AUTOMATED DOSE DISPENSING (ADD)

Guidelines on best practice for the ADD process, and care and safety of patients

Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care

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European Directorate for the Quality of Medicines & HealthCare (EDQM)

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Summary

The purpose of these guidelines is to propose standards and approaches to regulating and providing automated dose dispensing (ADD) services across Europe. The guidelines will assist national authorities to ensure that ADD is provided to a consistently high standard, which maintains the safe supply of medicines to patients. These guidelines are not legally binding but serve as a framework that can be used by ADD providers and the relevant national authorities to review and, where necessary, to introduce ADD services in an ordered and efficient manner. This is particularly important where no or *ad hoc* ADD standards are currently in place and where ADD is provided through different types of sites.

ADD is the dispensing of one or more medicinal products into an ADD container or pouch for a patient to take at a particular date and time. It is performed using a method involving an automated process. ADD is often used to present in a convenient manner the large number of doses that patients receiving polypharmacy and those on complex medication regimes must otherwise organise themselves. ADD is carried out by a variety of providers across Europe; for example, by licensed manufacturers, by companies/sub-contractors and by large- and small-scale hospital and community pharmacies. Regardless of the scale of production, or the setting in which the ADD site operates, the quality management system must ensure that the quality of the medication is maintained throughout the ADD process and that the final product is suitable for use by the patient.

In Europe, legislation on medicinal products focuses on three main domains: manufacturers, distributors (wholesalers) and pharmacies. ADD does not fit entirely into the core activity of any of these domains but elements overlap with each domain. There is no common set of criteria or standards available to guide regulators, providers and patients on how ADD should be carried out and how it should be regulated. As a result, there are significant disparities in the provision and regulation of ADD in different countries, which can create inconsistencies that are avoidable and unsettling for stakeholders.

These guidelines provide policy advice on best practice for the ADD process, and for the care and safety of patients. Part One sets out the standards pertaining to the ADD site and operations. This includes standards for the premises and equipment, training of personnel and the need to have a responsible pharmacist overseeing the management of activities relating to the pharmaceutical process at the ADD site. The suitability of medicines for the ADD process is also addressed. Part Two sets out the standards for patient care activities associated with the ADD process. This includes the need to carry out a suitability assessment for all patients prior to supplying medicines via ADD, along with regular reassessments and reviews of their medication, to ensure that it is enhancing patient care. The advantages of ADD for an individual patient should always outweigh any potential risks and suitability should be decided on a case-by-case basis.

Note

These guidelines should be read in conjunction with any national regulations, standards or guidance that apply in the country where the ADD site is located; for example, any existing requirements for the ADD process, or related activities such as labelling and record-keeping, requirements for disposal of waste medicines and responsibility for patient care activities. If an ADD site is a licensed manufacturer, Good manufacturing practice (GMP) and Good distribution practice (GDP) must also be adhered to and

these standards will supersede some elements of the policy advice provided in these guidelines.

National authorities should consider establishing a legal framework and developing standards or guidance to support the regulation of ADD, particularly where national regulations and the status and operation of ADD sites are not aligned. The proposals in these guidelines form a suitable basis for legislation and standards. GMP, GDP and relevant legislation in place in other European countries should also be considered. It is essential for each country to assess whether, and how, to set standards for the deployment and operation of ADD sites, so that these standards can be monitored and so that national authorities can drive quality improvement in a clear and consistent way.

The ADD guidelines have been developed by a working group of experts from industry, academia, pharmacy and government from across the region of the Council of Europe. They have been discussed and reviewed by stakeholders via a consultation and were subsequently revised and approved by the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care, co-ordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM – Council of Europe).

Preface

Automated Dose Dispensing (ADD) was originally developed as a tool to enable unit dose provision, especially in institutional settings, and as a technical aid to free up resources for patient care [1]. Barcode technology has extended the application and use of ADD systems. ADD is frequently used to supply the needs of patients in certain institutional settings across northern Europe [2-4]. ADD is also supplied to patients in ambulatory care. In the USA various forms of ADD have also been adapted to provide added security in the supply of certain types of medicinal products/preparations and to manage stock more efficiently within many different specialist units in large healthcare establishments [5, 6]. ADD has been associated with reduced distribution costs, fewer errors and better medication adherence. A study in the Netherlands [7] showed improved self-reported medication adherence in older patients receiving their medication via ADD.

However, the widespread uptake of ADD has led to concerns about the maintenance of the integrity of preparations and errors during the processes [1, 8], as well as the impact of ADD on the behaviour and attitudes of carers and patients [9, 10]. Dispensing of original packages using automated methods poses few problems, provided the packaging meets GMP standards. However, the re-packaging and re-labelling of individual units of medicinal products requires the opening of secondary packaging and the removal of primary packaging, which poses risks for quality and integrity, and quality defects and errors have been identified [11, 12]. Little work has been published on the stability of medicinal products re-packed in different types of compliance aids, and criteria for the suitability of their use in ADD have not yet been established and validated [13, 14]. Medication errors and discrepancies have been shown to be decreased under some circumstances [10, 15] and increased in others [16, 17]. However, ADD may also lead to continuation of supply of medicinal products that are no longer needed [17, 18], may influence the frequency with which changes are made to prescriptions and to the regularity with which medication reviews are requested and conducted [19, 20] and may reduce medication knowledge when compared to manually dispensed drugs [21].

Furthermore, the benefits claimed for the use of ADD have not been extensively investigated and the evidence that has been published is neither complete nor substantial [21, 22]. Questions about technical, managerial, regulatory and clinical issues have been addressed to some extent in guidelines and regulations but not at a comprehensive level [23-26], and no overall framework of guidance for policy-making is available [27].

Therefore, the use of ADD should be carefully considered with respect to the types of medicinal products involved, the type of patient and their clinical needs, and the care setting and type of supportive care that is available. Labelling is an integral element of a dispensed medicinal product, as advice on the use of such products for patients and healthcare professionals is essential to ensure safety, quality and efficacy in use. The advantages of ADD for an individual patient should outweigh the disadvantages of losing the original labelling. It is essential to assess whether, and how, to set standards for the deployment and operation of ADD sites, so that these standards can be monitored and can drive quality improvement in a clear and consistent way.

To date, policies and operational procedures have been developed, and evaluations of the technical and health service impact of ADD have been carried out, in countries using ADD. Significant disparities

in the ways in which ADD is deployed and regulated mean that there is no common set of criteria or standards available to guide regulators, providers and patients.

1. Scope

The Council of Europe Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC), supervised by the superior body of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH), decided to develop guidelines on ADD.

The core focus of the CD-P-PH/PC group is pharmaceutical practices and pharmaceutical care. The CD-P-PH/PC decided that the guidelines would address both the care of the patient, including the assessment of a patient's suitability for ADD, and the ADD process, including the issues to be considered when setting up an ADD site and the standards that should be applied to the ADD process.

The guidelines focus on the areas of the ADD process that present the greatest patient risk and the associated care of patients. Following on from a survey review of the different systems in place in different countries in Europe, and a stakeholder consultation which included responses from diverse stakeholders across Europe, the guidelines aim to propose standards and approaches to ADD. While acknowledging that within the European Union (EU)[1] the delivery of health and associated services remains a national competence, the guidelines aim to assist national authorities to ensure that ADD and associated patient care services are provided to a consistently high standard which ensures the safe supply of medicines to patients.

The topics to be addressed in these guidelines were decided by the CD-P-PH/PC. They were drafted by an ADD working party established by the CD-P-PH/PC, were reviewed and updated following a stakeholder consultation and the final guidelines were submitted for approval of the scientific and technical content by the CD-P-PH/PC. Finally, they were submitted for adoption by the CD-P-PH.

Excluded from scope

Manual dose dispensing (MDD) is excluded from the guidelines' scope. The CD-P-PH/PC considers MDD a well-established, routine activity in pharmacies. With the introduction of ADD, which is a relatively newer practice, it has been noted that some countries have seen a reduction in dispensing via MDD and increased ADD. It was also decided to exclude unit dose dispensing (UDD) from the scope of these guidelines. Notwithstanding that MDD and UDD are excluded from the scope of these guidelines, the CD-P-PH/PC acknowledges that much of the content of the guidelines can be adapted to the MDD and/or UDD processes.

Setting and scale

Most of the content of these guidelines is applicable irrespective of the setting of the ADD site or the scale of ADD activity at a site. However, the CD-P-PH/PC acknowledges the challenges of addressing the setting and scale of ADD. Large-scale facilities are often licensed manufacturers and in some countries their activities are addressed by specific legislation; in these situations GMP, GDP and legislative requirements will supersede certain elements of the guidelines. It is recommended that the content of these guidelines is considered when reviewing or updating national ADD legislation or standards.

The CD-P-PH/PC recommends that small- and medium-scale facilities, often pharmacies or similar, adhere to all elements of the guidelines, but acknowledge that this will be decided on a national basis and that alternative practices may be implemented to achieve the same standards. Irrespective of scale, the care of the patient and the standards of the ADD process and medications must be maintained.

2. Definitions

Automated dose dispensing: automated dose dispensing is the dispensing of one or more different medicinal products into an ADD container or pouch. It is performed using a method involving an automated process. One container/pouch contains either one, some or all units of medicine an individual patient needs to take at a particular date and time. The medicinal products may be removed from their (original) primary containers before they are dispensed via ADD; if the primary packaging container is a blister, this process is called 'deblistering'. Alternatively, medicinal products may be dispensed into the ADD containers/pouches in their primary packaging.
Unit dose dispensing (excluded from the scope of these guidelines): a method by which individual doses of medicinal products are repackaged into individually labelled containers/pouches, e.g. in a hos-

1. The Council of Europe includes both EU and other European countries.

pital setting. This method does not involve individual patient dispensing.

Manual dose dispensing (excluded from the scope of these guidelines): where the dispensing of medicinal products into individualised patient medication doses occurs manually (without the use of automated systems or using automated systems for limited elements of the process).

The World Health Organization (WHO) defines the manufacturer, manufacture and production as follows:

Manufacturer: a company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

Manufacture: all operations of purchase of materials and products, production, quality control, release, storage and distribution of medicinal products, and the related controls.

Production: all operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product [28].

Good manufacturing practice (GMP): the principles of Good manufacturing practice are stated in Directive 2003/94/EC. Within the European Union, GMP is defined as:

'"Good manufacturing practice" means the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use' [29].

WHO defines GMP as: 'Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimise the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. The main risks are: unexpected contamination of products, causing damage to health or even death; incorrect labels on containers, which could mean that patients receive the wrong medicine; insufficient or too much active ingredient, resulting in ineffective treatment or adverse effects. GMP covers all aspects of production from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process – every time a product is made' [32].

Good distribution practice (GDP): the principles of Good distribution practice are stated in EU guidelines 2013/C 343/01 [30] implementing Directive 2001/83/EC [31]. The European Medicines Agency (EMA) describes the concept of GDP as:

'Good distribution practice (GDP) ensures that the level of quality determined by GMP is maintained throughout the distribution network, so that authorised medicinal products are distributed to retail pharmacists and others selling medicinal products to the general public without any alteration of their properties' [33].

3. Setting and legal framework

A. Background

Medicinal products legislation in Europe focuses on three main domains: manufacturers, distributors (wholesalers) and pharmacies. ADD does not fit entirely into the core activity of any of these domains but elements overlap with each domain. Applying detailed patient information to a medicinal product and breaking units from manufacturers' original packaging typically occurs, in many countries, within community and hospital pharmacy settings. In other countries, pharmacies are required to supply original medicinal product packages to patients. The packaging/repackaging of medicinal products traditionally occurs within a pharmaceutical company, carried out by a pharmaceutical (licensed) manufacturer operating in accordance with GMP. GDP is also applicable where external supply occurs for distribution of medicinal products.

