European Association of Hospital Pharmacists (EAHP) Guidance on the Pharmacy Handling of Gene Medicines

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Introduction

The European Association of Hospital Pharmacists (EAHP) guidance for the handling of gene medicines specifies the requirements for each step in the process from storage, dispensing and administration to the disposal of all materials involved in handling such therapeutic agents. The guidance is based on the available evidence as well as practical experience, and is presented as the minimal requirements that are essential in any hospital pharmacy where a gene medicine will be used. For the purposes of clarity, the guidance is restricted to the use of licensed gene medicines involving genetically modified organisms (GMOs), including viral vectors that would be considered a level 1 or 2 biosafety hazard within Europe, and registered as approved for use within Europe. The guidance was developed by a consensus group of experts in pharmacy handling and dispensing of gene medicines from across Europe. During a series of meetings, the members reviewed key areas relevant to the handling of gene medicines and considered the strength of evidence for, and the practical implications of, the guidance generated. The recommendations were developed with extensive feedback from all the participants and were subsequently validated and approved by external experts – either pharmacists or biological safety officers. The guidance is presented herein and covers the storage, transportation, preparation, dispensing, administration and disposal of gene medicines, as well as decontamination and accidental exposure procedures for these agents.

Overview of the guidance development process

This guidance provides practical recommendations on the handling of gene medicines in Europe. A steering committee of representatives from the European Association of Hospital Pharmacists, representing Austria, the Czech Republic, Finland, Germany, the Netherlands, Spain, Sweden and the United Kingdom, led the development of this pharmacy guidance.

In order to ensure the quality of the current document, the criteria set out in the Appraisal of Guidelines for Research (AGREE) (1) were followed. These specify:

- **clear definition:** of the question that the guidance aims to address, the objectives of the guidance and the audience to whom the guidance is directed
- **rigour of development:** based on the strength of the evidence, expert judgment, and review by external experts prior to publication
- **clarity:** specific, unambiguous recommendations, clearly presented
- **applicability:** guidance developed with consideration of the potential for implementation
- **editorial independence:** all conflicts of interest disclosed.

The development process began with identification of ten European Association of Hospital Pharmacists (EAHP) members from eight EU countries who formed the Working Group for the Development of EAHP Guidance on the Pharmacy Handling of Gene Medicines. All ten representative members were locally recognised as gene medicine specialist pharmacists. Existing guidance on the handling of gene medicines was evaluated following a literature review of previously available recommendations, and evidence tables were created and sent to all members. Members of the working group completed a pre-meeting survey on the handling of gene medicines in their country/hospital pharmacy. This allowed an initial evaluation of the evidence to date, as well as providing an indication of current practices across Europe. Initial drafting of the guidance took place after the first meeting of the working group, and several subsequent drafts were produced, incorporating comprehensive review and input from all members of the working group. A series of meetings were held to discuss

the guidance and revise the text. Review of the current guidance was carried out by three external experts: Professor Gavin Brooks, School of Pharmacy, University of Reading, UK; Dr Marion Watson, Biological Safety Officer, Oxford Radcliffe Hospitals NHS Trust, UK; V'Iain Fenton-May, Pharmacy Department, University Hospital of Wales, Cardiff, UK.

Aims, scope and target of the guidance

Centres that already have a dedicated gene medicine suite are in the best position to prepare safely and administer gene medicines. However, as that will not always be the case, the current guidance aims to provide broad, practical recommendations for the handling of licensed gene medicines in clinical practice within Europe. It encompasses recommendations for all steps within the clinical setting, including storage, transportation, preparation, dispensing, administration, waste disposal, decontamination and accidental exposure.

The World Health Organization (WHO) defines gene therapy as 'the introduction of genetic material into an individual, or the modification of the individual's genetic material, in order to achieve a therapeutic objective' (2). The Health and Safety Executive (HSE) in the UK defines a genetically modified organism (GMO) as an organism (with the exception of humans) in which 'the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination using recombinant nucleic-acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic-acid molecules, produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation' (3).

In this document, the term 'gene medicine' is used to describe any therapeutic agent that meets the above descriptions, and involves the use of a licensed GMO for use in humans.

For the purposes of clarity, the guidance is restricted to the use of gene medicines involving a viral vector that would be considered a biosafety level 1 or 2 (4) within Europe. It also relates to the handling of a licensed medicine, and should be used in conjunction with the advice included in the European Medicines Agency (EMEA)-approved summary of product characteristics (SPC). According to the Centers for Disease Control (CDC), biosafety level 1 involves well-characterised agents not known to cause consistently disease in healthy adult humans, and of minimal potential hazard. Biosafety level 2 involves agents of moderate potential hazard. Biosafety level 3 is applicable to indigenous or exotic agents that may cause serious or potentially lethal disease as a result of exposure by the inhalation route. Biosafety level 4 refers to dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease (4). According to the HSE guidance in the UK, most activities with adeno-associated viruses (AAVs) can take place safely at containment level 1. Containment level 2 should be adopted as a minimum requirement for conditionally replicating virus vectors, unless the risk assessment or safety data show that this is unwarranted. It is important to note that biosafety level classifications are not consistent across Europe. Some guidance in the UK has separated the requirement for gene medicines specified as a biosafety level 1 versus 2 agent – we include a table for information; see Appendix 1.

The guidance is relevant to all staff involved at any stage of the handling of a gene medicine. In most situations, the staff will be pharmacists or skilled pharmacy technicians who are specialists in handling such agents; however, the guidance has been developed with consideration to informing physicians, theatre and ward nursing staff, biosafety/infection control officers, occupational health representatives and the cleaning and waste disposal staff in a manner that is relevant to their roles. The guidance is presented in the form of tables and flowcharts that detail the recommended steps and procedures for each stage of the handling of a gene medicine, from the time it arrives at the clinical facility until it is discarded. Before initiation of any treatment with a gene medicine, the product label or SPC must be consulted and it must be ensured that all practices comply with national legislation. For example, there may be a requirement to notify local health and safety or governance departments at the facility or a national environmental institute about the use and handling of these medicines. Procedures must be in place locally to ensure that the pharmacists are aware of the current status of national legislation on this topic.

Need for guidance on the handling of gene medicines

Gene medicines for a variety of medical conditions are currently under investigation. Although many approaches to gene delivery have been attempted, viral vectors, including adenoviral vectors, retroviral vectors, AAV vectors and pox virus vectors, have predominated (5). Due to the nature of the viral vectors used in gene medicines, special consideration is necessary for their handling as biological agents in the clinical setting, as is the case for other infectious agents such as Bacillus Calmette-Guérin (BCG).

