STU-APO-07 GMO procedure for UZ Leuven pharmacy

procedures ziekenhuisapotheek

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1. Purpose

This SOP describes the procedure and guidelines for responsible handling of genetically modified organisms within the hospital pharmacy UZ Leuven. This procedure is important to ensure the health and safety of both patients and staff, and to comply with legal regulations regarding genetically modified organisms.

2. Scope

This “Standard Operating Procedure (SOP)” applies to all trials in which “genetically modified organism” (GMO) containing “Investigational Medicinal Product (IMP)” is involved. This procedure describes all activities and responsibilities in the context of conducting a trial with GMO-containing IMP with focus on the clinical trials department of the hospital pharmacy of the University Hospital (UZ) Leuven.

3. Role and Responsibilities

All the members of the Clinical Trials Pharmacy team are responsible for the implementation of and compliance with this procedure, i.e. SOP “STU-APO-07 GMO procedure for UZ Leuven pharmacy”.

The Prevention & Environmental Department is responsible for advising and supervising activities with GMOs at UZ Leuven. The Prevention & Environmental Department works closely with the hospital pharmacy for this. The biosafety coordinator is responsible for submitting the technical file including risk analysis (and possibly the public file in the case of RL 2) to the Sciensano BioSafety and Biotechnology Unit (SBB) and for the assessment of each application for clinical trials with GMO-containing IMP.[14] The Prevention & Environmental Department has evaluated and approved SOP “STU-APO-07 GMO procedure for UZ Leuven pharmacy”.

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5. Abbreviations, terms and definitions

5.1 Abbreviations

AAV: Adeno-Associated Virus

ABS: Acrylonitrile Butadiene Styrene

ATMP: Advanced Therapy Medicinal Product

BSC: BioSafety Cabinet

BSL: BioSafety Level

CEN: European Committee for Standardization

CSTD: Closed System Drug-Transfer Device

CTC: Clinical Trial Center

DNA: Desoxyribo Nucleic Acid

FFP: Filtering Face Piece

FOD: *Federale Overheidsdienst* [Belgian Federal Public Service]

GMMs: Genetically Modified Microorganisms

GMO: Genetically Modified Organism

GMO-IMP: Investigational Medical Product based on a Genetically Modified Organism

GMP: Good Manufacturing Practice

GTMP: Gene Therapy Medicinal Product

HEPA: High Efficiency Particulate Air

HMW: Hazardous Medical Waste

HR: Hospital Room (hospital ward)

IMP: Investigational Medicinal Product

IPA: Isopropyl Alcohol

IWRS: Interactive Web Response System

L: Laboratory

MSC: Microbiological Safety Cabinet

PA: Polyamide

PBT: Polybutylene Terephthalate

PE: Polyethylene

PES: Polyethersulfone

PET: Polyethylene Terephthalate

PI: Principal Investigator

PIC/S: Pharmaceutical Inspection Co-operation Scheme

PPE: Personal Protective Equipment

PP: Polypropylene

ppm av cl: parts per million available chlorine

PTFE: Polytetrafluoroethylene

PTS: Potentially Toxic Substances

PUR: Polyurethane

PVC: PolyVinyl Chloride

REF: Reference

RL: Risk Level

RNA: Ribo Nucleic Acid

SBB: Sciensano BioSafety and Biotechnology Unit

SEBS: Styrene-ethylene-butylene-styrene

SOP: Standard Operating Procedure

SMT: Safe Microbiological Techniques

TPE: Thermoplastic Elastomer

UZ Leuven: *Universitair Ziekenhuis Leuven* [University Hospital of Leuven]

5.2 Definitions

A GMO, also referred to as a "genetically modified microorganism (GMM)", is any biological entity with the ability to replicate or transfer genetic material, of which the genetic material has been altered in a way that is not possible by reproduction or natural recombination.[1,2] Techniques that lead to the formation of an GMO consist of (1) recombinant DNA- and RNA- techniques using host or vector systems; (2) micro-injection, macro-injection and micro-encapsulation of genetic material; and (3) cell fusion or cell hybridization techniques that lead to cells with non-natural genetic material.[3] The excluded techniques are also strictly established. By listing these genetic modification techniques and by subjecting them to rules (without regulating the excluded techniques), the European guidelines focus on the methods of obtaining a GMO and not on (the properties of) the final product to carry out a risk assessment or not.[4]