B. Legal framework

National authorities should consider establishing a legal framework for ADD, which sets out the minimum standards that an ADD site must adhere to. This would support the regulation of ADD and is particularly important where national regulations and the status and operation of ADD sites are not aligned. It is recommended that national authorities establish guidelines or standards to facilitate compliance with relevant legislation. The proposals in these guidelines form a suitable basis for legislation and standards. GMP, GDP and relevant legislation in place in other European countries should also be considered.

C. Setting

In different countries in Europe, ADD practices occur in different settings and in some countries these practices occur in more than one setting. These settings are:

1. Community or hospital pharmacies supplying medicinal products to their own patients. In this circumstance the entire process, i.e. review of patients' medication, dispensing and supply of medication and any associated counselling, occurs at a single site.
2. Pharmacies supplying medicinal products to other pharmacies or healthcare institutions. In this circumstance dispensing is carried out by the ADD pharmacy, and patient care can be the responsibility of the dispensing pharmacy and/or the ADD site depending on the country of operation and legislation and frameworks in place.
3. Pharmaceutical manufacturers or other companies (sub-contractors) supplying medicinal products to pharmacies or directly to patients on behalf of the pharmacies. A company/sub-contractor[2] is an ADD site which operates to ADD standards and, if applicable, complies with GMP, GDP and national ADD regulations. In this circumstance, patient care is usually the responsibility of the pharmacy.

At present, depending on the legal framework of the country:

- An ADD site may be licensed as a manufacturer, pharmacy (direct dispensing or preparing) or as a company/sub-contractor operating in accordance with defined standards.
- The scale of the operation may be the deciding factor for whether an ADD site can operate as a manufacturer or pharmacy.
- In different European countries:
  - only pharmacies are permitted to prepare and supply ADD medicines and they:
    - may be permitted to supply medicines to other pharmacies. In some countries, these sites are permitted to be separate legal entities and in others they must be one legal entity.
    - may not be permitted to supply medicines to other pharmacies, i.e. may only supply medicines directly to patients (one site for all activities).
  - only licensed manufacturers and/or companies/sub-contractors are permitted to prepare ADD medicines and the associated care of patients is usually provided by a pharmacy.
  - manufacturers and/or companies/sub-contractors and pharmacies are permitted to prepare and supply ADD medicines.

Variations on the above set-ups and site titles are in place in different countries.

D. Licensing

Decisions on the requirements for authorising/licensing an ADD site should be taken at a national level and should take account of the licensing system and legislation in place in the relevant country and the content of these guidelines.

ADD should only be carried out at a licensed site, i.e. a licensed manufacturer, pharmacy or company/sub-contractor. Large-scale ADD should be carried out by a licensed manufacturer or company/sub-contractor operating in accordance with GMP and GDP. Depending on the national legislation in place, in certain countries an ADD site may not require a manufacturing authorisation if it is a company/sub-contractor or pharmacy. Notwithstanding the different definitions of a pharmacy and ADD site in legislation and diversity in pharmacy practice across Europe, in general, to be classified as a pharmacy, a site should only be supplying ADD medicines to patients of the pharmacy, and other pharmacy activities should occur at the site, e.g. the supply of medicines directly to patients and carers and associated patient care activities. It is acknowledged that some countries permit other types of pharmacy ADD sites.[3]

The distinction between a manufacturer, a pharmacy and, if applicable, a company/sub-contractor should be decided on a national basis, depending on the scale, setting and other operations occurring at the ADD site. National authorities should utilise the information in these guidelines and any other relevant information to determine the scale threshold at which an ADD site is required to be licensed as a manufacturer or at which GMP and GDP requirements apply.

Due to the additional requirements for ADD, for example specific training requirements and labelling of the pouch/container with dosage instructions for individual patients, national authorities should consider providing a specific authorisation/licence for ADD activities that occur at manufacturers' sites or pharmacies. Authorities could suspend or withdraw the licence depending on compliance with their conditions. Inspection prior to licensing, re-inspection at

2. Where these types of sites are permitted in a country, a variety of terms are used to describe them. The term company/sub-contractor has been used in these guidelines but it is noted that other terms may be used in different European countries.

3. Guidelines: Section 3C.

relevant intervals and the maintenance of a national register of ADD sites is recommended.

Where a site, for example a pharmacy, is commencing ADD activities and there is no requirement for an additional licence, they should as a minimum be required to notify the relevant authorities of their intentions in advance of commencing ADD activities and to provide regular updates or reports on their ADD activities.

E. Standards

If an ADD site is a licensed manufacturer, GMP and, if applicable, GDP must be adhered to. If the site is not a licensed manufacturer but is operating on an industrial scale or involved in external supply it is recommended that national authorities require the site to be licensed as a manufacturer or that legislation is implemented to ensure adherence to GMP and GDP. The additional standards in these guidelines should also be adhered to.

If an ADD site is operating on a smaller scale and fulfils the relevant national requirements, it may operate as a pharmacy and these guidelines and the relevant principles of GMP and GDP required to ensure that the quality of the ADD medication is maintained should be applied.

F. Product liability and ADD suitability information from manufacturers

A manufacturer's product liability[4] often does not extend to the use of their medicinal products in ADD unless relevant testing has occurred and a product's suitability for ADD is included in its marketing authorisation data. It is recommended that national/European authorities encourage marketing authorisation holders to include relevant stability data, and data regarding the suitability of a medicinal product for use in ADD, in the product's marketing authorisation data. These data should indicate the length of time the medicinal product may be removed from its original packaging and exposed to defined environmental conditions without quality impairment, and advise of any supplementary measures required to protect the removed medicinal product from deterioration, for example for hygroscopic or light-sensitive medicinal products. If deemed necessary, additional testing should take place to check interactions with common packaging materials, other medicinal products which are dispensed together and ADD equipment. Details of packaging materials and data on their suitability for ADD should be provided by packaging material manufacturers.

Where sufficient information on the suitability of a medicinal product for ADD is not included in the marketing authorisation, the liability for its use in ADD (including storage for ADD) does not sit with the manufacturer unless the starting medicinal product is defective. The manufacturers' original packaging has been approved as part of a medicinal product's marketing authorisation and when a medicinal product is repacked into an ADD, it is being used outside of this authorisation. In this context, consideration should be given to the professional issues, including potential legal liability issues, that may arise in providing this service.

4. At EU level, the Product Liability Directive applies to ADD if the starting medicinal product used in ADD is defective: Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products (OJ L 210, 7.8.1985, p. 29–33).

Part One: Automated dose dispensing: standards pertaining to the ADD site and operations

The packaging/repackaging of medicinal products traditionally occurs at a pharmaceutical (licensed) manufacturer's site operating in accordance with GMP. GDP is also applicable where the external distribution of medicinal products occurs. In different countries in Europe, ADD practices currently occur in different settings, including licensed manufacturers, companies/sub-contractors and pharmacies in ambulatory and hospital settings.

Regardless of the scale of production or the setting in which the ADD site operates, it must ensure that the quality of the medication dispensed by ADD is maintained and meets the standards that can be achieved by adhering to the content of these guidelines, the principles of GMP, GDP and, where applicable, relevant national legislation and standards. If an ADD site is a licensed manufacturer, GMP and, if applicable, GDP must be adhered to. If an ADD site is a manufacturer, pharmacy or company/sub-contractor any applicable legislation must also be adhered to.

4. Personnel and training

A. General

The responsible pharmacist at an ADD site establishes and maintains a system of quality assurance and ensures that the ADD facility operates according to appropriate standards. Successful operation of this system is dependent on qualified and trained personnel carrying out the tasks for which the ADD site is responsible. The roles, duties, responsibilities and job descriptions of staff at an ADD site should be mapped in an organisational chart or similar. Responsibilities should be clearly understood by individual staff members and documented. All personnel should be aware of relevant national legislation or standards, the principles of these ADD guidelines and relevant GMP and GDP, and should receive initial and continuing training relevant to their individual role.

The ADD site should have an appropriate number of staff with the necessary qualifications and practical experience to ensure that ADD is carried out effectively. Appropriate responsibilities should be allocated to these staff members. Managing or supervisory staff should have specific ADD-related job duties included in their job descriptions and have appropriate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of an appropriate qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those staff members involved in operation processes, quality control and quality assurance.

B. Responsible pharmacist

Responsibility for the management of activities at an ADD site must align with national legislation and frameworks. Every ADD site should have a designated pharmacist who is responsible for the management of activities relating to the pharmaceutical process at the ADD site. The nominated pharmacist must be a licensed/registered pharmacist in the country in which the ADD site is located.

A responsible pharmacist's training should align with national and/or EU training requirements and national training frameworks, as applicable. As a minimum, it is recommended that the responsible

pharmacist has sufficient knowledge of ADD standards, is available at the ADD site during core activities involved in dose dispensing, and supervises critical steps and takes critical decisions personally. The responsible pharmacist should be notified to the relevant authority. A deputy should be designated and available at the ADD site in the absence of the responsible pharmacist.

The responsible pharmacist should ensure that medication is dose dispensed in accordance with applicable ADD standards and the initial order and/or prescription. He/she can delegate certain tasks, such as checking finished ADD doses, to another pharmacist; however, critical policy and quality decisions should be taken by the responsible pharmacist personally.

The responsible pharmacist should approve and ensure the implementation of all processes, policies, procedures and instructions that are part of the quality system, including:

- compliance with all relevant legislation and standards/guidelines, including medicines legislation, any specific ADD legislation and other relevant legislation, e.g. data protection legislation;
- the implementation of processes relating to the dispensing process;
- the selection of medicinal products suitable for ADD;
- monitoring and control of the dispensing environment;
- setting and monitoring of storage conditions and storage times for all stages of the process, i.e. starting materials before deblistering, intermediate doses and dispensed ADD medication;
- hygiene and cleaning instructions;
- specifications and quality control procedures for all materials, including packaging materials, medicinal products before dispensing, intermediate doses and dispensed ADD medication;
- master validation of ADD orders/prescriptions (for suitability to be dose dispensed) and of production and control equipment and related software;
- contracts with external parties, clearly setting out the responsibilities of each party;
- authorisations to personnel, i.e. assignment of duties in line with expertise, qualifications and further education/training.

Furthermore, the responsible pharmacist should:

- ensure the correct implementation of ADD orders/prescriptions and, where this occurs automatically, approve the validation of the process;
- ensure that medicinal products for the ADD prescription/order are received, deblistered, dose dispensed, checked, controlled and released/supplied according to the appropriate standards and documentation;
- ensure that ADD prescriptions/orders are reviewed as appropriate for the patient and that the patient/carer receives all necessary counselling on the use and storage of the ADD medication (this may be delegated to a dispensing pharmacy if this is in accordance with local or national policy and/or is clearly stated in contracts);
- ensure that all ADD medication is checked and compliance of the dispensed medication with the prescription/order is confirmed by an authorised person;
- ensure that all necessary checks occur and records are authorised by the responsible pharmacist, deputy pharmacist or other authorised pharmacist before ADD medication is released or supplied;
- ensure premises and equipment are adequately maintained;
- ensure that the appropriate external and internal validations occur, including validation of all machines and software systems;
- ensure a sufficient number of pharmacists and other appropriately qualified and trained personnel are available for the type and volume of activity occurring at the ADD site;
- ensure that the required initial and continuing training of personnel is carried out and adapted according to need.

Depending on the scale of operations, the responsible pharmacist may delegate various tasks to other authorised personnel. However, only duties should be permitted to be delegated – not responsibilities.

C. Training

The ADD site should provide training for all personnel whose activities could affect the ADD process or quality of the product. Adequate training should be in place and should reflect applicable legislation, standards and the ADD process. Training should focus on key issues, including error minimisation and how to maintain medicinal product quality and ultimately patient safety. It should be standardised for ADD sites as far as possible; however, the

content and extent of training may vary depending on the scale and setting of the ADD site.

