the statutory responsibilities of chief pharmacists as established by The Pharmacy (Preparation and Dispensing Errors – Hospital and Other Pharmacy Services) Order 2022.
- The NHS Wales National Lead Pharmacy – Quality Assurance (and nominated deputies) in providing regulatory oversight and inspection of aseptic preparation activity, and auditing services against quality standards.
- The Welsh Government's Chief Pharmaceutical Officer who is responsible for commissioning the overarching governance and assurance process, providing oversight and supporting enforcement where necessary.

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Introduction

NHS hospital pharmacy aseptic services provide sterile, controlled environments in which highly qualified staff prepare a range of medicines including injectable systemic anti-cancer therapy (SACT), parenteral (intravenous) nutrition for people whose medical condition mean they are unable to absorb nutrients from the food they eat, and radiopharmaceuticals used in diagnosis and treatment of cancers. The use of these medicines enhances quality and safety, releases nursing time to be devoted to patient care, and facilitates care closer to people's homes.

In general, the aseptic preparation of unlicensed medicines in hospitals takes place either under a Medicines and Healthcare products Regulatory Agency (MHRA) manufacturer's 'specials' (MS) authorisation or under the supervision of a pharmacist permitted under section 10(1) of the Medicines Act 1968.

The MHRA is responsible for the inspection and oversight of facilities operating under MS authorisations, with NHS organisations responsible for the oversight of facilities operating under the section 10 exemption. To support NHS organisations and to ensure section 10 facilities operate under broadly the same conditions as MHRA authorised facilities, since 1997 NHS organisations in Wales have operated within an assurance process for the aseptic preparation of injectable medicines described in circular DGM(97)5.

Equivalent assurance processes were in place in other parts of the UK under the Department of Health Executive letter – EL (97)52 in England and equivalent publications in Scotland and Northern Ireland.

DGM(97)5 requires audits are undertaken, at least annually, of all NHS sites that perform aseptic preparation of medicines not covered by an MHRA MS authorisation. Authorised auditors undertake the audits and report their findings to health boards and trusts.

There have been concerns in all parts of the UK about the transparency of actions taken in response to these audits and the potential for misunderstanding within health boards and NHS trusts of their boards' responsibilities and accountabilities, particularly regarding the importance of implementing required remedial actions and the need to prioritise associated works.

NHS organisational structures, policies and governance frameworks have changed since DGM(97)5 was published in 1997 and in 2020, the Department of Health and Social Care's report Transforming NHS pharmacy aseptic services in England made a clear recommendation to "strengthen the accountability and responsibility around the unlicensed preparation of aseptic medicines under EL(97)52 guidance and the role of the Chief Pharmacist". Subsequently, EL(97)52 guidance was revoked in England in 2023 and replaced by the NHS Infusions and Special Medicines Programme: Guidance to replace EL(97)52 in England.

This guidance has been adapted from NHS England's guidance in order to ensure consistency and best practice in the assurance of aseptic preparation of medicines by NHS Wales health boards and trusts. The Welsh Government's Chief Pharmaceutical Officer commissioned this guidance which has been adapted for use in Wales by Owain Jones, Principal Pharmacist Quality Assurance and Quality Control, Aneurin Bevan University Health Board and Laura-Jayne Keating, National Lead – Pharmacy Quality Assurance, NHS Wales Shared Services Partnership, with the permission of NHS England's EL(97)52 Review Working Group. We are grateful to NHS England's EL(97)52 Review Working Group for their work in updating the original guidance and for their permission to adapt it for use by the NHS in Wales.

The scope of this guidance encompasses a range of aseptic activities that sit outside the section 10 exemption and outside the scope of MHRA MS authorisations. These include, for example, aseptic preparation/ reconstitution of investigational medicinal products (IMPs) and advanced therapy medicinal products (ATMPs) within NHS pharmacy aseptic facilities in Wales.