Medicines based on a GMO belong to gene therapy, which is classified as a 'Gene Therapy Medicinal Product' (GTMP), which in turn is covered by the umbrella term 'Advanced Therapy Medicinal Product' (ATMP), and therefore also falls under the European classification of ATMP.[5] GTMPs are subdivided into ex vivo and in vivo GTMPs, respectively, drugs aimed at the ex vivo or in vivo transfer of a recombinant part of nucleic acid to human or animal cells and the subsequent expression of the gene in vivo with a prophylactic, diagnostic or therapeutic effect. It is important to note that, within the UZ Leuven hospital pharmacy, GMO-based medicines only refer to in vivo GTMPs, in which gene transfer is almost always done by means of a virus. **In other words, ex vivo GTMPs such as CAR-T cell therapy are not considered GMO-based medicines and therefore do not fall within the scope of this SOP. Trials involving CAR-T cell therapy should therefore not be requested using the GMO-specific request form from the UZ Leuven hospital pharmacy.** The gene transfer in in vivo GTMPs, i.e. GMO-based medicines, takes place using an administration system, also referred to as a "vector", which can have a viral or non-viral (e.g. plasmid) origin. Viral vectors are viral particles that, when compared to the viral stem from which the vector is derived from, carries an artificially modified genome.[6,7] Based on the preservation or disappearance of the viral vectors ability to endlessly multiply, two

types of vectors can be distinguished. In the case of **propagating vectors**, the viral vectors themselves or their auxiliary particles are competent for replication and as a result, stringent containment conditions apply. **Non-propagating vectors** are deficient for replication. Examples of such include vectors derived from adenoviruses and the Adeno-Associated Virus (AAV). Containment conditions are less stringent, but the risk that these vectors occasionally acquire the ability to replicate must be taken into consideration.

5.3 EU regulatory framework on biosafety

The regulatory texts concerning the restricted use of GMOs [8,9] may be associated with the European regulations on the **protection of the health and safety of workers exposed to biological agents** (microorganisms, cell cultures and human endoparasites, that may result in infection or allergy, or could be toxic).[10] Since the protection of the living environment is a Flemish authority, the legal basis of these European regulations are provided by the Flemish regulation on the environmental permit or Vlarem.[11] These regulations classify the biological agents into **four risk levels (RL)**, that describe which **containment measures** must be implemented (depending on the nature of the activity, the risk assessment for the employees and the characteristics of the biological agent involved) and define the obligations of the employers.[12,13,14]

5.3.1 Classification of the biological agents into four risk levels

The biological agents, including the GMOs, are classified into four RLs as shown in Table 1.[12,13,14] For example, the adenoviruses mostly correspond to RL 2; vectors derived from these adenoviruses mostly correspond to RL 1 or 2.[13]

Table 1. Classification of the biological agents into four risk levels.[12,13,14] *BSL = BioSafety Level, GMO = genetically modified organism, RL = risk level.*

RL	**Pathogenicity** of the biological agent (e.g. GMO)	**Risk of infection** of the GMO	**Containment level** to protect people and the environment
1	Non-pathogenic: an agent unlikely to cause disease in humans.	No or negligible risk	Containment level 1 (BSL 1)

2	Weak pathogen: an agent that could cause illness in humans and pose a risk to the safety and health of the employees. Distribution of the agent in the population is unlikely and effective prophylaxis or treatment is available.	Low risk	Containment level 2 (BSL 2)
3	Moderate pathogen: an agent that can cause serious illness in humans and poses a great danger to the health and safety of employees and students. It is highly infectious but easily controllable or moderately infectious but hardly controllable.	Moderate risk	Containment level 3 (BSL 3)
4	High pathogen: an agent that causes a serious disease in humans and poses a great danger to the safety and health of employees. Distribution of the agent in the population is very likely and no effective prophylaxis or treatment exists.	High risk	Containment level 4 (BSL 4)