Besides introductory training on the background, theory and practice of ADD and the pharmaceutical quality assurance system, newly recruited personnel should receive training appropriate to the duties assigned to them. All personnel should be trained in the ADD site's policies and procedures as relevant for their role, and training content should be approved in accordance with internal procedures.

The concepts of quality assurance, critical control points and all measures for their implementation should be comprehensively addressed during the training sessions. Personnel should be retrained at regular, defined intervals with additional training provided when deemed necessary, e.g. when a process changes or new training needs are identified. The responsible pharmacist should also keep his/her knowledge of ADD up-to-date through regular training.

Training programmes should be available and training should be provided by persons with sufficient qualifications and knowledge in the relevant area. Personnel working in areas where contamination should be avoided, e.g. clean areas or areas where medicinal products with highly active, infectious or sensitising substances are handled should receive specific training. Training should be provided for each individual assigned task. Methods such as staff passing a qualification test and being provided with written authorisation prior to commencing an activity are recommended. Dated training records should be maintained. The practical effectiveness of training should be periodically assessed and staff should be encouraged to obtain additional relevant qualifications.

Untrained personnel should not be permitted entry into the operational areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and wearing appropriate protective clothing.

D. Elements of introductory ADD training for different staff

ADD sites should ensure that adequate training and support are in place for ADD pharmacists and other staff according to the appropriate competence.

Examples of topics that should be covered by staff training for different categories of staff include:

Pharmacist(s): quality systems, risk management, validation, stability, medicine suitability, GMP, GDP, ADD standards and any other area the responsible pharmacist identifies as a gap in knowledge. Pharmacists should engage in continuing professional development in ADD appropriate to their role. They should receive training in the ADD process and the patient care elements of ADD to ensure their knowledge is maintained at the highest level.

Pharmacy technician(s): specific training on critical control points, quarantine, corrective and preventative actions, validation, documentation systems, the 'Plan Do Check Act (PDCA) principle' and any area in which they operate where a gap in their knowledge is identified.

Other staff: the purpose of medicinal products and ADD, hygiene, equipment, procedures, instructions, records, labelling, principles such as one direction flow and critical square area (only one medicine or label in a certain space), double-checking and any other area specific to a staff member's role.

5. Premises and equipment

A. General

Premises and equipment should be located, designed, constructed, adapted and maintained to suit the operations to be carried out and the scale of ADD. Their layout and design should minimise the risk of errors and permit effective cleaning and maintenance, in order to avoid cross-contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products. They should be designed in such a way as to prevent adverse outside influences, especially contamination of premises, equipment, medicinal products or packaging. Every site should establish a hygiene programme, which should be adapted to the activities to be carried out in the facility and based on current best practice.

B. Premises

Premises should be situated in an environment which, when considered together with measures to protect operations, presents minimal risk of causing contamination of materials or products. All fixtures and fittings should be suitable for the intended purpose, and be of sound construction and compliant with all health, safety and environmental requirements. The finish of all fixtures and fittings should be professional, complete and well maintained. All walls, floors, ceilings, plaster and paintwork should be safe, non-shedding, easily cleanable, and clean. All surfaces that come into contact with medicinal products at any stage of the process, such as primary packaging materials, canisters, trays and interior surfaces of machines and equipment, should

be smooth, free from cracks and open joints, should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to written procedures. Premises should be designed and equipped so as to afford maximum protection against the entry of pests, i.e. insects or other animals.

Light fittings, information technology cables, ventilation points and other services should be designed and situated to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the operating areas. In cases where dust is generated, specific provisions should be in place to avoid cross-contamination and facilitate cleaning. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, the quality of the medicinal products during packaging and storage, or affect the accurate functioning of equipment.

Layout of the premises should ensure the ability to adequately supervise all activities at the ADD site. All steps of the ADD process should occur in areas connected in a logical order, corresponding to the sequence of the operations, thereby facilitating one direction workflow from the start to the end of the process.

ADD should not be carried out in the same area as other activities. Designated rooms or areas should be provided for each stage of the ADD process, i.e. deblistering or any other removal of medicinal products from their containers, operating the ADD machine (filling and dose dispensing), dose checking, and storage, etc. Whether dedicated rooms or areas are necessary should be decided based on an assessment of the scale, type of medication, and operation of the ADD site. All areas used in the ADD process should enable orderly and logical positioning of equipment and materials so as to reduce the risk of mix-ups between different medicinal products, unit doses or labels, avoid cross-contamination and reduce the risk of omission or incorrect application of any of the deblistering, dose dispensing or control steps.

Unauthorised persons should not be permitted to access the ADD site. In particular, storage, deblistering, dose dispensing control and dispatch areas should not be accessed by personnel who do not work in them. Every person entering the dose dispensing areas should wear protective garments appropriate to the operations being carried out, for example clothes, gloves, mouth masks and head covers.

C. Deblistering and dispensing area

Deblistering, dispensing and checking areas should be separated and effectively ventilated, with air control facilities (including air filtration) appropriate to the products handled, the operations undertaken, the scale of the operation and the external environment. During the deblistering and intermediate dispensing process, i.e. dispensing into storage containers, canisters and trays for subsequent ADD, preventive measures should be applied to avoid cross-contamination (including through the dust of medicinal products) and to facilitate cleaning. Areas should be well lit, particularly where final visual checks are carried out. In-process controls may be carried out within the dispensing area, for example on sealing or printing, provided they do not increase the risk of errors in the ADD process.

D. Storage areas

Storage areas should be of sufficient capacity to allow orderly and segregated storage of the various categories of materials and products: starting medicinal products, packaging materials, deblistered medicinal products, medicines in quarantine, released, rejected or returned medication and ADD medication recalled after supply. Storage areas should be clean and dry and maintained within acceptable temperature limits. Medicinal products should not be stored on floors and shelving should be non-shedding.

Reception and dispatch areas should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned, where necessary, before storage. Quarantine is usually ensured through physical quarantine. Any system replacing physical quarantine should provide equivalent security. Where quarantine status is ensured by labelling or storage in separate areas, the status should be clearly marked.

E. Ancillary areas

Rest and refreshment rooms should be separate from other areas. Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not be directly accessible from production or storage areas. Maintenance workshops should, as far as possible, be separated from operating areas.

Whenever parts and tools are stored in the production area, they should be kept in rooms, lockers or other segregated areas reserved for that use.

F. Equipment

Appropriate equipment should be in place for the safe and efficient operation of the ADD site. The equipment and quantities required will be dependent on the scale of the operation and usually include deblistering apparatus, intermediate storage containers, medicine trays, opaque storage containers, ADD machine(s), checking machines (medium and larger scale operations), protective equipment, cleaning equipment, information technology equipment and other equipment deemed necessary. Deblistering, dispensing and control equipment should be designed, located, validated and maintained to suit its intended purpose. Repair and maintenance operations should not present any hazard to the quality of the products.

Equipment should be designed so that it can be easily and thoroughly cleaned. This applies to all ADD equipment and all contact surfaces, including deblistering equipment, ADD machines, cassettes, canisters, other containers and the repair station. Equipment should be cleaned according to written, validated procedures, and stored in a clean, dry condition. Washing and cleaning equipment should not be a source of contamination, either because of design or use.

Equipment should be installed in such a way as to prevent any risk of error or contamination. Equipment should not present any hazard to medicinal products. The parts of the production equipment that come into contact with medicinal products cannot be reactive, additive or absorptive to such an extent that they will affect the quality of the product and thus present a hazard.

Balances and measuring equipment of an appropriate range and precision should be available, as required, for deblistering, dispensing and control operations. Measuring, weighing, dispensing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

Defective equipment should, if possible, be removed from deblistering, dispensing and control areas, or as a minimum be clearly labelled as defective and put in quarantine.

6. Prescriptions

A prescription, or other valid authority to supply medicinal products via ADD, written by an authenticated doctor or healthcare professional with the authority to prescribe, must be available at the ADD site prior to dispensing. In some countries, where two sites are involved in the ADD process, the prescription is transferred into a medication order prior to dispensing and this order is transferred to the ADD site. All ADD prescriptions/orders received at an ADD site are checked/validated prior to commencing the ADD process. Where an order is used to initiate the ADD process, the ADD site should have the ability to access the original prescription or a copy/scan of the prescription if required. Transfer of prescriptions and orders must be in line with any applicable legislation.

Prescriptions and any ADD supply orders are required to meet the requirements of applicable legislation and any pharmaceutical and clinical requirements. Particular attention should be paid to the period of validity, any specific requirements relating to the medicinal products prescribed (e.g. controlled drugs) and permissions related to generic substitution. Non-prescription medicinal products, vitamins and food supplements do not require a prescription; however, if they are to be included in ADD, they should be included in the prescription or order for the ADD medication. A prescription which is valid for repeat dispensing should be returned to the patient/carer in line with national legislation and practices.

Double-checking of the prescription/order details against computerised systems, the medicinal products and ADD patient labels should occur at relevant stages throughout the process, including as a minimum when prescription details are entered into the ADD site's computerised system and at the final dispensing stage where medicines are released/dispensed from the ADD site (to the patient or another site/pharmacy). Validated checking systems, combined with regular sample review may be permitted if in line with national regulations and standards.

Electronic prescribing and order transmission is used for ADD in some countries. The security and protection of personal data transferred using an electronic system must be maintained and any applicable legislation, including data protection or transfer legislation and standards adhered to. Data scrambling and decoding of password-protected details or another appropriate method may be used to ensure the security and confidentiality of personal information.

7. Medicinal products: traceability, suitability and stability

A. Traceability of medicinal products

An ADD site must source its medicinal products from approved suppliers in accordance with national regulations, i.e. authorised wholesalers or manufacturers. This is necessary to ensure the security and integrity of the supply chain and to ensure the quality, safety and efficacy of the medicinal product sourced. Distributors should supply the ADD site with consignment documents for the last step of the distribution chain.

Every ADD site should operate a comprehensive, auditable system for the sourcing, receipt and distribution of medicinal products. The authenticity of suppliers should be verified prior to their use and a list of authorised suppliers of the medicinal products should be maintained and routinely reviewed and verified as part of the quality management procedures. Documentation should be available which permits clear identification of the supplier of each consignment of medicinal products received by the ADD site and of the medicinal products therein, for example supplier invoices. Such documentation should be retained. Records should be adequately detailed and any additional necessary information should be available from the suppliers.

All medicinal products should be delivered to the ADD site in accordance with GDP. They should be checked for authenticity on receipt, in accordance with a written procedure. They must have a marketing authorisation issued by a competent authority. Under the Falsified Medicines Directive (2011/62/EU)[34] all medicinal products with a barcode safety feature will have to be decommissioned (authenticated/'checked out') at the ADD site. For non-EU Council of Europe (CoE) member states it is recommended that the spirit of the directive is followed to avoid the infiltration of falsified medicinal products in the course of ADD. Medicinal products should also be checked to ensure no damage occurred during the delivery process. Appropriate follow-up action should be taken in line with the directive (or its spirit for non-EU countries) if it is suspected that an ADD site has been offered or received falsified, defective or inappropriately authorised medicinal products. This action should include contacting the competent authority, segregating the product from legitimate stock and storing it in a designated quarantine area.

Throughout the ADD process, primary and secondary packaging materials and patient information leaflets should be handled and disposed of in a manner that prevents misuse, i.e. prevents access to materials which could potentially be used for falsifying (counterfeiting) medicinal products.