This guidance makes clear the accountability and responsibility of health boards and NHS trusts in relation to the unlicensed preparation of aseptic medicines and the role of health board and trust chief pharmacists. The guidance replaces DGM(97)5 and reflects current NHS management arrangements. The requirements described in this guidance come into force from the date of its publication and apply to all aseptically prepared medicinal products prepared within NHS pharmacy facilities under the section 10 exemption.

This guidance specifies the process for auditing, monitoring, assuring and reporting compliance of services and facilities with critical quality and patient safety parameters, and for responding to serious concerns about non-compliance. It also specifies the process for escalation of unresolved concerns and signposts to other key guidance and standards applicable to NHS aseptic preparation services and activities.

The guidance is predicated on universal implementation of a template for a digital, good manufacturing practice (GMP) based audit and compliance management system referred to as the interactive Quality Assurance of Aseptic Preparation Services (iQAAPS). This is supported by a web-based system that enables health board and trust chief pharmacists to develop and improve their services (see revised assessment process section and appendix 1 for further details).

The priority is that aseptic preparation is carried out to a consistently high standard and the products issued have an assurance of quality to the level of safety that patients legitimately expect.

Definitions

For the purposes of this guidance, 'aseptic preparation of medicines' focuses on activity performed within an aseptic facility with pharmacy oversight. This definition therefore encompasses reconstitution of injectable medicines when undertaken within NHS pharmacy aseptic facilities in Wales. For the avoidance of doubt, reconstitution of injectable medicines in clinical areas is out of the scope of this guidance. Manufacturing under a MHRA MS authorisation, a manufacturer/importer authorisation (MIA) or manufacturer/importer authorisation for IMPs (MIA IMP) are also out of the scope of this guidance. However sites which hold an MS authorisation are required to report against the quality indicators described in the assurance and performance management section of this guidance.

From a legal and regulatory perspective, aseptic preparation and dispensing should be seen as two separate but linked activities:

- *Aseptic preparation* is defined as: reconstitution of an injectable medicine or any other aseptic manipulation when undertaken within NHS aseptic facilities to produce a labelled ready-to-administer presentation of a medicine, in accordance with a prescription provided by a practitioner, for a specific patient; and
- *Dispensing* is defined as: supply of a finished product to a specific patient, or to the person responsible for its administration, in accordance with a prescription.

This guidance focuses on aseptic preparation and covers all directly associated activities up to the point of issue from the pharmacy aseptic facility.

Compliance with GMP is required in line with Royal Pharmaceutical Society's standards set out in the most recent edition of Quality assurance of aseptic preparation services.

For further detail regarding the definition of terms used in this guidance, see the glossary and explanatory notes in appendix 2.

Scope of guidance

The principles and processes described in this guidance apply to all aseptic preparation of medicinal products in NHS pharmacy aseptic facilities in Wales, other than those products manufactured under an MHRA authorisation. The guidance therefore applies to all NHS pharmacy aseptic facilities undertaking preparation of sterile medicinal products under the Section 10 exemption, even when provided from facilities that concurrently hold an MHRA MS authorisation.

The guidance applies to:

- Aseptic reconstitution of any medicinal products or IMPs, where this is performed in a pharmacy aseptic facility.
- Aseptic reconstitution of innovative therapies such as ATMPs where this is performed in any NHS aseptic facility with pharmacy oversight.
- All types of preparation made aseptically (e.g. it applies to formulations such as eye drop preparations under limited and defined circumstances, in addition to injections).
- All NHS radiopharmacy services in Wales, including those operating under an MHRA MS authorisation, whether within or outside pharmacy oversight, until specific national radiopharmacy guidance is produced.

This guidance does not apply to:

- Clinical service elements such as organisations' injectable medicines policies or NHS Wales Patient Safety Alerts or Notifications.
- Reconstitution of medicinal products in a clinical area; such activity should be in accordance with the marketing authorisation holder's summary of medicinal product characteristics (SmPC) or, for IMPs, in line with the requirements of the clinical trial protocol and any pharmacy manual for clinical trials.
- Manufacturing under a MHRA MS, MIA or MIA IMP authorisation except that sites which hold an MS authorisation are required to report quality indicators as described in this guidance.
- Aseptic preparation services provided by non-NHS facilities such as independent sector hospital pharmacies.