Procedures for handling gene medicines in hospital pharmacies are similar to those already in place for handling hazardous substances such as cytotoxic agents, and other preparations such as BCG. BCG is used for the treatment of superficial bladder cancer (6). As BCG contains live, attenuated mycobacteria, care must be taken in the preparation, handling, administration and disposal of this treatment. Persons handling the product should be masked and gloved. All disposable equipment and materials used for preparation and administration should be handled as biohazardous waste (6, 7). It is important to bear in mind that the hazards presented by gene medicines in a clinical setting are likely to be less than those posed by other infectious organisms that are commonly encountered in hospitals. In addition, there are a number of similarities in the precautions taken in the handling of gene medicines and cytotoxic agents. In the handling of cytotoxic agents, consideration must be given to the appropriate protective clothing to be worn at all times and an appropriate biosafety device is always used for preparation. Additionally, many of the same precautions are taken to clear up accidental spillages and disposal of waste products (8, 9). Thus, the handling of these gene medicines should be appropriate to the potential risk.

Review of existing guidance

To date, there has been little published

guidance on the pharmacy handling of gene medicines in clinical facilities. Guidance available to date mainly focuses on the use of such agents in a research setting. For example, the Gene Therapy Advisory Committee (GTAC) is the UK national research ethics committee for gene therapy clinical research, and has defined guidance according to the Medicines for Human Use (Clinical Trials) Regulations 2004 (10). In the absence of international guidance, each clinical facility or institute has developed its own standards of practice based on existing guidance and within the legislation of their own country (11, 12). This European-wide guidance seeks to achieve unity among local equivalents. European regulations related to this topic were also taken into consideration in the development of this guidance (13, 14). Although mainly directed to the laboratory use of biosafety level 1 or 2 agents, a number of key points are worth mentioning. The EU Council Directive 98/81/EC states that it is not necessary when dealing with these lower-risk agents to use an isolated laboratory suite or entry to the laboratory via an airlock (i.e. entry via a chamber isolated from the laboratory, where the clean side of the airlock is separated from the restricted side by changing or showering facilities). In addition, the facility does not require negative pressure relative to the pressure of the immediate environment or high-efficiency particulate air (HEPA) filtering of the extract and input air. However, access to the area where the gene medicine is being handled should be restricted and measures should be taken to minimise aerosol formation (13, 14).

A number of UK-based recommendations are also available (15), and the application of these in terms of standard operating procedures (SOPs) has also been demonstrated (16). The most recent guidance on this topic has been issued by the HSE in the UK (17), and the EAHP guidance presented herein is consistent with this guidance. Interestingly, the HSE provides guidance on the practical measures that are required for level 1 and level 2 containment, respectively (see Appendix 1). Previously available UK and European guidance is also consistent with that published in the US (18).

Standard operating procedures for handling gene medicines in hospital pharmacy

The SOPs for each step are outlined in the tables and charts that follow. All key information necessary for each procedure is included in the tables and charts and their associated footnotes, with additional information and points for consideration discussed in the text.

Table 1: General guidance regarding the handling of gene medicines and associated patient specimens

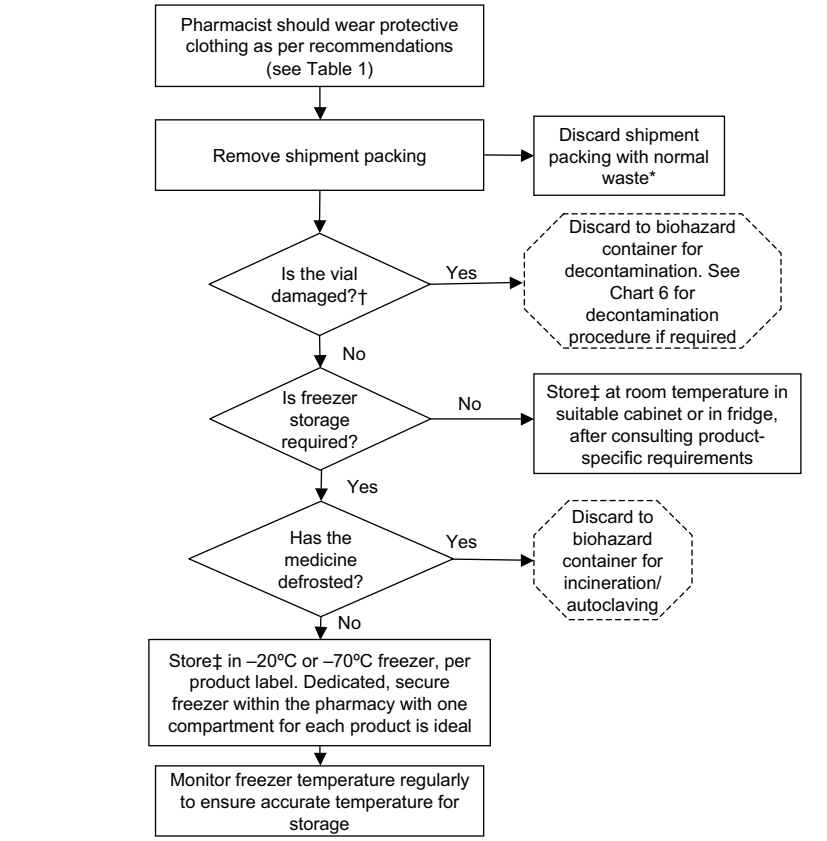
Universal precautions must be observed in the handling of gene medicines, clinical specimens (patient blood, tissue, body fluids) and materials or equipment contaminated by these substances following treatment.	
Wear suitable protective clothing to minimise the risk of microbiological contamination of the therapeutic agent during preparation. The clothing (see right-hand box) and its quality should be appropriate to protect the therapeutic agent from contamination	Ideally disposable apron or gown (or lab coat)* Safety glasses (or goggles) Gloves Mucous membrane splash protector
Use of a biological safety cabinet or pharmaceutical grade isolator (compliant with European standard EN 12469:2000) - dispensation and preparation of gene medicines (minimum class II, type B)	See Chart 2
Needles and sharps: take adequate precaution with use and disposal	See Chart 5
Ensure decontamination of work surface areas	See Chart 2
Clean/decontaminate patient bedding according to procedures used for blood- or body-fluid-soiled laundry*	See Chart 5 Specific isolation wards are not required
No special precautions for patient elimination of stools or urine, unless specified in the SPC for product-specific information	Patients may use normal bathroom facilities unless advised otherwise
Transport and storage of patient specimens must be in a closed, labelled leak-proof container	See Table 2
Disposal of products, contaminated waste (e.g. gloves, gowns, etc.) and patient specimens must follow the local procedures of the institution for decontamination	Materials to be decontaminated outside the immediate area should be placed in a robust, leak-proof container and closed for transport from the area (contaminated waste disposal). See Chart 5
*Disposable laundry is preferred unless there is solid evidence that the vector is not being shed.	