The ADD site should maintain adequate records to ensure the full traceability of every individual dose dispensed medicinal product, from receipt of the medicine through deblistering, intermediate storage and ADD dispensing, to the distribution of the finished dose dispensed medication to the patient. Relevant information, including the patient's name and contact information, the product name, strength, batch number, expiry date, product authorisation number etc. should be recorded for all medicinal products. It is important that the batch number of the product is accurately recorded to facilitate the efficient recall of a product. The record should be unalterable and easily searched and retrieved, in order to accurately identify patients who have been supplied with a particular batch of a medicinal product where necessary. Adequate records should also be maintained for packaging materials.

B. Suitability of medicinal products and packaging materials for ADD

Medicinal products

In general, only solid oral dosage forms are suitable for ADD. Non-oral dosage forms, e.g. pessaries or suppositories, and non-solid oral dosage forms, e.g. dissolvable sachets, should be excluded from ADD.

It is recommended that authorities encourage the inclusion of relevant data regarding the suitability of a solid oral dose medicinal product for use in ADD systems in the product's marketing authorisation data. If a medicinal product is deemed unsuitable for ADD, information should be provided by the marketing authorisation holder outlining why it is not suitable, based on stability or other relevant data.

National authorities should provide adequate information and support to enable ADD sites to make informed decisions on the suitability of medicinal products for ADD. This could be achieved by developing national standards, providing access to relevant ADD medication suitability information from other countries or by other appropriate methods.

A medicinal product which does not have information on its suitability for ADD included in its marketing authorisation should only be removed from the manufacturer's original packaging (e.g. deblistered) for use in ADD if sufficient, accurate data are available to make a suitability assessment and if it has been approved for this purpose by the responsible pharmacist. In general, solid oral dosage forms with good physical, chemical and pharmaceutical

stability may be used in ADD, provided that they are stable outside the original primary packaging at room temperature during a period covering deblistering, storage, dispensing, supply and use.

Release by the responsible pharmacist should be based on a documented and suitably verified risk assessment of the medicine's suitability taking into consideration, if available:

- data provided by the marketing authorisation holder, either in the medicinal product's Summary of Product Characteristics (SmPC) or other available data;
- data or lists provided by a national or local competent authority.

If the above information is not available, the decision to include a medicinal product in ADD should be based on a risk assessment performed by the ADD site. This risk assessment should assess the potential risks to the quality of the medicinal products and take into consideration:

- data from recognised international sources, e.g. from competent authorities in another country;
- data from literature or reference books, e.g. European Pharmacopoeia (Ph. Eur.), British Pharmacopoeia (BP), US Pharmacopoeia (USP) or other reputable sources.

A more extensive risk assessment is recommended prior to the inclusion of a medicine with little available stability data and/or a new medicinal product in an ADD system. The crucial criteria for assessing the suitability of a medicine for ADD include:

- physical, chemical and pharmaceutical stability of the medicine from deblistering, through intermediate storage, dispensing/repackaging and distribution to the patient;
- toxicity of the medicine and potential for cross-contamination;
- potential for physical and chemical interaction with other medicinal products.

Each medicinal product should be assessed with regard to:

- chemical and physical properties of the active ingredients and/or the excipients;
- formulation/dosage form;
- containers and closures;
- proposed storage conditions;
- stability influenced by the use or absence of antioxidants or preservatives.

Medicinal products with little available stability data or medicinal products never previously used in ADD should be assessed with particular care.

In addition, the following decisions should be taken and documented by the responsible pharmacist:

- If medicinal products which have potential for misuse or abuse, e.g. controlled drugs or psychotropic medicines, can be included. These medicinal products should only be included if permitted by national regulations and standards and if adequate processes to prevent their misuse/abuse are in place.
- If vitamins, minerals and other food supplements can be included in ADD. Where these products are available as authorised medicinal products, these should be used in preference to any unauthorised version. Caution should be exercised with unauthorised supplements.
- If split units of medicinal products can be dispensed. Only tablets scored for dividing, or tablets with appropriate information from the marketing authorisation holder on their suitability for splitting, should be split for ADD. In principle, split tablets should only be used if no authorised medicinal product or other alternative is available.
- If a medicine is suitable for inclusion in a multidose container or should be packaged alone. Medicines that may be considered unsuitable include unauthorised products such as supplements and split tablets, unstable medicines, controlled drugs and medicines that should not be handled.
- If local or national regulations apply, these must be considered prior to making decisions.

Certain medicinal products should be excluded from ADD unless the potential risk connected with their use can be overcome by special precautionary measures:

- Physically unstable medicinal products: including tablets that break or crumble easily, effervescent or dispersible tablets, sublingual or buccal tablets and certain hygroscopic and thermo- or light-sensitive tablets (depending on the stability data available). Large tablets cannot be included in some systems.
- Medicinal products with a high risk for cross-contamination: uncoated or poorly coated tablets and potentially other formulations containing highly active, highly toxic or highly sensitising tablets, such as certain hormones, cytotoxic and/or embryotoxic medicinal products or antibiotics, e.g. penicillins and cephalosporins. Capsule and coated tablet formulations reduce the risk of cross-contamination.

- Medicinal products that may be unsuitable due to patient care issues, e.g. medicinal products dispensed for intake 'as required' or according to an irregular schedule.

Precautionary measures which should be considered prior to dispensing a medicine via ADD include:

- Retaining the medicinal product in its primary packaging (not deblistered): e.g. for tablets with high friability: dispersible, effervescent, sublingual or buccal tablets.
- Inserting a desiccant in the ADD container/canister for intermediate storage: hygroscopic medicinal products.
- Using dedicated equipment: highly active, highly toxic or highly sensitising tablets.
- Inserting the medicinal products into the ADD machine using a manual tray.
- Removing the primary packaging just before adding the medicine to the manual section of the ADD machine: e.g. certain soft gelatin capsules.
- Packing the medicinal product alone, i.e. in a dedicated pouch/container.

All suitability assessments, precautionary measures, special instructions and decisions should be recorded in writing in adequate detail, approved by the responsible pharmacist and made available to all relevant personnel in a suitable form. Self-inspections or audits should be carried out and documented to ensure that the suitability assessments, decisions and precautionary measures have the intended effect.

Packaging materials

Consideration of the quality of packaging material is an integral aspect of the assessment of the appropriate storage duration for medicinal products. All packaging materials used in ADD should be assessed for suitability and released for use in accordance with the site's packaging materials specifications. This is particularly important for packaging materials that come into direct contact with medicinal products. The assessment should consider and document the suitability of the material for packaging medicinal products, including the material's certification for pharmaceutical use and whether it provides appropriate protection against the environment, humidity and oxygen, and where necessary, against light. The specifications for the packaging material used, including all critical parameters such as moisture and oxygen permeability, the number, quality and thickness of layers of material and, where relevant, information on light protection, should be available at the ADD site. The finished dispensed doses should be packed in packaging materials which provide sufficient protection during storage and transport and allow easy removal and opening by the patient or carer. For longer periods of storage, it is important that the quality of the packaging material is similar to the original packaging of the authorised medicinal product(s). The purchase, handling and control of packaging materials is carried out according to the ADD site's specifications. Roll-feed labels are normally preferable to cut labels to avoid mix-ups.

C. Stability of medicinal products

National authorities are advised to encourage marketing authorisation holders to include information on a medicinal product's stability after it is removed from its primary packaging in the SmPC.

For each medicine, the ADD site's responsible pharmacist defines the storage conditions and the maximum storage time for the deblistered medicines and the ADD dispensed medicines according to a defined procedure. This procedure assesses the impact of removing the medicine from its primary packaging on the quality of the medicinal product. Specifications for storage conditions should ensure the quality and stability of a medicinal product are not impaired after removal from the original primary packaging.

Stability data included in a medicinal product's SmPC and/or national standards on the stability of medicinal products take precedence over stability information from other sources. If there is no stability information in the SmPC, marketing authorisation holders should provide any available stability information relevant to ADD to ADD sites.

In the absence of appropriate stability data, medicinal products should be removed from their primary packaging for the shortest time possible. Particular care is required to ensure that these medicinal products are stored under controlled conditions in accordance with the relevant specifications, for example temperature, humidity and/or light protection. Other options, such as ADD of medicinal products in their primary packaging, should also be considered. Any stability information available on split tablets and supplements should be considered prior to their inclusion in ADD.

ADD dispensing and supply to patients should occur regularly and doses should not routinely be supplied to patients more than one month prior to their date of use (the default expiry date of the medicine once removed from its primary packaging). The

frequency of supply should be agreed with the prescriber, be in line with national legislation and reflect patient need and the characteristics of the medicinal products involved.

The maximum storage time for deblistered and ADD dispensed medicinal products should be set based on a documented quality risk assessment considering:

- local and national requirements;
- information in the medicinal product's SmPC or other information from the manufacturer;
- other stability data from reputable sources, where available or required;
- characteristics of the medicinal product;
- packaging materials;
- storage conditions;
- potential for interactions with other medicinal products, supplements or packaging materials;
- the time between dispensing and use of the medication by the patient;
- any other relevant information.

Each medicine, including medicinal products stored after deblistering in containers for intermediate storage, in canisters in ADD machines and finished ADD dispensed doses, should bear an expiry date for use, based on a justified decrease of the expiry date of the original medicinal product. In the absence of specific national or local requirements, stability data from manufacturers, requirements in monographs or other reputable stability data, it should be assumed that the expiration of the ADD dispensed medication is significantly reduced. Intermediate deblistered medicines stored under controlled conditions at the ADD site should not be stored for longer than two months,[5] unless an appropriate assessment demonstrates that stability is definitively maintained beyond this time. No medicine should be stored for longer than six months from the date of removal from the primary packaging to the date of use, and the expiry date assigned must not exceed the original expiry date. Whatever expiry date is assigned, there should be documented proof supporting the decision. Suitable measures must be taken to ensure that expired medicinal products are not used in ADD. It is recommended that medicinal products are not used for ADD within the month prior to the expiry date of the product.

5. Or three months from the date of deblistering to the date of use, on the basis that ADD medicines are not supplied to patients more than one month prior to their date of use.

D. Use of multidose ADD pouches/containers

National authorities may provide recommendations on medicinal products that should be packed individually and on the maximum number of medicinal products that should be packed in one container. They may also recommend that certain types of medicinal products, e.g. uncoated tablets containing highly active, highly toxic or highly sensitising medicinal products, controlled drugs and unstable tablets, should not be packed with other medicinal products.

The ADD site should consider the potential impact of packing a number of different medicinal products together in one container or pouch on the stability of these products. The responsible pharmacist should define the maximum length of time medicinal products can be packed together and which medicinal products cannot be packed together. Issues to be considered include cross-contamination, chemical and physical interactions, whether compatibility testing is necessary and how the medicinal products are distinguished during the checking process (e.g. by colour, shape, size, inscription, markings, weight and/or by using photographs or associated data). If medicinal products are known to be incompatible they should not be packed together. Other factors to be considered include the size of the medicinal products relative to the space available and the amount of information that can be safely printed on the pouch, container or label.

Examples of medicinal products which may, following review, be considered suitable for packing in multidose pouches include:

- oral solid dosage forms in approved bottles/multidose containers as the primary packaging;
- capsules and coated tablets.

An ADD site should maintain a list of which medications should be packed individually. Decision making should be based on information from manufacturers, any relevant local or national regulations, standards or requirements and information from other reputable sources.

E. Exchange of stability data

There should be national and international exchange of ADD medication suitability assessments, stability data and compatibility studies between competent authorities, marketing authorisation holders and ADD dispensing sites to ensure access to the most recent information. All technical information and medicinal product relevant factors, which are important for comparability of the data,

should be exchanged, for example details of the type of ADD technology used and different specifications for a medicinal product (excipients and form).