Restrictions for aseptic preparation

All NHS pharmacy aseptic preparation services operating under Section 10 exemption must meet the five criteria below.

1. Preparation is carried out by or under the supervision of a pharmacist (the definition of supervision in this context is being reviewed with changes anticipated in the future). It is critical that the person responsible for supervision has the necessary competence and technical expertise in GMP.
2. Preparation uses only closed systems with the exception that emergency eye drop preparation is allowed under defined circumstances.[1]
3. Preparation uses only licensed sterile medicinal products or, when appropriate, a sterile medicinal product with sufficient evidence to provide assurance of pharmaceutical quality.
4. Finished products are allocated a shelf-life of no more than 8 days and the allocated shelf-life is supported by validated stability data and an objective risk assessment.[2]
5. Preparation is carried out in accordance with the NHS professional standards referred to in this guidance.

It should be noted that some of these criteria have been updated from those specified in Medicines Control Agency's Guidance to the NHS on the licensing requirements of the Medicines Act, published in 1992, and which were documented in DGM (97)5 and the related 1997 Department of Health publication Aseptic dispensing for NHS patients – a guidance document for pharmacists in the United Kingdom (the Farwell report). The original five criteria are therefore specified within other extant published pharmacy standards documents, this guidance updates the original requirements.

1 For exceptional use of open systems, see Preparing eye drops in unlicensed aseptic units.
2 The extension of the maximum shelf-life from seven to eight days enables supply of full 7-day treatment courses and limits wastage, but only where it is safe and appropriate to do so, being supported by an objective risk assessment and microbiological, chemical and physical stability data. This may enable rescheduling of patients where clinically appropriate or the use of 7-day drug reservoirs more readily.

Roles and responsibilities

NHS Wales health board and trust Chief Pharmacists

- To appoint a GMP technical expert to provide leadership to the aseptic unit;
- To ensure all aseptic preparation is carried out in accordance with the most recent edition of the professional standards, quality assurance of aseptic preparation services (QAAPS);
- To adhere to the requirements of this guidance, in relation to reporting quality indicators no less frequently than every month to the National Lead – Pharmacy Quality Assurance using the iQAAPS system;
- To facilitate and respond constructively to audits undertaken by the National Lead – Pharmacy Quality Assurance or any nominated deputies;
- To implement and update action plans to agreed timescales;
- To ensure quality indicators are reported in a timely manner;
- To report and appropriately escalate serious incidents relating to aseptically prepared medicines; and
- To ensure all relevant information and changes regarding pharmacy aseptic services are notified to the National Lead – Pharmacy Quality Assurance.

National Lead – Pharmacy Quality Assurance

- To regularly audit NHS aseptic facilities;
- To monitor quality indicators and progress against audit action plans;
- To report audit outcomes and situation reports;
- To support enhanced compliance management of elevated risk facilities;
- To escalate concerns regarding aseptic services risks; and
- To require restrictions on and measures to be taken by NHS pharmacy aseptic facilities where deemed appropriate.

NHS Wales health board and trust Chief Executives

- To receive the post audit iQAAPS report from the health board or NHS trust chief pharmacist; and
- To support their chief pharmacist to implement a robust action plan in response to audit findings.

Welsh Government's Chief Pharmaceutical Officer

- To seek assurance that the governance and assurance arrangements for aseptic services are in place as part of regulatory framework and routine engagement conversations with NHS health board and trust chief pharmacists;
- To commission an overarching governance and assurance process;
- To oversee and support delivery of the governance and assurance process;
- To ensure that relevant NHS bodies follow up escalated concerns; and
- To ensure that enforcement action is taken where necessary.

Revised assessment process

Audit process to assess risk

Inspection of aseptic preparation is undertaken to audit practice and processes against the standards outlined in the most recent edition of the Quality assurance of aseptic preparation services. However, other relevant standards for assessment include, but are not limited to the MHRA's Good manufacturing and good distribution practice, Guidance for specials manufacturers and other guidance notes including good clinical practice, health and safety law and guidance, NHS guidance and national patient safety alerts and notifications.