Patient care and handling of gene medicines and patient specimens

General guidance regarding the handling of gene medicines and associated patient specimens is detailed in Table 1. This guidance focuses on the minimum requirements (although these may vary between countries, making it essential to consider local regulations). Depending on the class of agent, it is recommended that all personnel involved in handling gene medicines, at any stage, should be dressed in appropriate protective clothing. For class 1, use universal precautions unless risk assessment specifies class 2 precautions; for class 2, always wear protective clothing. For further specifications, see Appendix 1. It should be noted that the quality of protective clothing will differ, depending on the activity; for example, when the gene medicine is delivered on site for storage or when the gene medicine is prepared. The protective clothing and its quality should be appropriate to the process and the grade of the working area in the pharmacy. During the preparation of gene medicine, the protective clothing should be worn in such a way as to protect the therapeutic agent from contamination, as well as to protect the pharmacist or pharmacy technician from the therapeutic agent. A biological safety device, either a biological safety cabinet or a pharmaceutical grade isolator, should be used for dispensing and preparing gene medicines. The minimum requirement should be a class II, type B device (compliant with European standard EN 12469:2000) that removes air to the outside.

Adequate precautions need to be in place for needles and sharps decontamination and procedures for the decontamination of work surfaces should be in place before the decision is made to initiate treatment with a gene medicine. After administration, it is not necessary for all patient samples to be labelled as biohazard; for example, a biohazard label will not be necessary for patient samples where a gene medicine that is a biosafety level 1 agent has been administered. Cleaning and decontamination of patient laundry for inpatient/day-case patients should be carried out according to the defined procedures for blood- or body-fluid-soiled laundry unless there is data to show that the subject is not shedding viruses. In general, no specific precautions will be required for elimination of

Chart 1: Storage of gene medicines



patient stools or urine; however, the product-specific information in the label or SPC should always be consulted. In general, it is recommended that institutions deal with samples from patients who have received gene medicines in a similar way to handling of samples from patients with infectious diseases, following consultation with a multidisciplinary team. Transport and storage of patient specimens should always be in a closed, labelled, leak-proof container. Disposal of waste should follow the local procedures of the institution with regard to autoclaving, heat inactivation or incineration but should ensure decontamination of any remaining gene medicine.

Storage of gene medicines

Procedures for the storage of gene medicines are outlined in Chart 1. The pharmacy staff should always wear disposable protective clothing when removing the gene medicine from the container in which it is delivered, in case the packaging has been damaged during transit. Shipment packaging should be removed before storage but the primary package should only be opened in a biosafety cabinet. If the vial containing the gene medicine is damaged, it must be discarded to a biohazard container for safe disposal. Consult the product-specific requirements for storage temperature, then store in a suitable cabinet at room temperature, in the fridge or in the freezer. Where –20ºC or –70ºC freezer storage is required, it is ideal, and recommended, for gene medicines to be stored in a secure freezer within the pharmacy, which is temperature monitored and alarmed. Each gene medicine should ideally be contained on a separate shelf within the secure freezer, and personnel should have restricted access. However, it is recognised that it is not always possible to have storage facilities within the pharmacy. When stored outside the pharmacy, alternative locations must be inaccessible to unauthorised personnel and should not pose a risk of undue exposure. Other staff members should be informed of its location; for example, the physician and nurse. The person(s) responsible for such a freezer must be given instructions for handling the gene medicine, or alerting an appropriate person, in the event of freezer failure.

Preparation of gene medicines

Preparation of gene medicines should be conducted within an appropriate biological safety device as they may result in the generation of aerosols. An appropriate biological safety device would be a pharmaceutical-grade isolator or biological safety cabinet of minimum class II, type B that complies with CDC criteria (19) and latest European standards (EN 12469:2000) (see Chart 2). The biological safety device should not recirculate the air into the room; it should have an exhaust to the outside. Negative pressure is only essential if the risk assessment for a particular gene medicine states that it is required. Ultimately, a key consideration in selection of the biological safety device is to prevent cross-contamination. A biohazard sign should be posted on the outside of the door when a biosafety level 2 agent is being handled. With the correct procedures in place and when using a validated biological safety device, simultaneous preparations theoretically could take place in other biological safety devices within the same room, if there is no risk of cross-contamination. However, we recommend that when undertaking such work, if there is more than one cabinet in a room, only one should be used at any time, and separated from subsequent use by a time window per appropriate instructions for the product. As with all drug preparations, first check the availability and suitability of all materials required – plastic containers, needles, labels, etc – and the dose and expiry date of the gene medicine. Consideration should be given to the shelf life of the particular therapeutic agent, as preparation may need to be conducted quickly. All equipment that is used in the biological safety device (biological safety cabinet or pharmaceutical-grade isolator) must be sterile – it is recommended that all

Chart 2: Preparation of gene medicines and decontamination of biological safety devices used for gene medicine procedures

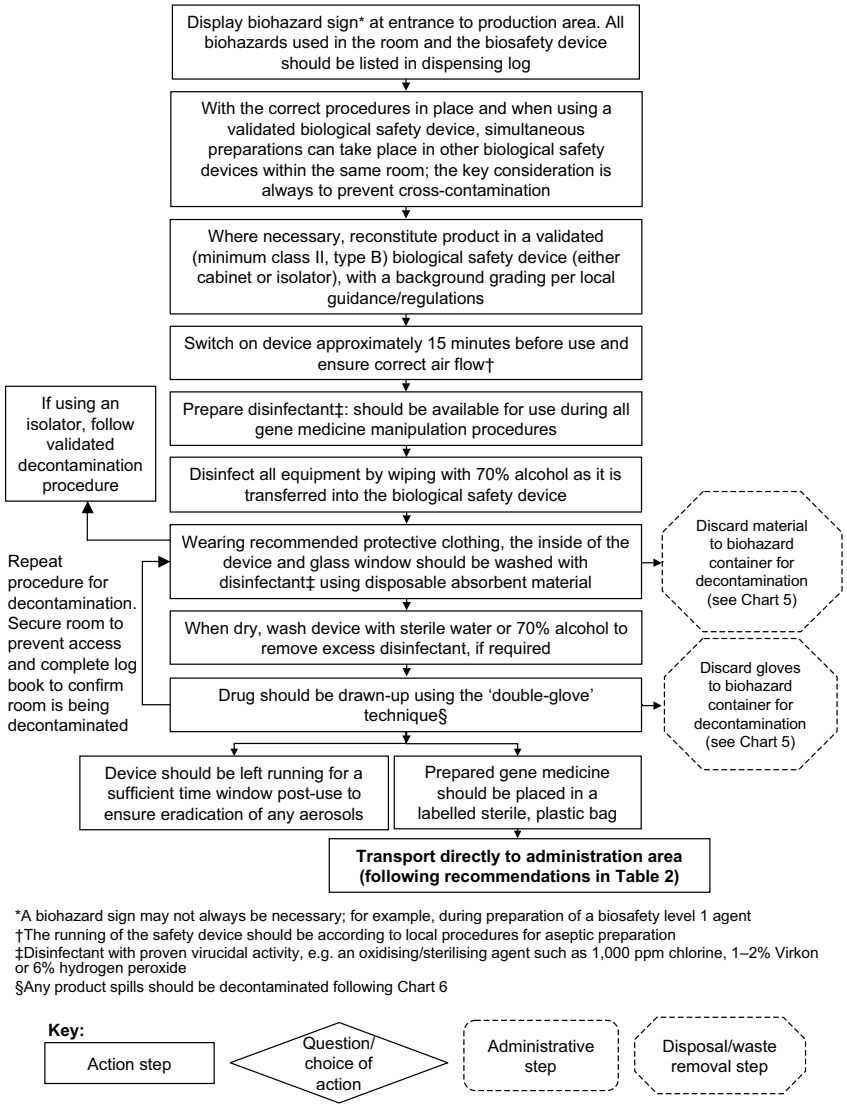


Table 2: Transportation of gene medicines

Transportation
Prepared gene medicine should be transported around the hospital in a leak-proof biohazard container, sealed in a plastic bag or other secondary container, following the guidance for the individual therapeutic agent with regard to temperature control. Transport kit should be marked on the outside showing that hazardous material is being transported.