8. Automated dose dispensing process

A. General

ADD follows clearly defined procedures which ensure that the medicinal products are packaged in accordance with the relevant order/prescription. Special attention is required to prevent mix-ups, to maintain storage conditions, to ensure the stability of the medicinal products and to avoid microbial or cross-contamination.

Any problem which might adversely affect the quality of a medicinal product or material should be investigated, recorded and reported to the responsible pharmacist. Incoming medicinal products and materials, deblistered medicinal products and ADD medication should be separated physically or by other appropriate measures. All materials and medicinal products should be stored under the appropriate conditions, in line with the marketing authorisation, and in an orderly fashion to permit batch segregation and stock rotation. Special precautions should be taken to prevent the generation and dissemination of dust from the medicinal products. This applies particularly to the handling of high risk (highly active or sensitising) medicinal products.

B. Prevention of cross-contamination

The ADD process ensures the contamination of a packaging material or medicinal product by another material or product is avoided. This risk of accidental cross-contamination mainly arises from the uncontrolled release of dust from materials and other medicinal products during the process, from residues on equipment and from operators' clothing. The importance of this risk is dependent on the contaminant (e.g. certain hormonal, cytotoxic and other highly active medicinal products) and the medicinal product at risk of being contaminated, and may be impacted by the scale of the operation. The use of coated medicinal products and capsules is recommended as the risk of cross-contamination is lower than for uncoated medicinal products.

Cross-contamination can be avoided by appropriate technical and organisational measures, including:

- having designated, segregated areas for deblistering and ADD;
- excluding certain medicinal products from the process or handling them in their primary packaging;
- providing appropriate air extraction;
- reducing the risk of contamination caused by entry, re-circulation or re-entry of untreated or insufficiently treated air;
- using cleaning and decontamination procedures of known effectiveness.

Measures and procedures to prevent cross-contamination should be checked and evaluated at regular intervals for their effectiveness.

C. Deblistering

Removal of medicinal products from the original primary container (deblistering in the case of a blister) can be required to prepare medicinal products for use in ADD. After deblistering, the units may be stored prior to ADD in a container at the ADD site. Deblistering should be performed by designated persons according to written procedures and all of these activities should take place in a designated area. At larger sites, this area should be segregated from the dose dispensing area.

Before starting the deblistering process, and between the deblistering of different medicinal products and different batches of the same medicinal product, line clearance (cleaning of the deblistering area and equipment) should be carried out and documented. Authorised personnel should approve line clearance and the release of containers of deblistered medicinal products for the ADD process according to standard procedures.

Deblistering requires that operators wear protective clothing to protect the product and themselves, for example gloves, head cover and beard mask. Gloves should be of a material/fabric with non-adhesive properties. Defective protective clothing should be replaced. Detailed written instructions should be followed by operators. At the point of deblistering and filling, an appropriate air-flow circulation system or dust extracting system should be in place and measures should be established to ensure temperature and humidity are maintained within a specified range. Clean and properly labelled containers are required for storing deblistered medicinal products. Only one type of label identification should be allowed in the deblistering or filling area at a time. In order to reduce errors throughout the deblistering

process, additional precautionary measures such as the use of colour coding may be helpful.

Prior to releasing a container with deblistered medicines for the ADD process, it should be double-checked: either by two people, by one person and a barcode check or by using another system which gives the same assurance. Deblistered medicinal products should be checked against their original packaging or via an alternative validated system, for example against a photograph of the original packaging. It is recommended that records of the deblistering process include date and time of deblistering, details of the medicinal product, operator, second operator, quantity deblistered, and documentation of cleaning and exceptional occurrences.

D. Storage of deblistered medicinal products

A designated area should be provided for the storage of deblistered medicinal products. The maximum expiry date should be defined and easily identifiable for each product. The following information should be included on the product label or be traceable in another manner:

- name, form and strength of the medicine;
- original manufacturer, product authorisation number and batch number;
- original expiry date;
- quantity;
- ADD batch number;
- date of deblistering;
- newly assigned expiry date.

To avoid cross-contamination between medicinal products and batches, containers should be clean prior to use and cleaned after use using validated cleaning methods. Only medicinal products with the same batch number should be stored in the same container. Light and humidity protection measures during storage of the medicinal product should be established, for example use of an opaque container or desiccant. The temperature in the storage area should be controlled, monitored and recorded. Humidity should be monitored and recorded and controlled if necessary. The acceptable temperature and humidity range should be based on requirements in the medicinal product's SmPC. Where no specific requirements are stated, they should be set by the responsible pharmacist, taking into account the quality of the medicinal product as well as aspects relevant to the ADD process. Records of these activities should be kept.

For a medicine that is not uniquely identifiable by shape, size, inscription and colour, the accompanying patient information leaflet could be placed, hygienically, in the intermediate container and this could be used as part of the double-check. Stock rotation should occur for deblistered stock and the 'First Expired, First Out' ('FEFO') principle applied.

E. Dispensing operations

Dispensing is to be performed by designated persons according to written procedures. Before any dispensing operation is started, measures should be taken to ensure that the work area and equipment are clean and free from any medicinal products, product residues or documents not required for the current operation.

The written procedures should cover the following points:

- information on the ADD equipment;
- preparation of the ADD equipment;
- detailed operating instructions;
- instructions regarding storage and labelling;
- any necessary precautionary measures;
- any other relevant information.

For all canisters used in ADD machines a database/logbook with the following information should be maintained:

- medicinal product name and strength;
- unique code;
- details of essential mechanical parts;
- calibration;
- start date of use;
- details of repair or recalibration;
- end date of use (canister).

For all medicinal products dispensed, including medicinal products included in the manual tray of the ADD machine, double-checking of the product's identity and recording of the batch number is necessary. In-process and environmental controls should be carried out and documented, for example monitoring the temperature within the ADD machine. Each dose dispensed medication should be traceable including the name of the patient, pharmacy, distribution group (if applicable), machine, operator, dispensed medicinal products, batch number and checks. The patient should be able to easily open the container or pouch containing the dose dispensed medication. It is recommended that in-process checks occur to confirm the easy removal and smooth opening of each dose. The relationship between the batch number of the medicinal product(s), the batch number of the primary packaging

material of the pouch and the batch number of the ADD medication should be traceable.

F. Checking process

A combination of automated and visual checking of ADD medicine is recommended. In particular, the use of automated checking equipment is recommended at larger scale ADD sites. If automated checking is not available, the ADD medication is checked visually. Double-checking should always occur and can comprise of an automated/visual or visual/visual double-check. Checking is be carried out by authorised personnel in accordance with written procedures.

If automated checking equipment is used, it should be externally and internally validated prior to use and at appropriate intervals afterwards. The checking equipment should be calibrated periodically and records of calibration maintained. The calibration software should be used on each medicinal product used for ADD. Part of the authorisation of personnel for visual checking should involve a test to demonstrate appropriate eyesight and visual abilities.

The number and identity of the medicinal products, the integrity of the container and the labelling should be checked. Medication should be checked against the original packaging or a photographic/barcode audit trail, the prescription/order and any other relevant documentation. The dose dispensed medication is then either released for supply or rejected. Rejected medication is removed from the area and quarantined pending correction or disposal, for example if the quality of the medicinal products is impaired or suspected to be impaired. It is recommended that a photograph is available for each dose dispensed medication unit that may be referred to in case of complaints. The number of ADD units (pouches) should be reconciled to ensure completeness of the packaging process against the number of individual medicinal products fed into the ADD system.

G. Correction of errors

The ADD site should set limits for errors and corrections. Rejected medication (medication not released for supply due to the detection of errors) should only be reintroduced back into the process after inspection, investigation and release in accordance with procedures. All corrections should be carried out in line with written procedures. Errors and corrective measures should be documented, analysed and regularly reviewed, and preventive actions should be taken to avoid similar errors in the future. The triggering event that caused the error should be recorded where known and should be included in the analysis. Preventive actions should include double-checking, reflection on training and other procedures, communication paths and other work routines. The following information should be recorded for each individual correction: date, time, operator or pharmacy (if applicable), patient name, medicine, strength, number, type of mistake, person undertaking the double-check, expiry date, etc.

H. Labelling and information

ADD sites must ensure adequate labelling and information requirements are in place according to applicable European and/or national legislation and standards.

In ambulatory/primary care settings, it is recommended that the following information is included on the final ADD medicines:

- name of the patient;
- dispensing pharmacy/ADD site;
- medicinal product name, strength and form;
- quantity of medicinal products;
- administration and dosing instructions;
- warnings and storage instructions as applicable;
- date of dispensing/use by or expiry date of the medication/date and time of medication use;
- identification number, batch number or electronic code to ensure full traceability;
- any additional information deemed necessary at national, local or site level.

Data may be printed on the final dispensed dose or, if adequate space is not available, certain information may be printed on an associated bag, pouch or other container, or a list may be provided. The information on the label must comply with any applicable local or national requirements. Information allowing for the identification of the individual medicinal products dispensed should also be provided.

Relevant distribution information and identifying details should be printed on the outside of the container or the associated packaging. This information should be sufficient to accurately identify the patient and should include the patient's name, and if applicable or where used as an identifier, their address, date of birth, insurance number, distribution group and any associated pharmacy. Other information that can either be printed on labels or stored in the ADD site's information system are the batch numbers of the individual medicinal products, prescriber details, details of the dispensing pharmacy – if different

from the ADD site – and additional patient or care centre details. Additional information on the ADD machine used, the operator who prepared the ADD medicines, the checks performed and the pharmacist who carried out the checks should be maintained in the information system of the dispensing organisation or in the corresponding records.

I. Medication approval/release

To ensure the accuracy of dispensed ADD medication it is necessary for the pharmacist to check all critical elements of the process for each patient's medication prior to approving it for release and supply. Adequate checking and approval records should be maintained and should clearly detail the critical parameters checked, the acceptance criteria for approval and the name of the checking pharmacist. If an ADD site is a licensed manufacturer, ADD medication release must comply with GMP and associated batch documentation and release requirements. The approval for supply of dispensed ADD medication to patients should only be authorised by a pharmacist in accordance with validated procedures approved by the responsible pharmacist.

J. Validation

When new equipment, machines or information technology systems are introduced at the ADD site, their suitability for use should be validated. This includes equipment used for the transfer of electronic prescriptions, information technology systems, deblistering equipment, ADD machines, control equipment and any other equipment which may have an impact on the consistent quality of ADD medication. The depth and extent of the validation should be determined on the basis of quality risk management and should include design qualification (DQ), installation qualification (IQ), operation qualification (OQ) and performance qualification (PQ) as required. When validated, the process should produce a product which consistently meets the required quality.

Information technology systems or materials, which may affect ADD quality or the reproducibility of the process, should be validated after significant amendments to the ADD process, including any change in equipment. The labelling process should be validated; checks should occur at appropriate intervals to ensure that electronic code readers, label counters and other similar devices are operating correctly.

Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results. The results of validation studies should determine when the next validation is required. If equipment does not perform as expected, it should be re-validated. Validated cleaning methods should be used on critical equipment surfaces, particularly in the deblistering and dispensing areas.

A master validation plan approved by the responsible pharmacist should be in place for the ADD site. The validation criteria for all equipment and each process should be listed in the plan. Completion of the master validation plan demonstrates that all machines used for production and quality control, and all IT systems, cleaning methods and processes are validated.

K. Reconciliation process

There should be records and/or inventory control in place to ensure that the quantities of different medicinal products handled at the ADD site are reconciled with deblistered medicinal products, medicinal product quantities in stock, dispensed medication and waste medication. Any deviations should be brought to the attention of the responsible personnel without delay, corrected and such corrections documented.

Reconciliation should be carried out after all important steps throughout the ADD process, i.e. deblistering, when medicinal products have been dispensed via ADD, after any corrections to ADD medication have occurred and at distribution. Records of these checks should be maintained.