5.3.2 Containment measures

Four basic containment levels are linked to the four risk classes.[14] In consideration of the substantive control of biosafety, they are also referred to as **BioSafety Levels (BSL)**. Containment of the hazards is achieved through the application of a combination of infrastructural measures and the use of special work instructions.[13] These measures are established for each level. The higher the containment level, the more requirements are imposed on infrastructure and work instructions.[13] In case of **infrastructural measures** it concerns physical containment such as the mandatory use of a Microbiological Safety Cabinet (MSC), also called a BioSafety Cabinet (BSC). The **special work instructions** deal with the way in which work is done, such as wearing gloves and other personal protective equipment (PPE). Regardless of the level of risk, there are always basic requirements in place[15] that form the principles of “Safe Microbiological Techniques (SMT)”.[13]

6. Procedure

UZ Leuven can only participate in clinical trials with GMOs of BSL 1 and 2, since the hospital obtained an environmental permit for activities of limited use of GMOs of a maximum RL 2 level for clinical trials, and this for an indefinite period based on decision number OMV/2018102597 (subject to regular update).

With every request for the limited use of a GMO in the context of trials at UZ Leuven, the biosafety coordinator of UZ Leuven must first submit the technical file including risk analysis (and possibly the public file in the case of RL 2) to the technical expert of SBB, who acts as a counsel to "*departement Omgeving*" [the environmental department in Belgium] for obtaining an environmental approval for limited use of the relevant GMO at UZ Leuven.[14]

Exception: If the GMO in the context of a trial concerns a medicine that is already authorised on the European and/or Belgian market, the involvement of the Department of Prevention & Environment (including the biosafety coordinator) as a support service is not necessary, as this then no longer falls under the 'contained use' regulations.

Hospital pharmacy clinical trials process description

6.1 Submission of an application for GMO trials

When submitting an application for a clinical trial with GMO-containing IMP at the clinical trial center (CTC) of UZ Leuven, the investigator, as the Principal Investigator (PI), receives an automatic email on whether or not to approve the application. By accepting the trial application, the PI automatically agrees with the pharmacy-specific GMO processes and procedures as described in this SOP (in particular, the closing schedule, see 6.5.4 Closing Schedule). In addition, the sponsor is responsible for submitting an electronic application form "Aanvraagformulier studies met GGO bevattend IMP ziekenhuisapotheek" [Application form for a clinical trial with GMO-containing IMP for the hospital pharmacy] to the hospital pharmacy through the external website of UZ Leuven - hospital pharmacy - clinical trials through https://www.uzleuven.be/nl/ziekenhuisapotheek/klinische-studies#nieuwe-klinische-studie-aanmelden. Since the application to the Prevention & Environmental Department has also been processed in this, both the biosafety coordinator and the hospital pharmacy receive the electronically submitted application form including all the necessary study-specific documentation. In consultation with the biosafety coordinator, the pharmacy assesses the feasibility of the reconstitution, delivery, supply, storage and accountability of the GMO-containing IMP. Based on the flowchart in Figure 1, the hospital pharmacy, together with the biosafety coordinator (and following the necessary consultation with the relevant "Trial Bureau" on site), assesses whether the reconstitution should take place in the hospital pharmacy or whether decentralization in the nursing unit (hospital ward) is possible and what requirements are imposed on this, in particular, with regard to the use of "Closed System Drug-Transfer Device (CSTD)."

