Automated Dose Dispensing (ADD) Guidelines:

Best Practice for the ADD Process, and Care and Safety of Patients

Deadline for comments: 24 February 2017

Comments should be sent to ADD@edqm.eu

The purpose of these guidelines is to harmonise the standards and approaches to automated dose dispensing across Europe and to help ensure that this service is provided to a consistently high standard which ensures the safe supply of medicines to patients.

- EDQM's work on this topic began with the identification of a need for guidance by the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC) in 2012.
- The document was then drafted by a Working Party of Experts in Automated Dose Dispensing.
- A workshop with stakeholders, interested parties and authorities took place in September 2015.
- This DRAFT guideline document was finalised by CD-P-PH/PC in summer 2016 and released by the Steering Committee, the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) at its meeting in September 2016.

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Summary

The purpose of these guidelines is to harmonise the standards and approaches to automated dose dispensing across Europe, to help ensure that this service is provided to a consistently high standard which ensures the safe supply of medicines to patients. These guidelines should be utilised by all pharmacies and manufacturers involved in automated dose dispensing, as well as by national authorities in countries where this service is provided.

Automated dose dispensing (ADD) is the dispensing, performed by a method involving an automated process, of one or more different medicinal products into an ADD container or pouch for a patient to take at a particular date and time. This approach is used to address the increase of polypharmacy, common for elderly patients. ADD is carried out in various settings across Europe, for example in licensed manufacturers or companies and 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, safety and efficacy of the medication dispensed into an ADD container is maintained.

In Europe, the medicinal products legislation 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 of ADD overlap with each domain. There is no common set of criteria or standards available to guide regulators, providers and patients about how ADD should be carried out, and therefore there are significant disparities in the way in which ADD is deployed and in how it is regulated in different countries.

These guidelines address the issues to be considered when setting up an ADD site, the standards that should be applied to the ADD process and the associated care of the patient. Part One details standards pertaining to the ADD site and operations. This includes requirements for the premises and equipment, training of personnel and the need to have a responsible pharmacist at the ADD site overseeing the management of all activities relating to the pharmaceutical process. Part Two details 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 adding value to the patient's care. The advantages of ADD for an individual patient should always outweigh any potential risks and 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 situated, for example regarding labelling and record keeping of dispensed medicines, requirements for disposal of waste medicines and responsibility for patient care activities. If an ADD site is a licensed manufacturer or distributor, Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP), must also be adhered to.

Disparities between national regulations and between statuses of ADD sites should lead national authorities to consider establishing a legal framework for ADD, as well as standards or guidance. This should facilitate compliance with relevant legislation based on the principles of GMP and GDP and these guidelines. 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.

The Automated Dose Dispensing Guidelines have been developed by a working group of experts from industry, academia, and government from across Europe and discussed, reviewed and approved by the Committee on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care coordinated by the European Directorate for the Quality of Medicines and 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]. Bar code technology has extended the application and use of ADD systems. The use of ADD to supply the needs of patients in certain institutional settings is frequent 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 in large healthcare establishments, within many different specialist units[5-6]. ADD has been associated with reduced distribution costs, fewer errors and better medication adherence. A recent study in the Netherlands [21] showed improved 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 the preparations, errors during the processes, [1,7] as well as the impact of ADD on the behaviour and attitudes of the carers and patients [8,9]. Dispensing of original packages by automated methods poses few problems, provided the packaging meets Good Manufacturing Practice (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 found [10-11]. 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 been established and validated [12-13]. Medication errors and discrepancies have been shown to be decreased under some circumstances [9, 14] 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 not complete and not substantial [22-23]. Questions about technical, managerial, regulatory and clinical issues have been addressed to some extent in guidelines and regulations but not at a comprehensive level [24-29], and no overall framework of guidance for policy-making is available[30].

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 a medicinal product 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. The significant disparities in the way in which ADD is deployed and in how it is regulated means 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 automated dose dispensing (ADD).