9. Distribution, supply to patients and recall

GDP should be applied to the distribution of ADD medication to pharmacies or institutions from ADD sites. If a distribution company is used they should be GDP certified. If sites supply ADD medication directly to patients/carers the applicability of GDP may be decided on a national basis. As a minimum, the elements of GDP required to maintain the quality of ADD medicinal products should be adhered to. The applicable elements of GDP may be decided on a national basis or, if permissible, following a documented risk assessment at the site which considers the areas set out below. Following the risk assessment relevant elements of GDP should be adhered to.

GDP, or relevant elements of GDP, should be implemented through a quality system operated by the ADD site, which ensures that:

- the ADD medicines distributed are authorised in accordance with legislation;
- storage conditions are observed at all times, including during transportation;
- contamination from, or of, other products is avoided;
- an adequate turnover of stored medicinal products takes place;
- ADD medicines are stored in appropriately safe and secure areas.

In addition, the quality management system should ensure that the right products are delivered to the right addressee (pharmacy, institution or patient) within a satisfactory time period.

The following information should be provided with each ADD medication delivery:

- date of delivery;
- quantity delivered;
- name and address of the ADD site;
- name and address of the patient(s);
- name and address of the pharmacy/institution (where applicable);
- duration of the ADD medication period;
- other identifying details as required.

There should be written policies, procedures and delivery agreements between the ADD site and addressee in place at the ADD site. These documents should clearly describe the distribution responsibilities of the ADD site. Temperature monitoring and, if necessary, controlled delivery should be used. The assessment of the level of temperature control required should depend on the medicinal products involved, the local climate and the stability of the medicinal products. Temperature limits should be set and the temperatures monitored and recorded.

ADD medications should be distributed promptly, safely and in a condition that is appropriate for use. They are required to be packed, transported and distributed in such a way that their integrity and quality are preserved. The transport containers should be packed so that the packaged products are not damaged during packaging or transportation. A secure distribution method should be used and medicinal products should be sealed in tamperproof containers. The containers used for transportation should be cleaned as often as necessary. If deemed beneficial, a system could be used to track the delivery and to provide additional control of the distribution process, i.e. a barcode system or equivalent. Distribution processes should be checked and checks recorded.

The distribution method used should incorporate a verifiable audit trail for ADD medications from the point at which they leave the ADD site to the point at which they are received by the addressee. Confirmation of the receipt of the ADD medication by the designated person(s) should be obtained, for example a signature. This documentation should be retained for review at the ADD site. Distribution records should be kept.

The distributer should inform the ADD site immediately if any delivery is missing or of any deviation during distribution which may affect the quality of the ADD medication. Records of issues identified should be maintained and appropriate follow-up actions/rectification of errors should occur. Misplaced deliveries should be actively traced to their destination or returned to the ADD site.

A procedure should be in place which enables the identification of dispensing errors and the recall of medication from patients to the ADD site.

10. Waste management

Rejected starting materials and medicinal products should be clearly marked as such and put in quarantine in a manner which prevents unauthorised access. They should be either returned to the supplier or destroyed as appropriate.

To ensure that no rejected dose dispensed medication is supplied, organisational measures, including procedures and checking, should be implemented.

Waste medication, including expired, damaged or returned medication, is never reused and should be handled and stored separately from ADD medication stock. Waste medication should be clearly labelled and stored in quarantine in a manner which prevents unauthorised access. Waste should be processed promptly into medicinal product waste bins, sealed when full and destroyed, via controlled procedures in accordance with local and national regulations.

Special attention should be paid to confidential waste containing personal information such as information about individual patients, prescriptions and used printing ribbon. Waste labelling, packaging materials and patient information leaflets should also be stored securely and promptly destroyed in a controlled manner. All necessary steps should be taken throughout the ADD process to reduce the risk of the reuse of waste medicinal products and packaging.

11. Quality assurance

A. General quality

Assurance is the sum total of the organised arrangements made with the objective of ensuring that medicinal products dispensed in ADD are of the quality required for their intended use. Robust quality assurance is required throughout the entire process.

The ADD site ensures that ADD medicines dispensed are suitable for use, comply with requirements and do not pose risks to patient safety and treatment efficacy. ADD sites are required to have an appropriate quality management system in place, based on the type of site, their licensing status and the scale of their operations. If an ADD site is a licensed manufacturer, GMP and, if applicable, GDP must be adhered to. If an ADD site is operating on a smaller scale, the quality system should be based on the content of these guidelines and, where applicable, the principles of GMP and GDP. Irrespective of the scale or setting, the quality management system must ensure that the quality of the ADD medicines dispensed is maintained. Further decisions on what standards are needed to ensure this should be made on a national basis following an appropriate risk assessment and should take account of the content of these guidelines.

There should be quality indicators and key performance indicators in place. Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge. Regular risk assessments should be carried out at each stage of the process to further reduce the potential for errors.

The responsible pharmacist should consider what principles are necessary to ensure the quality of the ADD medication. The 'one direction flow' principle (no crossing lines), the 'critical square metre principle' (only one medicinal product or label in a certain area), double-/triple-checking of all critical actions and other measures that reduce the risk of errors should be applied.

Procedures should be established for the prospective evaluation of planned changes and their approval prior to implementation, taking into account regular notification and approval where necessary. After implementation of any change, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended harmful impact on product quality.

Managerial responsibilities at different stages of the process should be clearly specified. The ultimate responsibility for the approval, oversight, supervision and control of the quality system at an ADD site lies with the responsible pharmacist.

B. Audit

Self-inspections should be conducted in order to monitor the implementation of, and compliance with, these ADD guidelines, national legislation and standards, relevant GMP, and if applicable, GDP, and to propose necessary corrective measures.

Personnel matters, premises, equipment, documentation, production, quality control, distribution of medicinal products, arrangements for dealing with complaints and recalls and self-inspection should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of quality assurance.

Every deviation that may have an impact on the quality of the medicinal product should be investigated, assessed, documented and approved by the responsible pharmacist. With respect to established deviations, corrective and precautionary measures should be taken on the basis of quality risk management.

Self-inspections should be conducted in an independent and detailed way by designated qualified, competent personnel employed at the ADD site or by the ADD site owner. The frequency with which an ADD site carries out self-inspections should be based on a risk assessment. Self-inspections should occur at appropriate intervals and the frequency should be increased in the case of ADD medication carrying a higher risk, or if there is a change in the process. Independent audits by licensed external experts are also recommended. All self-inspections and external audits, and the corrective and precautionary measures implemented, should be recorded.

C. Safety system and data collection

ADD errors and incidents should be reported. Barcode technology and electronic patient medication records are often used in ADD, and information contained in these systems can include patient, medicine, prescriber, pharmacist and operator data. Collection and sharing of these data (anonymised) is encouraged but must occur in accordance with data protection provisions.

12. Documentation: policies, procedures and data collection

A. General

ADD sites must maintain documentation and records as required by national legislation and standards.

Good documentation constitutes an essential part of the quality assurance system and is a key element of compliance with these ADD guidelines, GMP and GDP. The various types and formats of documents should be defined in the quality management system. Paper-based, electronic or photographic storage formats may be used. The main objective of a documentation system is to establish, control, monitor and record all activities which directly or indirectly impact the quality of ADD.

The quality management system should include sufficient instructional detail to facilitate understanding and implementation of the requirements, in particular recording of the processes and situational assessment.

There are two primary types of documentation for managing and recording adherence to requirements:

- instructions (directions/requirements, procedures and specifications);
- records.

Good documentation practices should be applied. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Documents containing instructions should be approved, signed and dated by the responsible pharmacist and be available to all relevant staff. They should have unambiguous contents, be uniquely identifiable, be laid out in an orderly fashion, be easy to check, and the style and language of documents should be appropriate for their intended use. The implementation and review dates should be defined.

Standard operating procedures, work instructions and methods should be written in an imperative, mandatory style. Documents within the quality management system should be regularly reviewed and kept up to date. Obsolete documents should be clearly marked and stored separately.

B. ADD documentation

The ADD site should carry out a risk assessment to determine the documentation that is required to be maintained and the level of detail required. There should be documents on policies, procedures, protocols, specifications, incident reports and follow-up actions, where appropriate, for the following processes:

- validation and qualification of processes including cleaning, equipment and systems;
- equipment assembly and calibration;
- maintenance and cleaning of equipment and facilities;
- personnel matters;
- training in ADD guidelines, relevant GMP and GDP and technical matters, as well as verification of the effectiveness of training;
- protective clothing and hygiene;
- environmental monitoring;
- pest control;
- complaints;
- returns of ADD medication;
- change control and management;
- investigations of deviations and instances of non-conformity;
- patient care issues (consent, data protection, patient suitability assessments, medication therapy review and counselling) as applicable;
- prescription/ADD order management and dispensing;
- ADD medication checking and release or supply;
- contracts with suppliers and consignees (pharmacies, residential care settings, patients, etc.), as applicable;
- data protection;
- distribution of ADD medication;
- waste management;
- internal quality/ADD guidelines and GMP compliance audits;
- any other element of the process deemed necessary.

Clear operating procedures should be available for all critical aspects of the ADD process and for maintenance and cleaning of the premises and all equipment. An inventory of valid documents within the quality management system should be maintained.

C. Records and retention of documents

Records provide evidence of various actions in compliance with instructions, for example activities, events, investigations, and a history of each ADD dispensed medication, including its distribution. Records include any raw data or photographs.

The ADD site should carry out a risk assessment to determine the records that are required to be maintained, the level of detail required and the duration of retention. The following records should, where appropriate, be maintained:

- ADD prescriptions/orders (hard or electronic copy, or the original if required by national legislation);
- training records detailing the policies and procedures that staff are trained in;
- records relating to medicinal products and, as applicable, other materials and products, including delivery documentation and medicinal product suitability assessments;
- records/logbooks for critical equipment and systems, including records of equipment/system set up, any use of an area, equipment/method used, environmental conditions, validations, calibrations and maintenance operations;
- process records, including deblistering, storage and ADD;
- checking and release of supply records;
- records of every ADD medicine dispensed, based on an assigned batch number;
- cleaning records, including details of the particulars cleaned;
- records of procedural deviations, including the rationale for the deviation and the conclusions regarding the impact on the quality of the final product or patient safety;
- error records, including details of corrective and preventative actions;
- distribution records, including details of the distribution of each ADD patient's medication;
- records of self-inspections and external audits, including all observations made and, where applicable, proposals for corrective measures. Statements on the corrective and preventative actions subsequently taken should also be recorded.

All records should be dated and include details of the personnel involved. Patient data should be handled and maintained with special care to avoid any misuse of the data by unauthorised persons. The ADD site, or if applicable, the associated pharmacy (depending on the contracts in place), should be required to maintain records of patient suitability assessments, patient consent, medication therapy reviews and counselling. Records of contracts with relevant healthcare sites (e.g. pharmacies or institutions) and professionals (e.g. physicians or pharmacists) should be maintained.

Records must be retained in accordance with national regulations or standards. In the absence of legislation, a risk assessment should determine the duration of record keeping for specific documents. The following retention periods are recommended:

- instructions, including procedures, and specifications: at least five years after they have been superseded;
- all records related to medicinal products used in the ADD processes: at least one year after expiry date of the medicinal product/starting material used or the longest dated expiry date of the medicinal product/starting material used in a dispensed dose;
- all other records: at least five years.

Part Two: Patient care activities associated with the ADD process

In addition to the ADD process meeting the best possible standards, the incorporation of ADD into the patient care process should also be understood by all of those involved in the patient's care. In many cases the patient's circumstances will require medicines provided both by conventional dispensing and by ADD. The simultaneous use of both methods will be the responsibility of the pharmacist who provides care directly to the patient and, where they differ, will depend upon communication and collaboration with the ADD-responsible pharmacist. Communication and collaboration with the patient and other members of the healthcare team is also essential. To ensure that patient safety is optimised in these instances, robust multidisciplinary procedures to review and manage all of the patient's medicines should be regularly and systematically undertaken.