Spill kit

Spill kit should be transported with the gene medicine so it is available at all times in case of accidental spillage. However, an alternative would be to have separate kits available at each location during the process (see Chart 6 for further details).

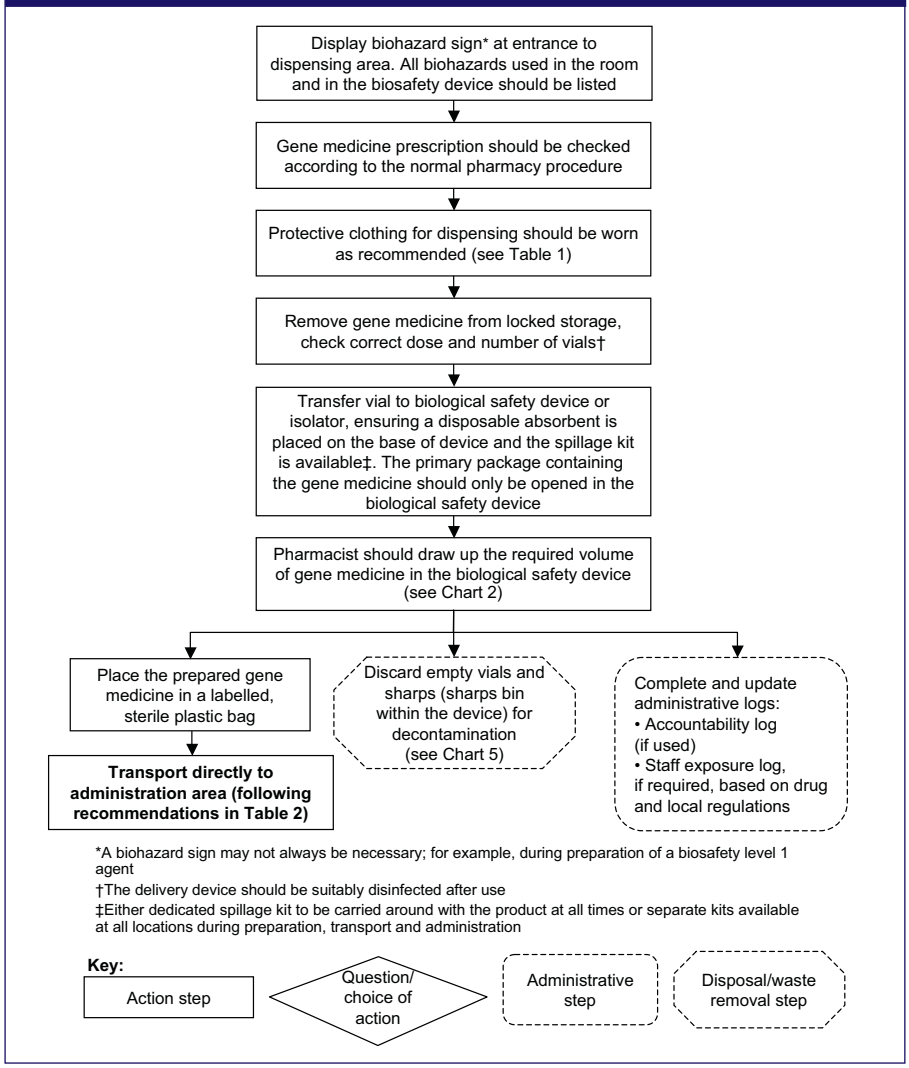
Minimum contents of spill kit:	
2 x disposable gowns or arm covers	2 x disinfectant sachets (or other prepared disinfectant)
4 x gloves	Absorbent paper towels
2 x masks	2 x disposable forceps
2 x aprons	2 x biohazard incineration bags
2 x goggles	Emergency contact number
4 x disposable shoe covers	Copy of spillage procedure

Administration
Gene medicine should be used immediately (best practice). Storage at administration site should be avoided to keep the number of places that are exposed to a minimum. This, of course, will be dependent on stability data for individual therapeutic agents (see Chart 4 for further details).

NB: Leak-proof biohazard container can be re-used following immersion in disinfectant and decontamination.

equipment is wiped with 70% alcohol as it is transferred into the device, and then allowed to dry prior to use; the process should be validated according to local procedures. An appropriate disinfectant must be prepared and available during all procedures involving the gene medicine. This includes having the disinfectant available in the biological safety device during the dispensing process, in case of any spillage. There is a need for solid, validated evidence for a range of disinfectants and procedures; however, in the absence of published data, the experience of this working group suggests that 1,000 ppm chlorine, 1–2% Virkon or 6% hydrogen peroxide are appropriate options. In all cases, the disinfection process should be selected based on product-specific data, which should be obtained from the manufacturer of the product in the SPC. It is recommended that a log book be kept in the room that is used for the preparation of gene medicines. This can be used by the person responsible for decontamination to confirm that the biological safety device is undergoing sanitisation, and serves to inform other members of staff. The device should be left running for a length of time post-use to ensure eradication of any aerosols that have formed; however, surface decontamination must subsequently be conducted. Current practices in the EU for post-use running of the device vary between 15 minutes and 8 hours, and again there is a dearth of published evidence for an exact timeframe under the conditions of a biological safety device. Some evidence in other laboratory conditions suggest that a short time window (15 minutes to 1 hour) may be sufficient (20–22); however, these conditions cannot be assumed to reflect those of a biological safety device. A key consideration is that the time window selected should be sufficient to ensure eradication of any aerosols. In general, between 15 minutes and 1 hour is sufficient; however, reference to specific timelines defined in the SPC should be sought to clarify for individual products. As with all medicine preparations, timing and planning are key considerations in the preparation of gene medicines. It is essential to coordinate preparation with the administration schedule so that defrosting and manipulation can be completed in a timely manner. This serves to reduce waiting time as well as to prevent the need for storage of a gene medicine at the administration site.