A number of trained quality assurance auditors, accredited by National Lead – Pharmacy Quality Assurance with suitable knowledge and experience in aseptic preparation and quality assurance, perform these audits. A national list of sites to be audited, including details of aseptic services provided, is maintained by the National Lead – Pharmacy Quality Assurance. Auditors are professionally accountable to the National Lead Pharmacy Quality Assurance and ultimately to the Welsh Government's Chief Pharmaceutical Officer.

Auditors document detailed audit findings in an audit report and summary report using the iQAAPS system (see Reporting section for further details).

Audit findings that include deficiencies against the defined standards are assessed and reported at one of four levels of significance:

- **Critical** – deficiencies that require immediate action (within 24 hours).
- **Major** – deficiencies that require corrective actions to start as soon as possible and progress to be demonstrated within three months.
- **Minor** (sometimes referred to as 'other') – deficiencies that require corrective actions and progress to be demonstrated within 12 months.
- **Satisfactory** – no adverse findings although suggestions for further improvement may be noted.

These deficiencies are grouped by the chapter headings in the Quality assurance of aseptic preparation services standards. A summary of the findings is documented and one of the four levels of significance is assigned. Any standards or chapters that are not audited are identified as 'not reviewed'.

An overall risk rating linked to patient safety is assigned to the aseptic unit. The categories of overall risk are:

- High
- Medium (which replaces the previous risk rating of 'significant')
- Low.

Audit frequency is risk-based with the maximum interval between audits for units other than those considered "low risk" no more than two years.

Where the National Lead – Pharmacy Quality Assurance deems an aseptic unit 'low risk' it may be agreed that a self-declaration approach to compliance can be adopted to fully or partly replace independent audits. Audits may still take place at the request of the health board or NHS trust chief pharmacist or the aseptic lead. Peer review of the self-declaration will be available from accredited auditors and feedback provided. The maximum interval between audits for units under the self-declaration approach is three years.

There may be situations or exceptional circumstances where short notice or targeted audits are necessary or where the audit period is reduced or extended from that originally proposed. Any escalation of risk results in more frequent service audit, and an aseptic unit that receives a critical deficiency or an overall risk assessment of 'high' will be reviewed within one month with subsequent reviews determined by the health board or NHS trusts response.

The interactive Quality Assurance of Aseptic Preparation Services (iQAAPS)

The interactive Quality Assurance of Aseptic Preparation Services (iQAAPS) is a digital, GMP-based audit and compliance management system used to manage a number of activities linked to the audit process and provide greater oversight of aseptic preparation.

Specifically, it:

- Facilitates the completion and submission of the pre-audit questionnaire and any other documentation aseptic facilities request;
- Facilitates the production and distribution of audit reports;
- Facilitates the creation, updating and close-out of action plans in response to audit findings by aseptic facilities;
- Enables auditors to have oversight of progress against agreed actions and timeframes in response to audit deficiencies;
- Provides a 'live' audit status for all aseptic facilities;
- Facilitates the submission of monthly quality indicators (QIs) for aseptic facilities;
- Enables auditors to have oversight of the QIs for aseptic facilities; and
- Collates data to enable trending and reporting as detailed in the Reporting section of this guidance.

In addition, a self-assessment function enables aseptic facilities to self-declare their compliance with the QAAPS standards. Evidence statements can be created to support the self-assessment rating. Action plans can also be produced in response to internal audit findings to drive quality improvement. Further detail about iQAAPS can be found in appendix 1.

Assurance and performance management

Quality indicators

Each facility, **including those which hold an MS authorisation**, must report a set of predefined quality indicators to the National Lead – Pharmacy Quality Assurance using the iQAAPS system on a monthly basis. These are iterative and the requirements will develop over time; the QIs in place at the time this guidance is published are detailed in appendix 3.