The CD-P-PH/PC decided that the guidelines would address both the ADD process and the associated care of patients, but would not address manual dose dispensing. The guidelines focus on the areas of greatest patient risk. Following on from a survey review of the different systems in place in different countries in Europe, the guidelines aim to harmonise the standards for ADD. The guidelines address the issues that should be considered and the standards that should apply to the ADD process, and the associated care of patients. The topics to be addressed in the guidelines were decided by the CD-P-PH/PC. The guidelines have been drafted by an ADD working party set up by the Committee of Experts CD-P-PH/PC, then submitted for approval of the scientific and technical contents by the Committee of Experts CD-P-PH/PC, and finally submitted for adoption by the CD-P-PH, Steering Body.

2. DEFINITIONS:

Automated Dose Dispensing (ADD): Automated dose dispensing is the dispensing, performed by a method involving an automated process, of one or more different medicinal products into an ADD container/pouch. 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 this guideline): a method by which individual doses of medicinal products are repackaged into individually labelled containers/pouches, e.g. in a hospital setting. This method does not involve individual patient dispensing.

Manual Dose Dispensing (excluded from the scope of this guideline): where the dispensing of medicinal products into individualised patient medication doses occurs manually (without the use of automated systems).

The World Health Organization[1] 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.

[1] WHO good manufacturing practices for pharmaceutical products: main principles, Annex 2, WHO Technical Report Series, 986, 2014,; www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf?ua=1.

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.

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'[2].

The 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[3]'.

Good Distribution Practice (GDP): The principles of Good Distribution Practice are stated in the EU guideline 2013/C 343/01 implementing Directive 2001/83/EC. The European Medicines Agency describes the concept of Good Distribution Practice 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'[4].

3. SETTING AND LEGAL FRAMEWORK:

A. Background: The 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 of ADD overlap with each domain. Applying detailed patient information to a medicinal product and breaking units from manufacturer's original packaging traditionally 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

[2] Directive 2003/94/EC (Article 2, Definitions, no. 6).
[3] www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/
[4] www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp

medicinal products traditionally occurs in 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. It is recommended that national authorities establish guidelines or standards to facilitate compliance with relevant legislation based on the principles of GMP and GDP and these guidelines.

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 occur at the one site.
2. Community pharmacies supplying medicinal products to other pharmacies or healthcare institutions. In this circumstance dispensing is carried out by the ADD pharmacy, and professional control is usually the responsibility of the dispensing pharmacy or divided between the ADD site and dispensing pharmacies.
3. Pharmaceutical manufacturers or other companies supplying medicinal products to pharmacies or directly to patients on behalf of the pharmacies. In this circumstance professional control 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 (company) or a pharmacy (direct dispensing or preparing and distributing);
- The scale of the operation may be the deciding factor for whether an ADD site can operate as a manufacturer or pharmacy;
- In some countries only pharmacies are permitted to prepare and supply ADD medicines and they may or may not be permitted to supply medicines to other pharmacies.

D. Licensing: The decision 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 or pharmacy. Large scale ADD should be carried out in a licensed manufacturer. An ADD site may receive an exemption from requiring a manufacturing authorisation if it is a pharmacy. 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 i.e. the supply of medicines directly to patients/carers and associated patient care activities. The distinction between a manufacturer and pharmacy should be decided on a national basis, depending on the scale, setting and other operations occurring at the ADD site.

Due to the additional requirements for ADD, e.g. specific training requirements and labelling of the pouch/

container with dosage instructions for individual patients, it is recommended that national authorities provide a specific authorisation/licence for ADD activities that occur in manufacturers or pharmacies. Authorities could suspend or withdraw the licence depending on compliance with its conditions. Inspection prior to licensing, re-inspection at relevant intervals and the maintenance of a national register of ADD sites is recommended.

Where a site, e.g. a pharmacy, is commencing ADD activities and there is no requirement for an additional licence, they should at 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 or distributor, GMP and, if applicable, GDP must be adhered to. If the site is not a licensed manufacturer or distributor but is operating on an industrial scale or involved in external supply it is recommended that the site is licensed as a manufacturer, to ensure adherence to GMP and GDP. If an ADD site is operating on a smaller scale and fulfils the relevant requirements, it may operate as a pharmacy and these guidelines and the relevant principles of GMP and GDP required to ensure that the quality, safety and efficacy of the ADD medication is maintained should be applied.