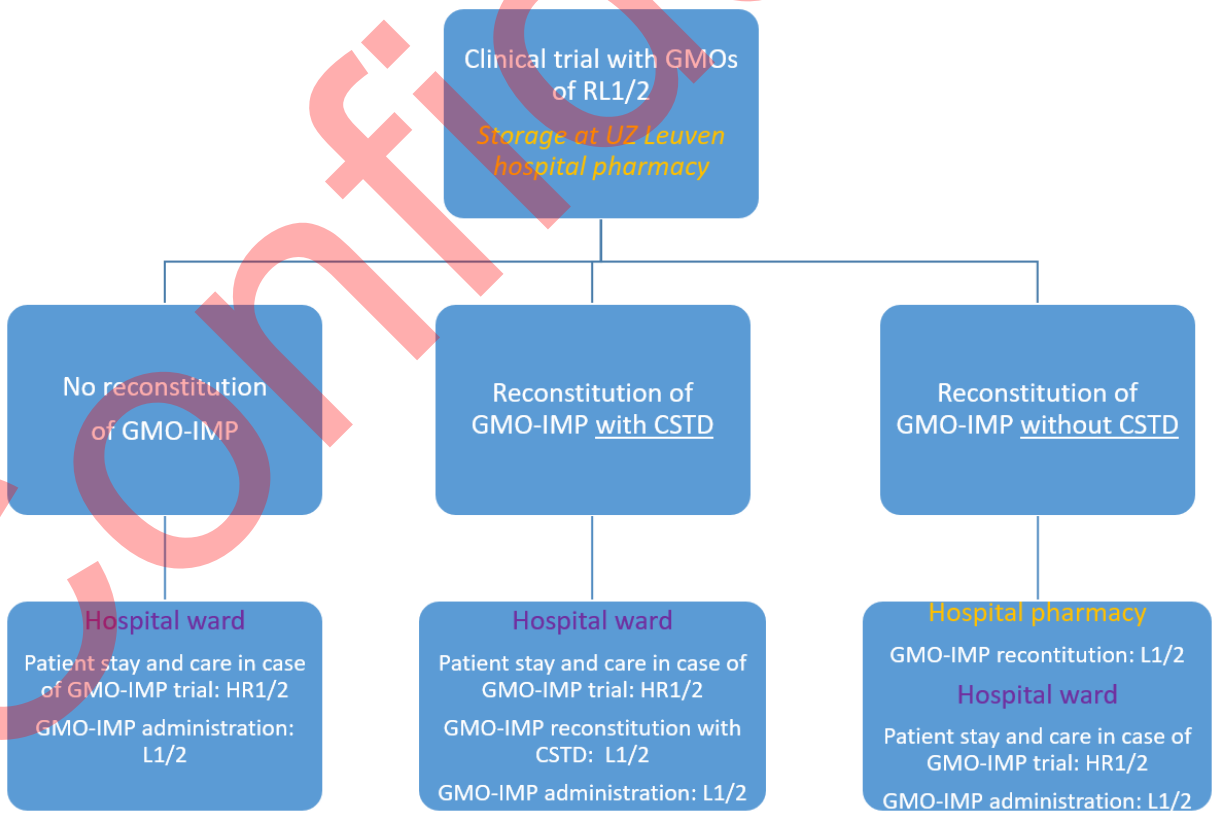

Figure 1. Flowchart with use of CSTD and location of reconstitution. *CSTD = Closed System Drug-Transfer Device, GMO = genetically modified organism, GMO-IMP = investigational medical product based on a genetically modified organism, HR = hospital room (hospital ward), L = laboratory, RL = risk level.*

The further assessment of the application form is carried out by a staff member of the hospital pharmacy. It is thereby assessed whether all materials can be provided and assesses the feasibility of other possible preparations and/or deliveries that will go through the hospital pharmacy. The hospital pharmacy finally decides whether or not to approve the entire trial on the activities for the hospital pharmacy. The hospital pharmacy communicates this decision to the CTC by electronic approval/rejection of the application form. The trial application otherwise follows the standard procedure (CTC and other supporting departments).

6.2 Start of a GMO-IMP trial

For the start of a study with GMO-containing IMP, it is required that during the initiation of the hospital pharmacy, an explanation is provided on the biosafety specific to the GMO-IMP by the sponsor's responsible contact. The biosafety coordinator at UZ Leuven is invited for this explanation.