The health board or trust chief pharmacist is responsible for ensuring that:

- QI data are submitted monthly;
- QI data are routinely monitored locally;
- Appropriate actions are taken when QIs indicate deteriorating performance;
- Any significant results are reported to the auditor; and
- Supporting information is provided to the auditor on request, including Pharmaceutical Quality System records and investigations.

The failure to submit QIs or to take appropriate action in response to results may impact on the re-audit frequency of the site or in escalation in accordance with the compliance management and escalation section of this guidance.

Patient safety incidents

Any patient safety incident that is categorised as a 'serious untoward incident' arising from work undertaken in a pharmacy aseptic service is to be addressed and reported in accordance with the NHS Wales Executive's National Policy on Patient Safety Incident Reporting & Management, The Duty of Candour Procedure (Wales) Regulations 2023, and local organisational procedures. At the same time as undertaking a critical root cause analysis under the health board or trust's pharmaceutical quality system, the health board or trust chief pharmacist is required to provide a summary of any such incident to the National Lead – Pharmacy Quality Assurance.

Communicating audit findings

Following a site inspection:

- The auditor will meet with health board or trust chief pharmacist or their nominated deputy and the accountable pharmacist to discuss and confirm the audit findings (the debrief);
- The auditor will document the audit findings on the iQAAPS system;
- The auditor will publish an audit report and summary report on iQAAPS system;

- The audit report and summary report is issued to the health board or trust chief pharmacist and accountable pharmacist using iQAAPS;
- A copy of the summary report is sent to the health board or trust chief executive; and
- Where an audit finds a facility represents a HIGH RISK to patient safety, a copy of the summary report is sent to the Welsh Government's Chief Pharmaceutical Officer.

In addition:

- The National Lead – Pharmacy Quality Assurance sends an annual national situation report to the Welsh Government's Chief Pharmaceutical Officer (generated from iQAAPS); and
- The National Lead – Pharmacy Quality Assurance provides site-specific audit reports or access to iQAAPS to other regulators on request.

Process for ongoing oversight

- The auditor approves health board and trust action plans created in response to audit deficiencies, including timeframes for completion, using iQAAPS;
- The health board or trust chief pharmacist and the auditor monitor progress against action plans through to closure of identified deficiencies;
- The health board or trust chief pharmacist and the auditor monitor QIs;
- Concerns regarding facilities that fail to make adequate progress with corrective and preventative actions, fail to submit QIs or for which the QI data demonstrate a loss of control are escalated in accordance with the compliance management and escalation section of this guidance; and
- Re-audit frequency is reviewed by the auditor based on received intelligence.

Compliance management and escalation

Compliance management is automatically triggered for every service that is identified as having a HIGH RISK rating, and also for any site identified as having a MEDIUM RISK rating but which is failing to make adequate progress with corrective and preventive actions, to submit QIs, or for which the QI data demonstrates a loss of control.

The health board or trust chief pharmacist is responsible for notifying their board when sites are placed under compliance management and for ensuring that ongoing updates of progress and risk are provided.

Compliance management comprises two stages:

Stage 1 compliance management: Enhanced oversight

- Service placed under stage 1 compliance management by National Lead – Pharmacy Quality Assurance;
- National Lead – Pharmacy Quality Assurance requires service restrictions if deemed necessary;
- Site-specific situation report prepared and distributed in accordance with the Reporting section of this guidance;
- Auditor closely monitors progress with action plans and QIs and supports, if necessary, until service is removed from compliance management; and
- Auditor reviews re-audit frequency in line with service response.