F. Product Liability and ADD Suitability Information from Manufacturers: A manufacturer's product liability[5] 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 the product's marketing authorisation data. It is recommended that national authorities require 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. This data should indicate how long 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 e.g. for hygroscopic or light sensitive medicinal products. If applicable, additional testing should take place to check interactions with common packaging materials, other medicinal products which are dispensed together and ADD equipment.

Where sufficient information on the suitability of a medicinal product for ADD is not included in the medicinal product's 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 the product's marketing authorisation. In this context consideration should be given to the professional issues, including potential legal liability issues that may arise in providing this service.

[5] 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 in a pharmaceutical (licensed) manufacturer 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 or companies and pharmacies in ambulatory and hospital settings.

Regardless of the scale of production or the setting in which the ADD site operates, the ADD site must ensure that the quality, safety and efficacy of the medication dispensed into an ADD is maintained and meets the standards that can be achieved by adhering to the principles of GMP, GDP and the content of these guidelines. If an ADD site is a licensed manufacturer or distributor, GMP and, if applicable, GDP must be adhered to.

4. PERSONNEL AND TRAINING:

A. General: The responsible person at an ADD site must establish and maintain a system of quality assurance and ensure that the ADD facility operates according to appropriate standards. Successful operation of this system is dependent on qualified personnel carrying out the tasks for which the ADD site is responsible. An organisational chart for the ADD site should be in place and should contain clear definitions of roles, duties, responsibilities and job descriptions. Responsibilities should be clearly understood by individual staff members and documented. All personnel should be aware of the principles of the ADD guidelines, relevant GMP and GDP, and receive initial and continuing training, as 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: Every ADD site should have a designated pharmacist who is responsible for the management of all activities relating to the pharmaceutical process at the ADD site. The nominated responsible person must be a licensed/registered pharmacist in the country in which the ADD site is located. They should have sufficient knowledge of ADD standards, be available at the ADD site during all activities involved in dose dispensing and should supervise critical steps and take critical decisions personally. The responsible pharmacist should be notified to the relevant authority. A deputy should be designated and available in the absence of the responsible pharmacist.

The responsible pharmacist must ensure that medication is dose-dispensed in accordance with current

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 decisions must be taken by the responsible pharmacist personally.

The responsible pharmacist approves and ensures 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 medication 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, medeicinal products before dispensing, intermediate doses and dispensed ADD medication;
- Master validation of ADD orders and prescriptions (for suitability to be dose-dispensed for an individual patient) and of production and control equipment and related software;
- Contracts with external parties, clearly setting out responsibilities of the different parties;
- Authorisations to personnel, i.e. assignment of duties in line with expertise, qualifications and further education/training.

The above mentioned tasks of the responsible pharmacist cannot be delegated.

Furthermore, the responsible pharmacist is required to:

- ensure the correct implementation of the ADD orders/prescriptions and, where this is done automatically, approve the validation of the process;
- ensure that medicinal products for the ADD prescription/order are received, deblistered, dose dispensed, checked, controlled, released and supplied according to the appropriate standards and documentation;
- ensure that ADD prescriptions 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 (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 signed by the responsible pharmacist or deputy pharmacist before ADD medication is released;
- ensure premises and equipment are adequately maintained;
- ensure that the appropriate external and internal validations occur, including that all machines and software systems are validated;
- 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 certain tasks to other authorised personnel. However, only duties can be delegated – not responsibilities.

C. Training: The ADD site should provide training for all personnel involved in storage, warehousing, deblistering, dispensing, control and supply and those accessing those areas (including technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product. Training should be standardised for all 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 staff 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. Staff should be retrained at regular intervals, e.g. when a process changes or new training needs are identified, and at a minimum annually. 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 only 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 strongly-acting, infectious or sensitising substances are handled should receive specific training. Training for each individual assigned task is necessary and staff should pass a qualification test and be provided with written authorisation prior to commencing an activity. 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:

Pharmacist(s): Specific training on 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, and 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 of one direction flow, critical square area (only one medicine or label in a certain space) and double checks.