The remainder of the start-up of a trial with GMO-IMP follows the common procedure as described in the SOP "STU-APO-01 Procedure van de procedures[7] [Procedure of the procedures]" and SOP "STU-APO-02 Opstarten nieuwe klinische studie[8] [Initiation of a new clinical trial]" in which the maximum efforts are realized to use pharmacy-specific "internal" templates to increase uniformity. If necessary, a study-specific training is provided for the employees (staff) of the hospital pharmacy clinical trials.

6.3 Delivery and receipt of GMO-IMP

The delivery, receipt and storage of GMO-IMP takes place in the hospital pharmacy clinical trials, regardless of the location of reconstitution. The storage conditions are in accordance with the requirements of the study protocol. Receipt of the GMO-IMP is documented in the documents provided by the sponsor and, if required, confirmed in an electronic dial-in system e.g. "Interactive Web Response System (IWRS)". The conformity of the delivery is checked using an internal delivery checklist (see SOP "STU-APO-03 Ontvangst en bewaring studiemedicatie[9] [Receipt and storage of trial medication]").

6.4 Dispensation of GMO-IMP (without reconstitution)

If no reconstitution is required, the GMO-containing IMP (both from RL 1 and from RL 2) will be dispensed as "ready to use" on an individual prescription by the hospital pharmacy to the responsible contact of the involved Trial Bureau. Until the moment of dispensation, the GMO-containing IMP will be stored in the hospital pharmacy where the proper storage conditions can always be guaranteed. It is therefore not possible to send GMO-containing IMP immediately upon receipt to the relevant Trial Bureau to store it in a decentralized way, i.e. GMO-IMP trials can never be classified as "Transit Trials" within UZ Leuven hospital.

7 https://wiki.uz.kuleuven.ac.be/x/sbyoHw
8 https://wiki.uz.kuleuven.ac.be/x/eL2oHw
9 https://wiki.uz.kuleuven.ac.be/x/k8SoHw

6.5 Reconstitution of GMO-IMP

The role of the hospital pharmacy in the preparation activities of the registered clinical trial with GMO-containing IMP is evaluated by the hospital pharmacy in consultation with the biosafety coordinator of UZ Leuven hospital, using the flowchart in Figure 1.

6.5.1 BioSafety Level (BSL) 1

Since BSL 1 applies to a clinical setting in which microorganisms are handled where the activities (preparation and administration) present a negligible or no infection risk, only minimal safety requirements are established in the environment in which BSL 1 activities are being carried out. The operational practices concerning BSL 1 activities, as well as the facility where the BSL 1 activities take place, must meet the requirements of **containment level L1** ('containment level laboratory 1'), which in UZ Leuven is possible both in the **hospital pharmacy L1** and **decentralised L1**, i.e. in the hospital ward (nursing unit) where the GMO-IMP is administered.[14] In this context it is important to distinguish between the specific BSL 1 activities: the operational practices and environment of BSL 1 activities must meet the requirements of containment level HR1 ('containment level hospital room 1') when they are limited to patient stay and care on the hospital ward in the case of a study with GMO-IMP, while the requirements of containment level L1 must be met for BSL 1 activities beyond patient stay and care, such as reconstitution and administration of GMO-IMP with RN 1. A varying containment level within a room is allowed, provided that prior to lowering/rating the containment level the room was 'released'. By 'release' is meant an 'adequate' decontamination of the room, i.e. work surfaces, devices, equipment, visible contamination as well as the removal of biological waste. See also: https://wiki.uz.kuleuven.ac.be/display/preventie/Bioveiligheid .

The UZ Leuven hospital pharmacy complies with the following **infrastructural BSL 1 requirements**[14,16] in the preparation area for GMOs: presence of coat racks for PPE, presence of a wash basin as a decontamination facility for the personnel, water impenetrable walls, floor and ceiling, work surfaces that can be thoroughly cleaned, and mandatory warning signs on the access door (containment level and name of the responsible contact). Although access restriction is not required by law for BSL 1, this is met. With regard to **required work instructions**[14,16] basic guidelines on microbiological safety and microbial practices are always being followed: wearing PPE, complying with local regulations for hazardous medical waste (HMW), hygiene (washing hands at the start and end of the preparation), prohibition of drinking, eating and smoking, training of personnel, and maintaining a spill procedure available (see *5.5.5.4 Spill box for incidents*). In addition, all GMO-related activities are recorded in a register.