Chart 3: Dispensing procedure for gene medicines



Transportation of gene medicines

Gene medicines should be transported around the clinical facility as outlined in Table 2. Once prepared, the gene medicine should be carried around the hospital in a leak-proof, labelled biohazard container, sealed in a plastic bag or other secondary container, following the guidance for the individual therapeutic agent with regard to temperature control. A spill kit should be available at all times, either one spill kit carried with the gene medicine or multiple kits available along the way (see Chart 6 for further details). Ideally, the gene medicine will be used immediately, rather than using a second storage area at the place of administration (see Chart 4 for further details).

Dispensing gene medicines

General recommendations for dispensing gene medicines are given in Chart 3. All prescriptions should be checked based on normal pharmacy procedure. Wearing appropriate protective clothing, the gene medicine should be transferred to the biological safety device, ensuring that a disposable absorbent is placed on the base of the device and a spillage kit is available. As soon as possible following removal from its locked storage, the gene medicine should be transferred to the biological safety device and the pharmacist should dispense according to requirements and the product-specific label. Once drawn up by skilled pharmacy staff, the prepared gene medicine should be placed in a plastic bag (sterile bag if syringes are required to be sterile prior to administration) for transport to the site of administration as soon as possible and in accordance with the guidance in Table 2. It is not essential that the gene medicine is transported in a secondary sterile bag, as long as it is transported in a secure manner with at least two layers. The empty vials and sharps should be discarded for decontamination. The end-user must be notified if they need to wear appropriate clothing before handling a gene medicine.

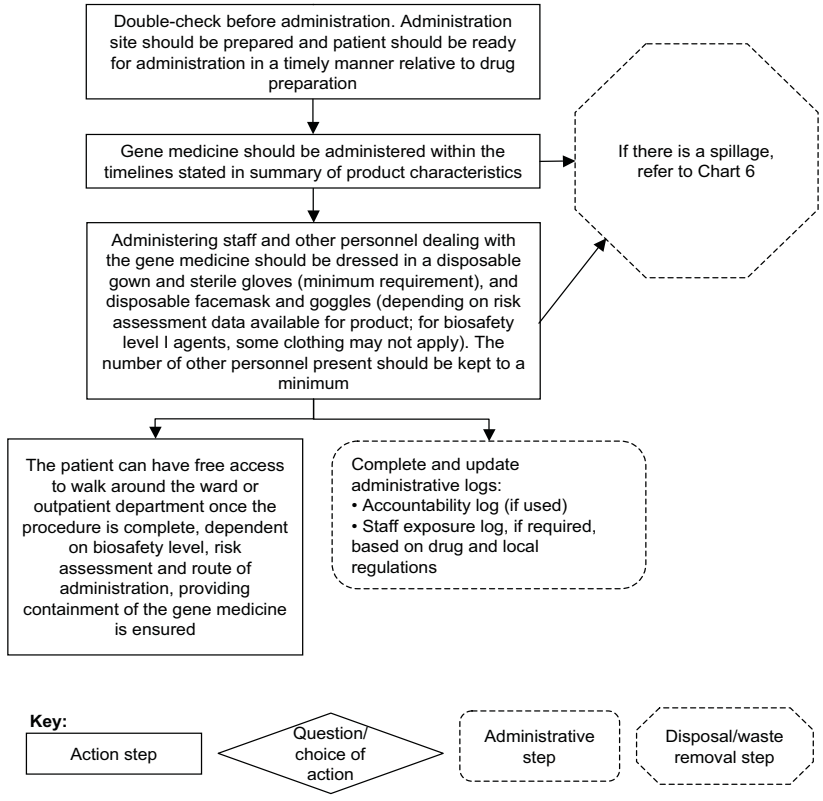
A number of important administrative tasks should be completed following dispensing. An accountability log can be a useful document for tracing steps in the handling of a gene medicine, where necessary. This is optional for standard treatments once they become available and widely used in practice. Staff exposure logs are also recommended, although not mandatory, as exposure will be wider than the pharmacy and will include nurses, doctors and other staff members. There is no requirement for health surveillance but, for gene medicines that are a biosafety level 2 or above, there may be a requirement to do so under the Control of Substances Hazardous to Health (COSHH).

Therefore, the decision as to whether a staff exposure log will be created should be based on the drug being used and local regulations; the log should be held centrally, for example by the occupational health department, and should be retained for a timeframe consistent with local regulations. Where there is a possibility that individual staff could be at increased risk, they must be given sufficient information to self-assess that risk and be provided with the opportunity to talk to an occupational health professional in confidence. Such cases might include pregnant or immuno-compromised staff, or staff with persistent infections related to the virus used to generate the gene medicine, e.g. a herpes simplex virus (HSV)-derived gene medicine and staff with an active herpetic cold sore.

Administration of gene medicines: guidance for clinical staff to generate standard operating procedures

Chart 4 outlines some broad guidance regarding the administration of a gene medicine that clinical staff can use and expand for generation of their own SOPs. As already discussed, preparation for administration should be coordinated between the pharmacy and medical/clinical/surgical staff in order to prevent the need for storage at the administration site. Timing and coordination between the teams are essential in this process and, ideally, the administration site should be prepared and ready in a timely

Chart 4: Administration procedure for gene medicines: Guidance for clinical staff to develop SOPs



manner to coincide with the gene medicine preparation.

Gene medicine waste disposal

All waste products involved in all stages of the handling of a gene medicine must be disposed of using the correct procedures outlined in Chart 5. The key consideration in the waste disposal process is to limit contact with the environment and people. All disposable materials used in the procedures should be disposed of as in Chart 5 as soon as possible. Non-disposable items must be cleaned with an appropriate disinfectant. It is important to note that, depending on country regulations, it may be necessary to autoclave waste before incineration for gene medicines of a certain biosafety level. However, there may be circumstances when this is not feasible and, therefore, best practice would be to remove the waste for incineration. All waste must be labelled appropriately in a plastic container for transport. Additional consideration should be given to whether contractors who may be involved in handling waste need a special licence; again, this will depend on local regulations. Pharmacists involved in the

Table 3: Model for roles and responsibilities for handling gene medicines

Handling stage	Chief pharmacist	Pharmacy staff	Physician	Theatre / ward nurse	Biosafety officer**/ hospital hygiene / infection control	Occupational health	Cleaners	Porters	Waste services
Initiation of gene medicine treatment and setting up conditions, including environmental considerations	CI	CI	R	CI	CI	CI	CI	I	CI
Assessment: ability to handle, staff training*	R	S	RA		RS	S			
Screening gene medicine prescriptions (patient basis)	R	RS	AC	CI	†	†			
Reception of gene medicine from the manufacturer and inspection	R	S	CI	CI	†	†			
Transportation	RA	S	IC	IC	SC	C		I	
Storage	R	S			SC	†			
Preparation and decontamination of biological safety device (biological safety cabinet or pharmaceutical-grade isolator)	R	SI			SC				
Dispensing	RA	S							
Administration (product-dependent)			R	RS					
Waste disposal	R	S	R	R	SC		S	S	S
Decontamination of gene medicine spills	R‡	R‡S	R‡	R‡	CIA	IC	SI		
Accidental exposure	R‡	R‡	R‡I	R‡I	CIA	IC			

R = responsible person; A = person to whom 'R' is accountable; S = can be supportive; C = should be consulted; I = should be informed

* Training will be limited to pharmacy training for pharmacists
**In organisations where there is no appointed biosafety/infection control officer, the responsibilities should be taken by a member of the infection control body
† Inform once at start of process when conditions for use of gene medicine are being established
‡ The person who spilled the gene medicine, or was accidentally exposed, should be responsible for initiating the decontamination. Ultimate responsibility for ensuring the spill is appropriately decontaminated remains with the pharmacist

handling of gene medicines should continually review local legislation for changes/updates that may occur.