Stage 2 compliance management: Escalation

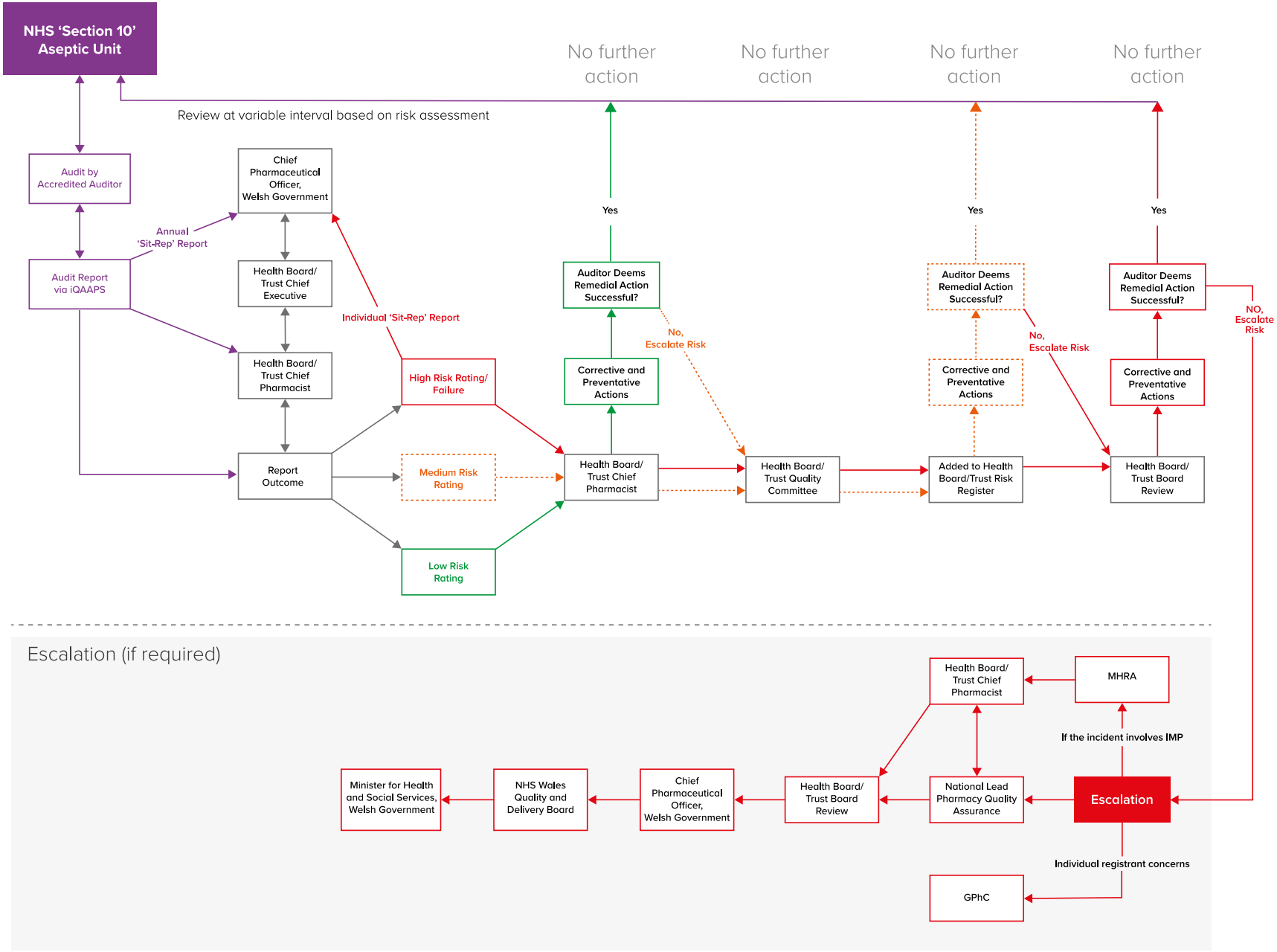
- Service placed under stage 2 compliance management by National Lead – Pharmacy Quality Assurance for failing to meet stage 1 compliance management requirements;
- Site-specific situation report prepared and distributed in accordance with the Reporting section of this guidance;
- Additional restrictions and measures to be imposed by National Lead – Pharmacy Quality Assurance, as deemed appropriate. (In exceptional cases this may include enforced unit closure.); and
- Failure to demonstrate the necessary improvement will lead to escalation to the Welsh Government Chief Pharmaceutical Officer, and subsequently into NHS performance management arrangements including the NHS Wales Quality and Delivery Board for example.