5. PREMISES AND EQUIPMENT:

A. General: Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. 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. It 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 the operations, presents minimal risk of causing contamination of materials or products. All fixtures and fittings must be suitable for the intended purpose, of sound construction and compliant with all health, safety and environmental requirements. The finish of all fixtures and fittings must be professional, complete and well maintained. All walls, floors, ceilings, plaster and paintwork must be safe, non-shedding, easily cleanable, and clean. All surfaces that come in 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 detailed 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 responsible pharmacist can 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 segregated 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 segregated 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, e.g. clothes, gloves, mouth masks, 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 and the external environment. During the deblistering and dispensing process, i.e. the intermediate 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 e.g. 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, de-blistered medicinal products, medicines in quarantine, released, rejected, returned or 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 the physical quarantine should provide equivalent security. Where quarantine status is ensured by labelling or storage in separate areas, the status must 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 must be in place for the safe and efficient operation of the ADD site, including deblistering apparatus, intermediate storage containers, medicine trays, opaque storage containers, ADD machine, checking machines (depending on scale of operation), protective equipment, cleaning equipment, information technology equipment and any other necessary equipment. 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 and validated procedures, and stored only in a clean and 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 of contamination. Equipment should not present any hazard to medicinal products. The parts of the production equipment that come in contact with medicinal products must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

Balances and measuring equipment of an appropriate range and precision should be available 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 at 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 entities are involved, the prescription is transferred into a medication order prior to dispensing and this order is transferred to the ADD site. In this instance a copy of the prescription should also be supplied.

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 and order for the ADD medication. A prescription which is valid for repeat dispensing should be returned to the patient/carer in line with the national legislation and practices.

Double checking of the prescription details against computerised systems, orders, the medicinal products and ADD patient labels should occur at relevant stages throughout the process, including at a minimum when prescription details are entered into the ADD site's computerised system and at the final dispensing stage where medicines are released.

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. 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 in order 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 the 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, e.g. supplier invoices. Such documentation should be retained. Records should be adequately detailed and/or 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 Medicinal Products Directive (2011/62/EU) all medicinal products with a bar code safety feature will have to be decommissioned (checked for authenticity) 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 counterfeit/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 counterfeit, 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, ADD dispensing, to the distribution of the finished dose dispensed medication to the patient. Relevant information, including the name and contact information for the patient, 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 must be unalterable, 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: It is recommended that national authorities require the inclusion of relevant data regarding the suitability of a medicinal product for use in ADD systems in a medicinal product's marketing authorisation data. 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 is available to make a suitability assessment and if it has been approved for this purpose by the responsible pharmacist. In general, solid single-dose 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.

The 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 must be based on a risk assessment performed by the ADD site. This risk assessment should assess the potential risks to the quality, safety and efficacy 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. Ph. Eur. (European Pharmacopoeia), BP (British Pharmacopoeia), USP (US Pharmacopoeia) or other reputable sources.

A more extensive risk assessment is required 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 individually with regard to:

- Chemical and physical properties of the active ingredients and/or the excipients;
- Manufacturing procedures;
- 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 adequate procedures 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 must 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: e.g. tablets that break or crumble easily, effervescent or dispersible tablets, sublingual or buccal tablets, hygroscopic and thermo or light sensitive tablets. Large tablets can't be included in some systems.
- Medicinal products with a high risk for cross-contamination: 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.
- Medicinal products that are not suitable 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:

- 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;
- Tablets used in ADD should be coated where possible.

All suitability assessments, precautionary measures, special instructions and decisions should be written 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 duration for the storage for medicinal products. All packaging materials used in ADD should be assessed for their suitability and released for use with specific ADD medication 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, at a minimum, 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 registered medicinal product(s). The purchase, handling and control of packaging materials must be carried out according to the ADD dispensing 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 require 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 procedure. This procedure must assess the impact of removing the medicine from its primary packaging on the quality, safety and efficacy of the medicinal product. Specifications for the storage conditions should ensure the quality and stability of a medicinal product is 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 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 must be taken to ensure that these medicinal products are stored under controlled conditions in accordance with the relevant specifications, e.g. temperature, humidity, 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. These products should also be removed from their primary packaging for the shortest time possible.