13. Legal basis

Patient care activities associated with dispensing medication via ADD must be carried out in accordance with applicable national regulations and standards. If national regulations and standards are not in place, national authorities should consider establishing a legal framework setting out standards for patient care activities, in particular patient care activities associated with ADD. National guidelines or standards to facilitate compliance with relevant legislation are recommended.

14. ADD prescription/order and responsibility for patient care

A. ADD orders

ADD is carried out in various settings in Europe. ADD medication is prepared at the sites of manufacturers, companies/sub-contractors and large and small-scale hospital and community pharmacies, and supplied in ambulatory and in-patient short- and long-term care.[6]

An order for medication to be dispensed via ADD can be made, depending on the national framework in place, by the treating physician (health professional with prescribing authority) or a pharmacist. The treating physician can request that a patient's prescribed medication be dispensed via ADD or pharmacists may decide ADD is the most suitable method of providing medication to certain patients in consultation with the treating physician and the patient/carer/care institution. The decision to supply medication via ADD should occur following a patient suitability assessment involving all members of the healthcare team, including the patient/carer. The decision should be documented either on the prescription or in an order in line with national legislation and frameworks.

In certain countries, a medical prescription may be transcribed into an ADD order, via a medication plan, at the request of the patient or a care institution. The medication plan forming the basis of an ADD order should be based on a valid prescription from a physician or other authorised healthcare pro-

6. Refer to Section 3.C Setting.

fessional with access to the patient's medical records, and should only be initiated following a patient suitability assessment.

Not all of these mechanisms of requesting ADD medicines are permitted in all European countries. It is recommended that national authorities determine how ADD requests should be received/managed and, if applicable, how prescriptions should be transcribed into a medication plan prior to forwarding an order to the ADD site.

B. Responsibility for patient care

Responsibility for patient care must be assigned in accordance with national regulations and standards. However, in many countries these responsibilities have not been fully clarified; clarity regarding where responsibility for patient care lies is necessary.

To enable the ongoing review of an ADD patient's medication therapy, assessment of the patient's suitability and the provision of the correct information and appropriate counselling, it is recommended that there is consistency in the responsibility for patient care. Effective communication channels and systems between healthcare providers and between healthcare providers and patients are essential. National frameworks for the management of ADD patients should encourage and enable patients to be managed by a healthcare team, which involves the same medical practitioner (or team of medical practitioners) and pharmacist (or team of pharmacists) for each dispensing, review and assessment.

Because ADD occurs in various settings in different European countries, the patient care aspects of the ADD process may be carried out by pharmacists employed by the ADD site or by an associated dispensing pharmacy or similar.

One site: where ADD and supply of medication to a patient/carer occurs at one site, for example a pharmacy:

- The pharmacist, in particular the responsible pharmacist, at that entity is responsible for the ADD process and the quality of the resulting medication.
- The pharmacist is also responsible for patient care, including:
  - patient suitability assessments;
  - ensuring patient consent has been obtained;
  - the review of medication therapy;
  - the provision of patient information and counselling.

Two sites: where the ADD service and supply of medication to the patient and/or the patient care services are provided at two sites, such as a manufacturer, pharmacy or company/sub-contractor that supplies ADD medicines to a pharmacy or directly to patients. Pharmacists at the ADD site and at the associated pharmacy (or similar) bear different responsibilities for patient care:

- pharmacists at the ADD site are responsible for the ADD process and medication;
- pharmacists at the ADD site and/or at the associated pharmacy may have responsibility for patient care activities. This varies depending on the country of operation or the contacts in place. In many countries, the associated community or hospital pharmacy is responsible for most or all non-ADD site-specific activities.

Where the ADD service and supply of medication to the patient and/or patient care services are provided by separate legal entities, unless responsibilities have been decided by national legislation or standards, responsibilities for the different elements of patient care should be established and documented in a service provision contract. It is important that the contract outlines the ADD and patient care responsibilities of each entity.

Where the ADD service and supply of medication to the patient and/or patient care services are provided by two sites within one legal entity, unless responsibilities have been decided by national legislation or standards, responsibilities for the different elements of ADD and patient care should be established, agreed between both sites and documented.

C. Healthcare teams

As with other complex patient care activities, it is recommended that multidisciplinary healthcare teams manage the care of ADD patients. The teams should be responsible for ensuring patient-centred care, and in particular for assessing the appropriateness of the use of ADD for patients. Teams should include prescriber(s), who have knowledge of patients' medical and care status and access to patients' medical records, and pharmacist(s), who have medicinal product knowledge and responsibility for reviewing prescriptions for therapeutic appropriateness and counselling. Other healthcare professionals, for example nurses where patients are in a care setting, and the patient are also integral team members. Patients can provide valuable information on their individual circumstances and any barriers to their medication adherence.

Information systems should enable the sharing of all relevant information between the members of the healthcare team, for example to ensure pharmacists and prescribers both have access to patients'

medical and medication records. Data protection and any other applicable national legislation must be considered prior to sharing patient information.

Unless healthcare team members' responsibilities have been decided by national legislation or standards, responsibilities for the different elements of patient care and the roles of different members of the healthcare team should be established within each team.

D. Education

Health professionals caring for ADD patients should ensure their ADD knowledge is maintained and improved. Education about the ADD process and its place in the provision of medicines to patients is required for prescribers, pharmacists and nurses, so that healthcare teams may function effectively and safely when providing care to patients receiving ADD medicines. It is recommended that ADD education is included in the undergraduate training of relevant health professionals, and that these professionals engage in continuing professional development and postgraduate education relevant to their role in the ADD process and the associated care of patients.

15. Patient suitability

A. General

Dose-dispensing systems do not provide benefits for all patients; therefore, prior to initiating ADD there should be a documented assessment of a patient's suitability to have medicinal products supplied via ADD.

ADD-dispensed medicines should only be supplied to patients on the basis of an assessment of an individual patient's suitability by a healthcare team, who conclude that ADD is the best way to meet the patient's needs. The advantages of supplying medicinal products via ADD need to be balanced against the disadvantages. Advantages can include increased adherence and disadvantages can include the reduced involvement of patients in the management of their medication and risks associated with the manipulation of medicines as part of the ADD process.

These systems are suitable for use by patients who are willing to take their medication and who possess the visual acuity, dexterity and cognitive skills required to use the system. They are also suitable for patients who are managed by a carer. They are often unsuitable for use by those whose medication regimen is unstable and subject to frequent changes, unless these patients are closely monitored.

Prior to the provision of a dose dispensed system to a patient, alternative adherence support should be considered and support, advice and services should be provided based on a patient's individual circumstances. This support may also be used alongside ADD if considered appropriate. Examples of supporting actions that should be considered include:

- simplification or tailoring of the medication regimen, e.g. removing unnecessary medication, altering times of administration or using combination products;
- reminder charts;
- visual aids, e.g. large font information sheets, magnifying glasses, pictograms;
- memory aids, e.g. software applications, timed alarms or calls from a relative;
- involvement of a carer or relative to help administer medication.

Medicine review may identify further barriers to adherence which may be overcome by interventions such as a change in formulation or the use of non-child-resistant closures on containers.

B. Suitability assessments

Prior to deciding to supply a patient's medicine via ADD, a documented assessment of a patient's suitability should occur. This assessment should consider both patient-specific and medication-specific issues and should, as a minimum, address:

- the ability of the patient to manage their medication and adhere to their medication regime;
- the likelihood that alternative adherence support will improve adherence and/or that a dose dispensing system will improve adherence;
- patients' preference for a dose dispensing system or conventional dispensing;
- patients' health status and circumstances, e.g. patients with literacy problems or memory problems;
- the ability of the patient to use conventional dispensing systems and their ability to use ADD systems, e.g. patients with physical disabilities;
- the impact of the loss of independent decision making and decrease in patients' involvement in the management of their medical condition and therapy;
- the impact of the loss of information and patient safety features, e.g. information in braille and opening devices;

- the setting in which the patient is located, e.g. dose dispensed medicinal products are not usually necessary if a healthcare professional is administering the medication;
- the possibility of confusion if not all of the patient's medications are suitable for inclusion in a dose dispensing system, e.g. injections, suppositories, effervescent tablets, 'as required' medication or medication for acute conditions. Note: there are some ADD systems that can contain non-oral formulations; however, these guidelines recommend that only oral medicines are included in ADD. The type of ADD system and its capabilities can also form part of the assessment.

It should not be assumed that all patients in a particular setting, e.g. hospital or long-term institutional care are suitable for ADD. Assessment tools for determining suitability, e.g. a grading system for different types of patients and/or an assessment of the personnel responsible for medication administration, could form part of the patient suitability assessment. Decisions on hospital or institutional policy regarding patient suitability assessments and the use of ADD should involve all members of the healthcare team and may, if considered appropriate, also involve relevant managers.

C. ADD suitability

Dose-dispensing systems are not considered a suitable intervention:

- where simplification of the medication regimen or other adherence support (as outlined above) will achieve the same levels of adherence and patient safety;
- for intentional non-adherence: if a patient does not want to take their medication, discussing and addressing the reason for non-adherence is the correct approach;
- for an institution or carer's convenience: the decision to supply medicinal products in an ADD system should be based on patient need and appropriateness rather than the requirements of any establishment or institution. All patients on similar medication or in the same care setting or institution should not automatically receive their medicines via ADD.

Dose dispensing systems are a suitable intervention:

- where, following a documented assessment, it has been decided that provision of medication via ADD will bring benefits to the patient and it is likely that adherence will be achieved. In particular this applies where a patient is on a complex drug regime and/or other adherence supporting actions have been tried and, despite the best intention of the patient, failed;
- for patients who are willing to take their medication and have the visual acuity, dexterity and cognitive skills required to use the system;
- for patients taking a lot of medication, who find it difficult to manage taking the right medicines at the right times;
- for patients whose medication is frequently altered, particularly where this may cause confusion or where high-risk medicines, e.g. warfarin, are involved. These patients may require frequent supply and additional review, assessment and monitoring.
- for patients managed by a carer, particularly confused patients. Many patients in institutions fall into this category. Adequate training of carers providing medication to patients via ADD is essential.

D. Suitability reassessments and risk of no assessments

Periodic reassessment of the suitability of ADD medicines for a patient is an important part of the process. Reassessment should occur at appropriate intervals for each individual patient.

They should occur:

- when the patient's medication changes: when medication is added, stopped or the dose or frequency changes;
- when the patient's health status or circumstances change: if a new condition is diagnosed, if there is significant deterioration in a condition or if the patient has moved into residential care;
- at minimum defined intervals, where there is no change that warrants earlier reassessment.

Risks associated with a lack of patient suitability assessments are:

- patients not taking their medication or only taking some of their medication
  - due to intentional non-adherence, or
  - because of reduced involvement in their medication management;
- the introduction of the inherent risks of manipulating medicines via ADD without a benefit : risk ratio assessment.

ADD medicines should only be provided where the benefit : risk ratio is favourable and this has been determined by a patient suitability assessment.

Records of all initial assessments and re-assessments should be maintained by members of the assessment team and a copy provided to the patient/carer.

16. Patient consent

Prior to supplying a patient's medication via ADD, every patient (or person authorised to take decisions on the patient's behalf) should be asked if they would prefer to receive their medicinal products in a conventional manner or via ADD.

Voluntary informed consent should be obtained. Adequate information on the benefits and risks of receiving medicines via ADD should be included on the consent form. Informed consent should be documented for each patient receiving ADD medicines. Consent to any associated data transfer should also be documented.