Review process

Services placed under stage 1 enhanced oversight or stage 2 escalation may request a review of the decision. The health board or trust chief pharmacist must, in writing, request a review from the National Lead – Pharmacy Quality Assurance; the request must detail any concerns being raised, provide evidence to support the request and must be countersigned by the health board or trust chief executive.

This request may generate a formal peer review of the audit by an auditor who is independent of the previous audit. Their decision is final.

Flow chart summarising audit process and escalation pathways



Reporting

Audit reports

The auditor documents all audit findings in an audit report and summary report. Reports are prepared and published electronically using the iQAAPS system.

The health board or trust chief pharmacist and accountable pharmacist are alerted by email when a report is published and is available to be viewed in the iQAAPS system. They should confirm that they have read the report in the iQAAPS system.

A copy of the summary report is sent to the health board or trust chief executive.

Situation reports

The National Lead – Pharmacy Quality Assurance produces an annual national situation report to provide an overview of the status of all NHS pharmacy aseptic facilities in Wales for the Chief Pharmaceutical Officer – Welsh Government.

The National Lead – Pharmacy Quality Assurance produces site-specific compliance management reports for all sites placed in stage 1 enhanced oversight and stage 2 escalation. Updates to the report are produced monthly. The reports are shared with the Welsh Government's Chief Pharmaceutical Officer, health board or trust chief executive, and health board or trust chief pharmacist. Reports are shared with other regulators on request.

Audit summary of findings report

The National Lead – Pharmacy Quality Assurance periodically reviews audit data collated in the iQAAPS system to identify common areas of weakness and areas of good practice. An anonymised summary of findings report is published annually.

Glossary

Health Board or Trust Chief Pharmacist

A chief pharmacist, in relation to a pharmacy service, is a pharmacist who:

- plays a significant role (irrespective of whether other individuals also do so) in the making of decisions about how the whole or a substantial part of the activities of the pharmacy service are to be managed or organised, or the actual managing or organising of the whole or a substantial part of those activities;
- has the authority to make decisions that affect the running of the pharmacy service so far as concerns the sale or supply of medicinal products; and
- is responsible for securing that the pharmacy service is carried on safely and effectively.

Manufacturing

Activity that produces medicinal products under an MHRA manufacturer's 'specials' (MS) authorisation, manufacturer/importer authorisation (MIA) or manufacturer/importer authorisation for investigational medicinal products (MIA IMP).

Manufacture includes any process carried out in the course of making a medicinal product but specifically excludes dissolving or dispersing the product in, or diluting or mixing it with, some other substance used as a vehicle for the purposes of administering it.

Reconstitution

Manipulation (dissolving or dispersing the product in, or diluting it or mixing with, some other substance used as a vehicle) to enable the use or administration of a medicinal product in accordance with the marketing authorisation (MA) holder's summary of medicinal product characteristics (SmPC) (or, for investigational medicinal products (IMPs), in line with the sponsor pharmacy approved documentation).

Reconstitution may be performed within either a clinical area or an NHS pharmacy aseptic facility.

Preparation

Aseptic preparation is the reconstitution of an injectable medicine or any other aseptic manipulation when undertaken within NHS aseptic facilities to produce a labelled ready-to-administer presentation of a medicine, in accordance with a prescription provided by a practitioner, for a specific patient.

Assembly

Relates to packaging and labelling only and not to the preparation of medicines from their ingredients/starting materials.

Dispensing

Supply of a finished product to a specific patient, or to the person responsible for its administration, in accordance with a prescription.

Appendix 1: Interactive Quality Assurance of Aseptic Preparation Services (iQAAPS)

iQAAPS is a browser-based, electronic audit tool developed by SPS QA to support external audits of unlicensed NHS pharmacy aseptic units.

iQAAPS incorporates the quality assurance of aseptic preparation services, 5th edition standards by kind permission of the Royal Pharmaceutical Society and NHS Pharmaceutical QA Committee.

iQAAPS is accessible via all modern internet browsers at vision.quiqcloud.com/login, but access is restricted. An account to access the system will be created for all trust chief pharmacists and accountable pharmacists. The accountable pharmacist may request access for additional users by emailing admin@quiqsolutions.com.