ADD dispensing and supply to patients should occur regularly and doses should not 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 and reflect patient need and the characteristics of the medicinal products involved. Weekly dispensing is recommended.

The maximum storage time for deblistered and ADD dispensed medicinal products should be set based on a documented quality risk assessment taking into account, at a minimum:

- 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.

Each medicine, including medicinal products stored after deblistering in containers for intermediate storage, in canisters in ADD machines and finished ADD dispensed doses, must 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 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. Medicinal products should not be used for ADD within the last month of the expiry date of the product.

D. Use of Multidose ADD Pouches/Containers: National authorities may provide recommendations on the 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 medicinal products, e.g. 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/pouch on the stability of these medicinal products. The responsible pharmacist at the ADD site should define the maximum length of time medicinal products should be packed together and what medicinal products should not be packed together. As a minimum, issues to be considered include cross-contamination, chemical and physical interactions, whether compatibility testing is necessary and if the medicinal products can be distinguished during the checking process (e.g. by colour, shape, size, inscription, markings or weight). Other factors 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/ label. 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 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, e.g. 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 must follow 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 the 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: Contamination of a packaging material or medicinal product by another material or product must be avoided. This risk of accidental cross-contamination mainly arises from the uncontrolled release of dust from materials and other medicinal products in 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. The use of coated medicinal products 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 before 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 an area 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, e.g. 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 must 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 is maintained within a specified range. Clean and properly labelled containers must be used for deblistered medicinal products. Only one type of label identification is 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 a person and a bar code check or by using another system which gives the same assurance. Deblistered medicinal products should be checked against their original packaging, using the “four eyes’ principle”. Records of the deblistering process should 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 by 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, e.g. use of an opaque container or desiccant. Temperature in the storage area should be controlled, monitored and recorded. Humidity should be monitored and recorded and if necessary controlled. 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, magnitude, inscription and colour, the accompanying patient information leaflet could be placed, in a hygienic way 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 must 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 at least the following points:

- Information on the ADD equipment;
- Preparation of ADD equipment;
- Detailed operating instructions;
- Instructions regarding storage and labelling;
- Any necessary precautionary measures.

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, e.g. monitoring and control of the temperature within the ADD machine. Each dose-dispensed medication should be traceable from 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/ pouch containing the dose-dispensed medication. It is recommended that in-process checks be made 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 in large scale ADD sites. If automated checking is not available, the ADD medication must be checked visually. Double checking should always occur and can comprise of an automated/visual or visual/visual double check. Checking must 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 the 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 and prescription/order. The dose dispensed medication is either released for supply or rejected. The rejected medication must be removed from the area and quarantined pending correction or disposal, e.g. 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 in-house limits for errors and corrections. Rejected medication 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 must 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: In ambulatory/primary care settings, the following information should be 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 instuctions as applicable;
- Date of dispensing/Expiry date of the medication/Date and time of medication use;
- Identification or batch number or electronic code to ensure full traceability.

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

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 address and if applicable or used as an identifier, their date of birth, insurance number**,** distribution group and any associated pharmacy. Other information that can either be printed on the 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 to 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 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 their medication 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 can only be authorised by a pharmacist – either the responsible pharmacist or a deputy pharmacist.

J. Validation: When new equipment, machines or information technology systems are introduced at the ADD site, they should be validated regarding their suitability for use. 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 DQ, IQ, OQ and PQ (Design Qualification, Installation Qualification, Operation Qualification and Performance Qualification) as required. The process when validated should produce a product which consistently meets the required quality.

Information technology systems or materials, which may affect ADD quality and/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 revalidated. Validated cleaning methods should be used on critical surfaces of equipment, 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 medicines 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 changes 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, patients or carers from ADD sites. In some circumstances pharmacists may supply ADD medication directly to patients/carers; in these circumstances the relevant elements of GDP required to maintain the quality of the medicinal products supplied should be adhered to.

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 within a satisfactory time period.