Decontamination of gene medicine spills

Required contents for a spillage kit, as well as recommendations for decontaminating gene medicine spills, are outlined in Chart 6. The spillage kit should contain at least the following items: 2 disposable gowns or arm covers, 4 gloves, 2 masks, 2 aprons, 2 pairs of goggles, 4 disposable shoe covers, 2 disinfectant sachets (or other prepared disinfectant), absorbent paper towels, 2 disposable forceps, 2 biohazard disposal bags, an emergency contact number, and a copy of the cleaning procedure to be used in the event of spillage. As stated, the spillage kit should be available during all steps in the handling of a gene medicine, either by carrying it with the gene medicine (recommended) or making separate kits available at each location used during preparation, transport and administration. Different procedures are outlined for spills of a gene medicine that occur within, and those that occur outside, the biological safety device. Accidental spillage of the gene medicine should be dealt with depending on the location of the spill as outlined. The person who spilled the agent must be responsible for initiating the decontamination of the area; thus, appropriate training on decontamination procedures should be provided to all staff involved in the handling of gene medicines. Ultimate responsibility for ensuring that the spillage is correctly decontaminated remains with the pharmacist.

Accidental exposure to a gene medicine

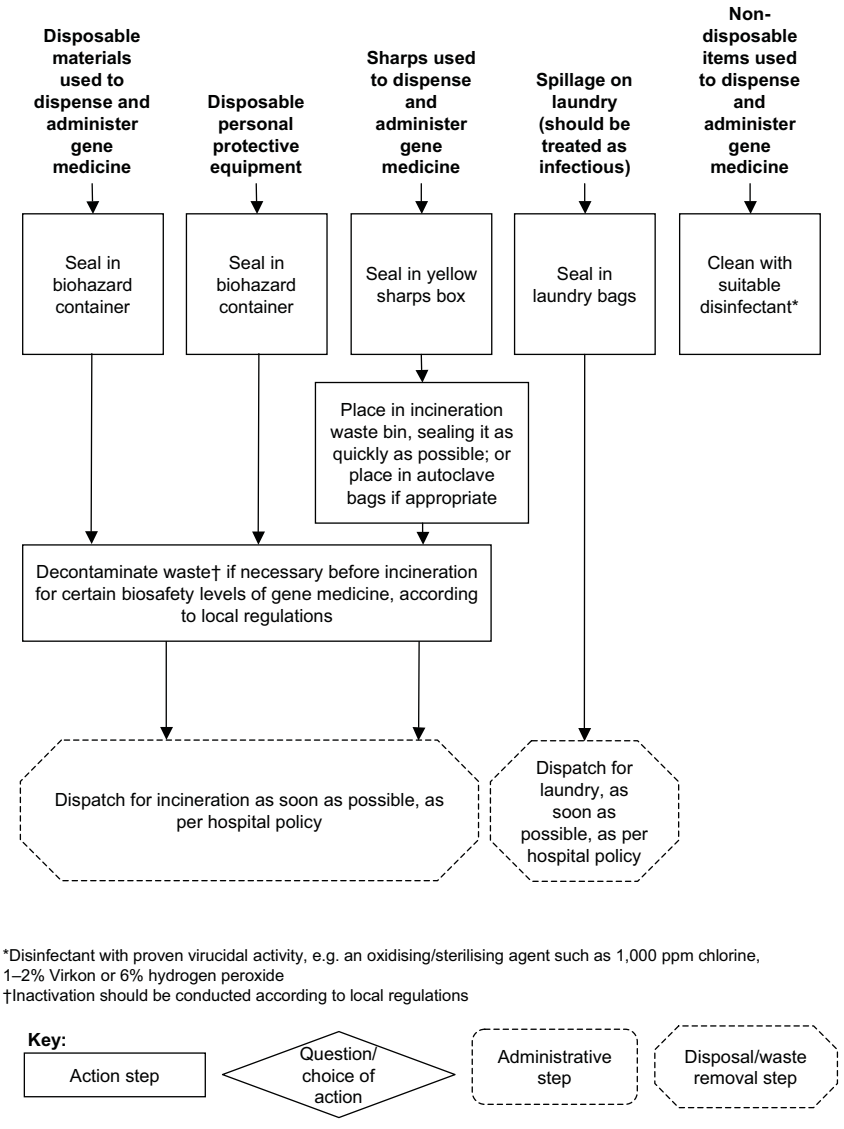
Accidental exposure to gene medicines should be treated according to procedures outlined in Chart 7 and medical attention should be sought in all cases. All manufacturers should include information on procedures for accidental exposure in their package insert, and this must always be available to those handling the gene medicine. It is important to document all accidental exposure according to normal hospital procedure. Occupational health, the biological safety officer and the incident report group, where present, must be aware of the gene medicines that are being used in the hospital and their potential risks and side effects.

Model for the roles and responsibilities involved in the handling of a gene medicine

It is important for all parties involved in the handling of gene medicines to understand clearly their roles and responsibilities at each step of the process. Table 3 uses the 'RASCI' model (23) to provide a working model for the roles of hospital staff in each of the steps involved in handling a gene medicine. As each country, and even individual facilities, will have different management structures and distributions of responsibilities, this chart should be considered as just one suggestion of a working model. Each centre using a gene medicine will need to consult local legislation and regulations. The physician, the chief pharmacist, pharmacy staff (skilled pharmacists and technicians) and others involved in this process are, of course, ultimately accountable to the hospital management in the decision-making process. This is not explicitly captured in this model as it is assumed to be the case.

When a decision is first made to initiate treatment with a particular gene medicine, responsibility for ensuring that the appropriate conditions are established at the facility for the handling and administration of such agents lies with the treating physician. Extensive consultation with the chief pharmacist, pharmacy staff, nursing staff, the biosafety/infection control officer, occupational health, and waste disposal services is essential

Chart 5: Gene medicine waste disposal



at this stage to establish the local processes at each step in the handling, administration and disposal of the gene medicine. Effective collaboration between all parties involved at this stage should ensure that later stages work smoothly and efficiently.