17. Review of medication therapy, counselling, information provision and education

A. Review of a patient's medication therapy

Healthcare teams should carry out regular reviews to assess the pharmaceutical and therapeutic appropriateness of patients' medication therapy. A review involves considering each medicinal product individually and collectively, including screening for any potential therapy problems which may arise from the use of the medicinal products. Both general and ADD-specific patient care elements should be considered as part of the review.

Important elements of a review include, but are not limited to:

- the requirement and indication for each medication;
- therapeutic duplication;
- interactions with other medicinal products (including interactions with non-prescription medicinal products, herbal products or foods);
- incorrect dosage or duration of treatment;
- allergies;
- previous adverse reactions;
- clinical abuse and/or misuse.

The review should also identify whether patients are taking medicines that may not be suitable for inclusion in a dose dispensing system, e.g. medicines administered by non-oral routes or effervescent tablets.

Review of a patient's medication by the relevant healthcare professional (prescriber or pharmacist) should occur each time a medication is prescribed and dispensed.

More detailed, structured medication reviews should occur at an appropriate frequency. These should examine a patient's medication with the objective of reaching an agreement about treatment between the prescriber, pharmacist and patient. Their aim is to optimise the impact of medicines and minimise the number of patient-related problems. The patient's healthcare team should participate in the interdisciplinary review of each patient's medication. The patient should also be involved where possible, to ensure they are an active participant in their care, to identify any patient-specific issues, and to empower the patient. Patients' adherence to their medication regime should form part of the review. Records of participation in these reviews should be retained.

Risks associated with a lack of regular structured medication reviews include:

- the continuation of medication that is no longer needed or a delay in including a new medicine in the system;
- reduction of the frequency with which changes to medication are made: the patient's health status may not be reassessed if a patient is categorised as a long-term ADD medicine user and patients may remain on unnecessary medication;
- inclusion of a new medicine without considering all necessary factors;
- lack of patient and carer feedback on whether the system is helping or hindering their adherence.

In addition, regular communication/meetings as a forum to discuss patients' care and treatment and any issues which the pharmacist or medical practitioner, in their professional judgment, deems appropriate are recommended. Individual multidisciplinary patient care plans and/or patient healthcare records can also be beneficial. The primary aim should be to ensure patients receive an appropriate standard of care.

B. Patient information and counselling

Patients should receive comprehensive instructions and counselling. Patients should be adequately introduced to ADD, particularly patients

switched from conventionally dispensed medicine to ADD, and should be provided with information on why the system is suitable for them. The pharmacist should ensure at each supply that the patient has sufficient information and advice for the proper use and storage of the ADD medication.

As with all supplied medicinal products, it is important that prescribers and pharmacists offer counselling to the patient, or their carer, on any matters relating to ADD medicines and medicines supplied in an alternative manner that they, in the exercise of their professional judgment, deem significant. This may include but is not limited to:

- the identification of medicinal products supplied via ADD. Pictures of medication should be provided to aid identification where more than one medicine is packed in a container;
- explanations of any changes since the last dispensing;
- storage instructions, e.g. protecting the ADD medication from light and the safe storage of the ADD containers 'out of the reach of children';
- the therapeutic benefit which may be expected from the use of medicinal products supplied via ADD and in an alternative manner;
- any special directions and precautions;
- any severe side-effects, interactions or contraindications;
- any other matters which may be included or referred to in the SmPC for the medicinal product concerned.

It is important to ensure that patients and their carers are provided with, or have access to, current patient information leaflets and any relevant information on the authorised packaging of the medicinal products supplied. ADD sites should also ensure that the font and labelling on pouches is clear, legible and of an appropriate size for an individual patient's circumstances.

Information on additional adherence support that may be used in conjunction with the ADD system should be provided if such aids are available and considered suitable for an individual patient, for example:

- if a dose is missed some ADD devices provide signals or trigger a message to the patient/carer;
- medication applications may be used for tracking medication administration or providing patient information leaflets.

C. Patient education

It is recommended that ADD is accompanied by concomitant programmes for improving patients' health literacy, education and empowerment through expert-patient programmes that develop self-efficacy and adherence. ADD service providers, other health professionals and patient organisations should provide such information to patients.

18. Documentation and records

ADD sites and/or associated pharmacies responsible for patient care activities must maintain documentation and records as required by national legislation and standards.

If documentation requirements are not defined, the ADD site/pharmacy should carry out a risk assessment to determine the documentation that is required to be maintained and the level of detail required. Documents (policies, procedures, specifications) and records should be in place for the following patient care processes:

- the division of patient care responsibilities between sites (if applicable);
- obtaining informed patient consent;
- patient suitability assessments and reassessments;
- ADD order management;
- medication therapy review (individual and multidisciplinary);
- the provision of patient information leaflets and information on medication changes;
- additional counselling;
- data protection;
- contracts and interactions/meetings with relevant healthcare professionals, e.g. physicians or other pharmacists;
- pharmacovigilance.

Records should be maintained at the site or sites responsible for a particular activity. Where two sites are involved, it may be considered appropriate to maintain some records at both sites, for example, orders/prescriptions and contracts. Records must be retained in accordance with national regulations or standards. In the absence of legislation, a risk assessment should determine the duration of record keeping for specific documents. It is recommended that records are maintained for a minimum of five years. Copies of relevant records, including patient suitability assessments, medication reviews and patient consent forms, should be provided to patients.

References

1. Dijstelbloem-de Jong Y, Hartling HW, Krings AWH. Centralised Automated Dose Dispensing Systems. *EJHP Pract* 2006; 12: 50-51.
2. The Association of Finnish Pharmacies – Annual Review: Medicines in pre-packed doses; 2003 – Available at: https://goo.gl/BAAgU7.
3. Larsson A, Åkerlund M. ApoDos: the Swedish model of multi-dose. *EJHP Pract* 2007; 13: 51.
4. Danish Health and Medicines Authority: Dose dispensing – Available at: https://goo.gl/NfQYEK.
5. Schwarz HO, Brodowy BA. Implementation and evaluation of an automated dispensing system. *Am J Health Syst Pharm* 1995; 52: 823-828.
6. Fanikos J, Erickson A, Munz KE, Sanborn MD, Ludwig BC, Van Hassel T. Observations on the use of ready-to-use and point-of-care activated parenteral products in automated dispensing cabinets in US hospitals. *Am J Health Syst Pharm* 2007; 64: 2037-2043.
7. Kwint HF, Stolk G, Faber A, Gussekloo J, Bouvy ML. Medication adherence and knowledge of older patients with and without multidose drug dispensing. *Age Ageing* 2013; 42: 620-626.
8. Barker KN. Ensuring safety in the use of automated medication dispensing systems. *Am J Health Syst Pharm* 1995; 52: 2445-2447.
9. Herborg H, Haugbølle LS, Lee A. Automated dose dispensing in Danish primary health care – a technology under construction. *Pharm Pract* 2008; 6: 103-112.
10. Wekre LJ, Bakken K, Garåsen H, Grimsmo A. GPs' prescription routines and cooperation with other healthcare personnel before and after implementation of multidose drug dispensing. *Scand J Public Health* 2012; 40: 523-530.
11. Gilmartin JF, Hussainy SY, Marriott JL. Medicines in Australian nursing homes: a cross-sectional observational study of the accuracy and suitability of re-packing medicines into pharmacy-supplied dose administration aids. *Res Social Adm Pharm* 2013; 9: 876-883.
12. Bergkvist A, Midlöv P, Höglund P, Larsson L, Bondesson A, Eriksson T. Improved quality in the hospital discharge summary reduces medication errors – LIMM: Landskrona Integrated Medicines Management. *Eur J Clin Pharmacol* 2009; 65: 1037-1046.
13. Blister-strip warning. *Pharm J* 1996; 256: 85.
14. Church C, Smith J. How stable are medicines moved from original packs into compliance aids? *Pharm J* 2006; 276: 75-81.
15. Wekre LJ, Spigset O, Sletvold O, Sund JK, Grimsmo A. Multidose drug dispensing and discrepancies between medication records. *Qual Saf Health Care* 2010; 19: e42.
16. Balka E, Kahnamoui N, Nutland K. Who is in charge of patient safety? Work practice, work processes and utopian views of automatic drug dispensing systems. *Int J Med Inform* 2007; 76: S48-57.
17. Johnell K, Fastbom J. Multi-dose drug dispensing and inappropriate drug use: A nationwide register-based study of over 700,000 elderly. *Scand J Prim Health Care* 2008; 26: 86-91.
18. Sjöberg C, Edward C, Fastbom J, Johnell K, Landahl S, Narbro K, Wallerstedt SM. Association between multi-dose drug dispensing and quality of drug treatment – a register-based study. *PLoS One* 2011; 6 (10): e26574.
19. Sjöberg C, Ohlsson H, Wallerstedt SM. Association between multi-dose drug dispensing and drug treatment changes. *Eur J Clin Pharmacol* 2012; 68: 1095-1101.
20. Larsen AB, Haugbølle LS. The impact of an automated dose-dispensing scheme on user compliance, medication understanding, and medication stockpiles. *Res Social Adm Pharm* 2007; 3: 265-284.
21. Sinnemäki J, Sihvo S, Isojärvi J, Blom M, Airaksinen M, Mäntylä A. Automated dose dispensing

service for primary healthcare patients: a systematic review. *Syst Rev* 2013; 2: 1.

22. Bell JS, Johnell K, Wimmer BC, Wiese MD. Multidose drug dispensing and optimising drug use in older people. *Age Ageing* 2013; 42: 556-558.
23. Apoteket AB: Annual report 2009 – Available at: https://goo.gl/AzoaHs.
24. Order of the automated dose dispensing – Available at: https://goo.gl/peKfFe.
25. The Medicines Act of Finland – Available at: https://goo.gl/zT49i5.
26. ASHP Guidelines on the safe use of automated dispensing devices. *Am J Health Syst Pharm* 2010; 67: 483-490.
27. Department of Health. Assessing the effects of health technologies: Principles, practice, proposals. London: Department of Health, 1992.
28. WHO good manufacturing practices for pharmaceutical products: main principles, Annex 2, WHO Technical Report Series No. 986, 2014 – Available at: https://goo.gl/VoFc2i.
29. Directive 2003/94/EC (Article 2, Definitions, no. 6) – Available at: https://goo.gl/esA4Th.
30. Guidelines on Good distribution practice of medicinal products for human use (2013/C 343/01) – Available at https://goo.gl/ceU9pp.
31. Directive 2001/83/EC – Available at https://goo.gl/at4RZo.
32. WHO. GMP Question and Answers – Available at: https://goo.gl/wzcgPI.
33. EMA. Good manufacturing practice – Available at: https://goo.gl/Igq8XE.
34. Directive 2011/62/EU – Available at: https://goo.gl/UHX5fW.

Automated Dose Dispensing (ADD) is the dispensing by means of an automated process, of one or more different medicinal products into an ADD container/pouch for a patient to take at a particular date and time. This is a commonly used approach in Europe to address the increase of polypharmacy and complex medication regimens.

The purpose of these guidelines is to propose standards and approaches to regulating and providing ADD services across Europe to ensure that they are provided to a consistently high standard, thus maintaining the safe supply of medicines to patients. The advantages of ADD for an individual patient should always outweigh any potential risks and suitability should be decided on a case-by-case basis.

These guidelines should be read in conjunction with any national regulations, standards or guidance that apply in the country where the ADD site is located.

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The Council of Europe is the continent's leading human rights organisation. It comprises 47 member states, 28 of which are members of the European Union. The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a directorate of the Council of Europe. Its mission is to contribute to the basic human right of access to good quality medicines and healthcare and to promote and protect public health.

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