The following minimum written information should be provided with ADD medication delivery dockets:

- Date of delivery;
- Quantity delivered;
- Name and address of the ADD site;
- Name and address of the patients;
- 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 must 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 must be packed, transported and distributed in such a way that their integrity, quality, safety and efficacy are preserved. The transport containers should be packed so that the packaged products are not damaged during packaging or transportation. The distribution method must be secure and medicinal products must be sealed in tamperproof containers. The containers used in transportation should be cleaned as often as necessary. There should be a system (i.e. barcode or equivalent) in place to track the delivery. Distribution processes should be checked and checks recorded.

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

The distributer should inform the ADD site immediately if any delivery is missing, or of any deviation during the 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 and tracing system 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 sealed or locked containers. 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. The ADD site should accept the return of unused ADD medication.

Waste medication, e.g. expired, damaged or returned medication, must never be reused and should be handled and stored separately from ADD medication stock. Waste medication should be clearly labelled and stored in quarantine under the control of the responsible pharmacist. This will prevent unauthorised access. Waste should be processed promptly into medicinal product waste bins, sealed when full and destroyed, via controlled procedures in accordance with local/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 must ensure that ADD medicines dispensed are suitable for use, comply with requirements and do not pose risks to patient safety and treatment efficacy. ADD sites must 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 or distributor, 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 principles of GMP and the content of these guidelines and, if distribution occurs, GDP. Irrespective of the scale or setting, the quality management system must ensure that the quality, safety and efficacy of the ADD medicines dispensed are 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 for 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 lies with the responsible pharmacist.

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

Personnel matters, premises, equipment, documentation, production, quality control, distribution of the 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 the deviation established, 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 least on an annual basis, or more frequently in the case of ADD of 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. Pharmacovigilance and Safety System and Data Collection: A specific pharmacovigilance and safety system for reporting ADD errors, incidents and adverse effects should be established. The system should be coordinated across Europe and encourage the sharing and analysis of data and comparison of the rate of errors, incidents and adverse effects with traditional dispensing.

Bar code 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 this data (anonymised) is encouraged but must occur in accordance with data protection provisions.

12. DOCUMENTATION: POLICIES, PROCEDURES AND DATA COLLECTION

A. General: Good documentation constitutes an essential part of the quality assurance system and is a key element of compliance with GMP, GDP and these ADD Guidelines. 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 on 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 these ADD guidelines and relevant GMP and GDP:

- 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 date 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: 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 non-conformances.
- 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;
- Contracts with suppliers and consignees (pharmacies, residential care settings, patients etc.), as applicable;
- Data protection;
- Distribution of ADD medication;
- Waste management;
- Internal quality/GMP and ADD guideline compliance audits.

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, e.g. 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 maintain the following records:
- A copy of ADD prescriptions/orders (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 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 impact on the quality, safety or efficacy 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, and if applicable the associated pharmacy (or similar), should maintain records of patient

suitability assessments and patient consent. The ADD site, or if applicable the associated pharmacy (depending on the contracts in place), should maintain records of medication therapy reviews and counselling. Records of contracts with relevant healthcare 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, 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 ACTIVITES 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 must 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 must 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 Prescription/Order: ADD is carried out in various settings in Europe. ADD medication is prepared in manufacturers, companies and large and small scale hospital and community pharmacies and supplied in ambulatory and in-patient short and long term care.[6]

An order/request for medication to be dispensed via ADD can be made by:

- the treating physician (health professional with prescribing authority), or
- the patient/carer, or
- a care institution for a patient who has been prescribed the medication.

The treating physician can request that a patient's prescribed medication be dispensed via ADD. This should occur following a patient suitability assessment involving all members of the healthcare team and the patient/carer. Alternatively, the medical prescription(s) may be transcribed into an ADD order, via a medication plan upon the request of the patient or a care institution on the basis of a patient suitability assessment. The medication plan forming the basis of an ADD order should be based on a valid prescription by a physician or other authorised healthcare professional with access to patient medical records. Additionally, pharmacists may decide ADD is the most suitable method of providing medication to certain patients on the basis of a patient suitability assessment conducted in consultation with the treating physician and the patient/carer.