A detailed assessment should be conducted to decide on the ability of the facility to handle such medicines and the training needs of the staff who will be involved. This assessment is the responsibility of the chief pharmacist, the prescribing physician and the biosafety/infection control officer. Together, these individuals should be able to evaluate the equipment and training necessary at the key stages of the process that are relevant to their specialty. Staff training should ensure the correct use of equipment, safe handling of the gene medicines and adherence to local requirements and regulations. Appropriate training will also give staff confidence in the handling and use of gene medicines. The chief pharmacist is responsible for ensuring that the appropriate equipment is available in the pharmacy and that pharmacy staff receive adequate training. The physician is responsible for ensuring that the necessary medical and surgical facilities are available, and that staff are aware of the procedures and requirements related to the use of a gene medicine. The biosafety/infection control officer should cover all other areas of assessment.

Screening gene medicine prescriptions on a patient-by-patient basis is the responsibility of the chief pharmacist, with support from pharmacy staff. Where appropriate, the chief pharmacist may delegate this responsibility to a member of the staff. In performing this activity, a pharmacist is accountable to the physician and should consult with them if there is any query. Theatre/ward nursing staff may also be consulted, if necessary. If the correct process has been established from the outset and the appropriate conditions put in place for the use of gene medicines at a facility, it should not be necessary to inform the biosafety/infection control officer, hospital hygiene services or the occupational health professional every time that a prescription for a gene medicine is issued, only when a medicine is issued for the first time.

Receipt of the gene medicine from the manufacturer and inspection of the same is the responsibility of the chief pharmacist, with support from the pharmacy staff, delegated as appropriate. The prescribing physician and theatre/nursing staff involved should be consulted and informed as appropriate. Again, with the correct procedures in place from the outset, it will not be necessary to inform the biosafety/infection control officer, hospital hygiene services or the occupational health professional each time that a gene medicine is received. Transportation of the gene medicine is the ultimate responsibility of the chief pharmacist, with support from the pharmacy staff. The physician and the nursing staff should be consulted and informed as appropriate. If necessary, the biosafety/infection control officer, the hospital hygiene services or the occupational health professional should be informed. When the gene medicine is stored, the chief pharmacist is responsible for ensuring that the storage is appropriate to the product, with support from the pharmacy staff. In some cases, more than one person can be responsible for an activity; for example, dispensing the gene medicine can be carried out by the pharmacist or by a technician, if delegated by the chief pharmacist. Again, it will not be necessary to inform other hospital staff (e.g. biosafety/infection control officer, hospital hygiene services or

Chart 6: Decontamination of gene medicine product spills

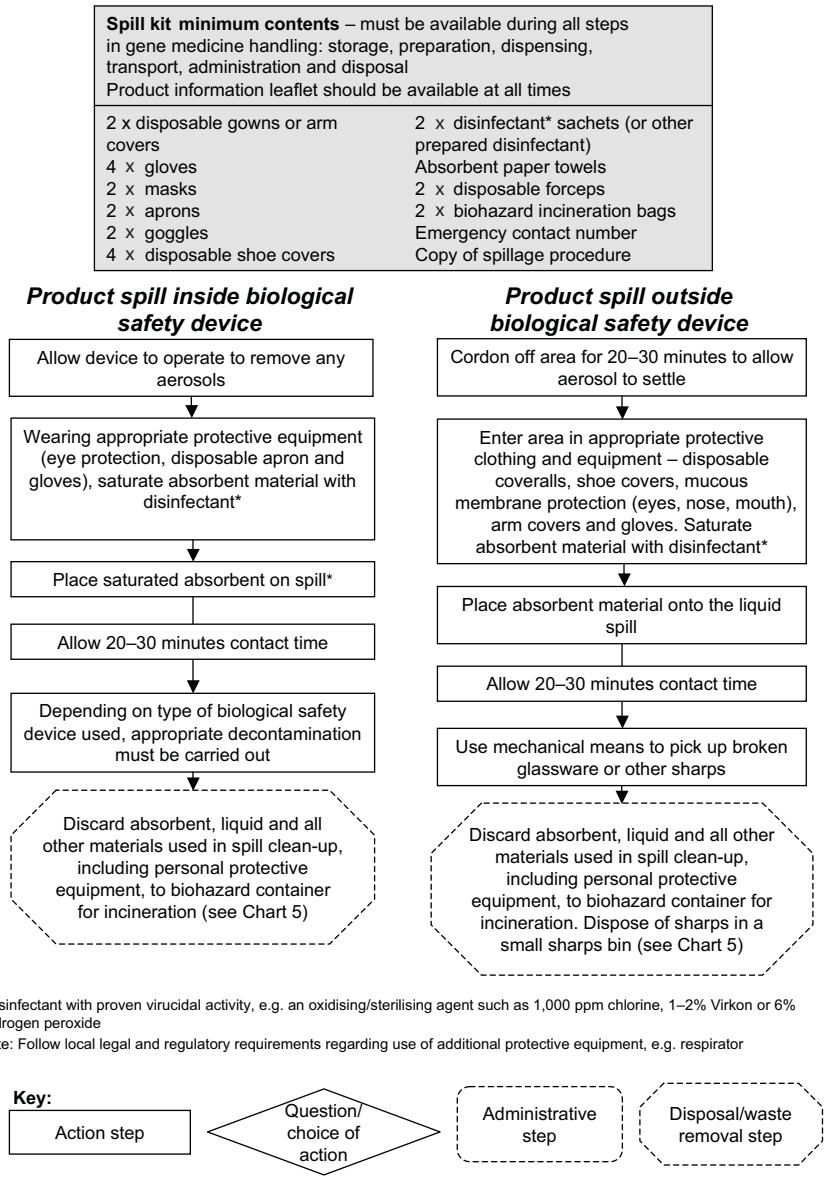
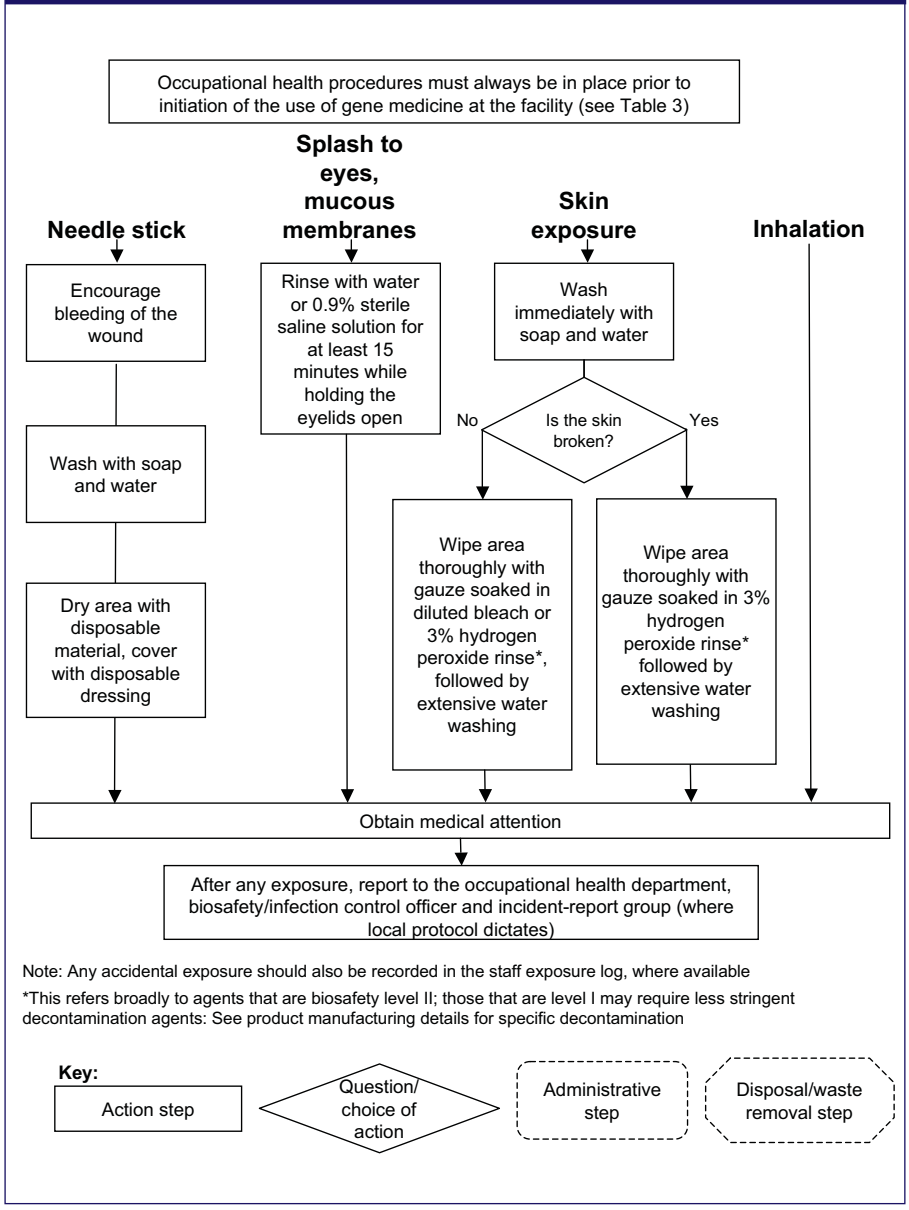