Training resources including a system user guide, 'how to' videos and a recording of a training session are available on the iQAAPS system. For further information please contact iQAAPSadmin@liverpoolft.nhs.uk.

Appendix 2: Explanatory notes regarding definitions

As detailed in the Glossary, for the purposes of this guidance, 'preparation' is undertaken in an NHS aseptic facility with pharmacy oversight to produce a labelled ready-to-administer presentation of a medicine. This may or may not be performed in line with the summary of product characteristics (SmPC) for marketed medicines.

'Reconstitution' is the activity of dissolving or dispersing the medicine in, or diluting it or mixing it with, some other substance used as a vehicle for the purposes of administration. Where reconstitution is performed in a clinical area, this should be in line with the SmPC for marketed medicines or as specified in sponsor pharmacy approved documentation (often a specific pharmacy manual) in a clinical trial.

Although reconstitution may be performed in a clinical area or within a pharmacy aseptic unit, it is classed as a preparation activity within the scope of this guidance when it is performed in the latter.

The regulatory explanation for this is as follows:

The definition of 'manufacture' specifically excludes reconstitution activities. Manufacture of medicinal products must occur under a MHRA authorisation in Wales.

The definition of 'assembly' relates to packaging and labelling. It is therefore clear that while the reconstitution of an aseptic product is not an assembly activity, the act of labelling the syringe is considered to be assembly. Assembly activity is a type of 'manufacturing' activity and is routinely performed under a manufacturer's authorisation.

Section 10 of the Medicines Act gives a specific exemption for the need for a manufacturer's authorisation where activities, including preparation and labelling, are performed under the defined conditions laid out in this guidance. Section 10 exemption applies to products that hold a marketing authorisation (licensed medicines) and to unlicensed medicines.

In the context of investigational medicinal products, Regulation 37 of the Medicines for Human Use (Clinical Trials) Regulations 2004 provides an exemption for hospitals and health centres to allow labelling activity to be undertaken by a person operating under the supervision of a pharmacist.

Hence, although reconstitution is neither manufacture nor assembly and is therefore technically outside the scope of both Section 10 and MHRA licensing, the act of labelling the reconstituted products requires the use of the Section 10 exemption or the Regulation 37 exemption for licensed and unlicensed medicines, and IMPs, respectively. Hence this guidance is applicable where reconstitution and the subsequent necessary labelling is undertaken within pharmacy facilities, so we encompass it within the term 'preparation'.

This guidance is therefore also applicable to aseptic services reconstituting ATMPs according to an SmPC or sponsor approved clinical trials documentation within pharmacy aseptic facilities.

Appendix 3: iQAAPS quality indicators

Each site needs to continually monitor a range of quality indicators (QIs), and from these a number have been specified for review in iQAAPS to provide auditors, health board/trust chief pharmacists and accountable pharmacists with oversight of the site's performance. These are liable to evolve over time and the QIs in place at the time of publishing this guidance are as detailed below:

1. Number of operator validations, process validations, End of Session Media Fill (EOSMF) and sterility tests performed.
2. Number of operator validations, process validations, EOSMF and sterility tests failed.
3. Number of grade A samples performed, e.g. settle plates, contact plates, swabs and finger dabs.
4. Number of grade A samples out of specification, e.g. settle plates, contact plates, swabs and finger dabs.
5. Number of errors detected internally, e.g. prior to release.
6. Number of errors detected externally, e.g. post release.
7. Number of items produced.
8. Internal error rate (number of errors detected prior to release, expressed as percentage of number of items produced).
9. External error rate (number of errors detected post release, expressed as percentage of number of items produced).
10. Number of days over locally defined safe working capacity this month.
11. Number of EL audit actions past agreed target date.