[6] Refer to Section 3.C Setting.

Not all of these mechanisms of requesting ADD medicines are permitted in all European countries. It is recommended that national authorities determine how prescriptions/ADD requests should be received/managed and, if applicable, how prescriptions/orders should be transcribed into a medication plan prior to forwarding an order to the ADD site. The original prescription or an authorised copy of the prescription should be supplied to the ADD site where more than one entity is involved in the supply. It should detail the intention of the prescriber/healthcare team to have the patient's medication dispensed via ADD.

B. Responsibility for Patient Care: Responsibility must be assigned in accordance with national regulations and standards. However, in many countries these responsibilities haven't 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. Patients should always receive their medication from the same pharmacy and should be managed by a healthcare team, which involves the same medical practitioner (or team of medical practitioners) and pharmacist (or pharmacy) for each dispensing, review and assessment.

Because ADD occurs in various settings in different European countries[13], 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 Entity: Where ADD and supply of medication to a patient/carer occurs in one entity, 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, for example assessing the suitability of a medicine for inclusion in ADD.
- The pharmacist is also responsible for patient care, including:
    - patient suitability assessments,
    - ensuring patient consent has been obtained,
    - the review of medication therapy, and
    - the provision of patient information and counselling.

Two Entities: Where the ADD service and supply of medication to the patient and/or the patient care services are provided by two entities, such as a company, manufacturer or pharmacy 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. This varies depending on the country of operation. In some 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 two entities, unless responsibilities have been decided by national legislation or standards, responsibilities for the different elements of patient care are established and documented in a service provision contract. It is important that the contract outlines the patient care responsibilities of each entity.

C. Healthcare Team: An ADD healthcare team should be established to ensure the patient-centric care of ADD patients. The team has responsibility for patient care and assessing the appropriateness of the use of ADD for each patient. This team should include the prescriber, who has knowledge of the patient's medical and care status and access to the patient's medical records, and the pharmacist, with their medicinal product knowledge and responsibility for reviewing prescriptions for therapeutic appropriateness and counselling. Other healthcare professionals, e.g. nurses where patients are in a care setting, and the patient themselves, are also integral members of the team. 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.

Unless responsibilities of each member of the healthcare team 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 clearly established within each team.

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

15. PATIENT SUITABILITY:

A. General: Dose dispensing systems do not provide benefits for all patients; therefore 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 the healthcare team, concluding 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 confused patients who are managed by a carer. They are unsuitable for use by those whose medication regimen is unstable and subject to frequent changes.

Prior to the provision of a dose dispensed system to a patient, alternative adherence supports should be considered, including:

- 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 supports will improve adherence and the likelihood 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. 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 a suitable intervention:

- Where other simple adherence supports (as outlined above) will achieve the same levels of adherence;

- For intentional non-adherence: if a patient doesn't want to take their medication, discussing and addressing the reason for non-adherence is the correct approach;
- For convenience purposes: 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 other adherence supports 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 on a lot of medication, who find it difficult to manage taking the right medicines at the right times;
- For confused patients if they are managed by a carer. 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 the 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;
- As a minimum, at yearly 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 all 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: The healthcare team 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 out of the use of the medicinal products. Both general and ADD specific patient care elements are to 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 if patients are taking medicines that may not be suitable for inclusion in a dose-dispensing system, e.g. 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 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 no regular structured medication reviews include:

- The continuation of medication that is no longer needed or 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 communications/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 medicinal products supplied, 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 medication 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 Summary of Product Characteristics for the medicinal product concerned.

It is important to ensure that patients and their carers are provided with or have access to the 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 supports that may be used in conjunction with the ADD system should be provided if such aids are available, 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: ADD should be 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 information to patients.

18. DOCUMENTATION AND RECORDS:

There should be documents (policies, procedures, specifications) and records in place for the following patient care processes:

- Obtaining informed patient consent;
- Patient suitability assessments and reassessments;
- Prescription/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 entities are involved some records should be maintained at both entities, for example, prescriptions and contracts. All records should be maintained for five years. Copies of relevant records including patient suitability assessments, medication reviews and patient consents should be provided to patients.

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