Chart 7: Accidental exposure to a gene medicine



occupational health professional) every time that a gene medicine is dispensed, providing that the correct process was established following initiation of gene medicine use.

Preparation, dispensing and decontamination are all the responsibility of the chief pharmacist, with support from pharmacy staff. Administration is often the responsibility of the physician, with support from nursing staff. However, in some cases, responsibility for administration may belong to the nursing staff.

The responsibility for waste disposal is dependent on where the waste is generated, and the person who generates the waste should take responsibility for correct disposal, whether that is the chief pharmacist, the physician or the nursing staff. Cleaners, porters and waste services should all be supportive in this process. It is important to note that the person responsible for the step will vary for the decontamination of gene medicine spills and accidental exposure depending, respectively, on who spilled the gene medicine or who was accidentally exposed. Thus, initiation of the decontamination of a gene medicine spill may be the responsibility of the chief pharmacist, the pharmacy staff, the physicians or the nurses. Ultimate responsibility for decontamination of the spill remains with the pharmacist/pharmacy staff. The biosafety/infection control officer is ultimately accountable to ensure that appropriate procedures are in place for decontamination of the spill. Occupational health personnel should be consulted in all cases of a gene medicine product spill, and the biosafety/infection control officer, hospital hygiene services, occupational health services and cleaners should all be informed. Similarly, if an accidental exposure occurs, the chief pharmacist, pharmacy staff, the physician or the nurse will be responsible depending on where the exposure took place. The biosafety/infection control officer and occupational health professional should always be consulted. The physicians, nurses, biosafety/infection control officer, hospital hygiene services and occupational health staff may all need to be informed, as appropriate to the particular case.

Discussion

As gene medicines develop and become increasingly used in clinical and pharmacy practice, it is essential that standards are set and maintained for the handling and preparation of these novel therapeutics.

Pharmacists are ideally placed to lead the way in setting these standards. Preparation of a gene medicine is a pharmaceutical process that should be carried out under the control of a pharmacist in suitable facilities, to minimise the risk of microbiological contamination and medication errors. Pharmacists can play a role in setting standards at all stages of handling gene medicines, from receipt, storage and preparation of these medicines to accidental spillage and emergency management. As the guidance is based on the practical experience of a group of European experts in this field, as well as the available published evidence, the guidance sets out the minimal requirements essential in any hospital pharmacy where a gene medicine will be used, in an easily accessible format. There are, of course, limitations associated with the creation of general guidance, and the national legislation must always be consulted and reviewed regularly for latest updates. Of course, it is to be expected that any new agent that becomes available may have specific requirements, distinctive to that product, and the prescribing information (PI) or full SPC should always be consulted to ensure compliance of the handling procedures with the requirements defined therein.

Appendix 1: HSE 2007 guidance on containment measures required for gene medicines in a clinical research setting

Containment measure	Level 1	Level 2
Autoclave	Required on site	Required in the building
Access restricted to authorised personnel only	Not required	Required
Specific measures to control aerosol dissemination	Not required	Required so as to minimise
Protective clothing	Suitable protective clothing required	Suitable protective clothing required
Gloves	Not required	Required where and to extent the risk assessment shows it is required
Specified disinfection procedures in place	Required where and to extent the risk assessment shows it is required	Required
Safe storage of gene medicine	Required where and to extent the risk assessment shows it is required	Required
Inactivation of gene medicine in contaminated material and waste	Required by validated means	Required by validated means

Note 1: 'Level' in the table refers to containment level and not to biosafety level of the agents themselves. However, there is a direct correlation between biosafety level of the agent and the containment level, e.g. biosafety level 2 agents require containment level 2.

Note 2: This table details the requirements from a containment perspective; it should be borne in mind that additional precautions, e.g. gloves, may be required to protect the product.

With the increased availability of agents in this group of 'gene medicines', we will increase our knowledge of these novel therapeutics. With increased knowledge will come decreased uncertainty. Over time, pharmacy practice for handling gene medicines will become more assured, and we can tailor the appropriate level of caution with confidence. Adherence to this guidance for the handling of gene medicines in clinical and pharmacy practice will ensure consistency of best practice across Europe. This, in turn, will promote the safest and most effective use of these new therapeutics. Undoubtedly, as this area of medicine is rapidly evolving, so too must our guidance, and future revisions and updates are to be expected.

Acknowledgement

Editorial support for the preparation of this manuscript was provided by Michelle O'Donovan, PhD (Ogilvy Healthworld Medical Education). All authors contributed to all drafts of the guidance and editorial control remained with the authors at all times. Ark Therapeutics provided unrestricted funding for the establishment of this working group and the development of this guidance. The authors would also like to thank Anna de Goede (Hospital Pharmacy, Erasmus University Medical Centre, Rotterdam, the Netherlands) who provided valuable input and assistance with development of the guidance.

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