In terms of microorganism control and containment, a **BSC is not required for BSL 1.**[13] An environment for BSL 1 activities therefore mostly includes a (sterile) workplace without the use of special contamination equipment and does not need to be isolated from the surrounding sites. Consequently, activities such as reconstitution of GMO with RL 1 can be carried out at the nursing unit (hospital ward) where the GMO-containing IMP will also be administered, providing that the unit at the hospital ward must comply with the aforementioned required infrastructural measures and work instructions. For reasons with regard to personnel safety at the unit, the decentralized preparation activities are limited to those preparations where the reconstitution of GMO-IMP can take place by means of a needle-free closed transfer system or CSTD (see *5.5.3 Use of "Closed System Drug-Transfer Device (CSTD)"*). The reconstitution will be carried out in the hospital pharmacy, specifically in a BSC, when the use of CSTD cannot be approved by the sponsor due to legitimate reasons and the reconstitution with a syringe and needle must take place or when there are additional preparation steps associated with the preparation of the GMO-IMP, which increases the complexity.

6.5.2 BioSafety Level (BSL) 2

Since BSL 2 applies to a clinical setting in which microorganisms are handled where the activities (reconstitution/preparation and administration) present a low infection risk, in addition to the minimum BSL 1 safety requirements, additional requirements are established for both the operational practices and the environment in which BSL 2 activities are carried out. This concerns the requirements of **containment level L2** ('containment level laboratory 2'). See also guideline L2: https://wiki.uz.kuleuven.ac.be/display/preventie/Bioveiligheid .

The rooms of the UZ Leuven hospital pharmacy meet the following additional **infrastructural BSL 2 requirements**[14,16]: a closed "lockable" environment and access restriction to employees who are informed of the procedures. The additional **BSL 2 work instructions** [14,16] are also complied with: presence of the abovementioned warning signs with addition of a biohazard sign on the access door, as well as on the fridges and an SOP on pest control.

Further, **BSL 2 also does not require a BSC, although this is optional**[13] as doors and windows must be closed at all times during the activities so that the area acts as a closed system in which viable microorganisms are physically contained. Consequently, BSL 2 activities can also take place in the hospital ward (nursing unit) on condition that the ward meets the additional BSL 2 requirements. In this context it is important to distinguish between the specific BSL 2 operations: the operational practices and environment of BSL 2 activities must meet the requirements of containment level HR2 ('containment level hospital room 2') when they are limited to patient stay and care on the hospital ward in case of study with GMO-IMP, while the requirements of containment level L2 must be met for BSL 2 activities that go beyond patient stay and care, such as reconstitution and administration of GMO-IMP with RN 2. A varying containment level within a room is allowed provided that prior to lowering/rating the containment level, the room was 'released'. By 'release' is meant an 'adequate' decontamination of the room, being the work surfaces, devices, equipment, visible contamination as well as the removal of biological waste.

The location (pharmacy L2 or decentralized L2) where reconstitution will be carried out is in this case also determined based on the possibility of using CSTD (see 6.*5.1 BioSafety Level (BSL) 1)*.

For making a GMO with RL 2 ready for administration, also referred to as "reconstitution of a GMO", the hospital pharmacy clinical trials has a hatch (location 407.21.02.75) and a closed area ("cleanroom") (location 407.21.02.74) with **1 BSC** (BioVanguard B4)[17]. The hatch also provides access to a second enclosed area (location 407.21.02.76) with 1 BSC (identical in marking and type), which can also be used in exceptional situations for reconstitution of GMO-IMP. These BSCs meet international biosafety standards NSF49 **(Class II Type A2),** EN12469 (Class II), and DIN 12980 (Class II), and PIC/S. The work surface is classified as ISO 14644-1 (Class 5) and GMP Annex 1 (Class A).[17] Both the incoming and the outgoing air is being filtered with HEPA filters (EN 1822, H14) where 30% of the filtered air is being pushed out the BSC and 70% is being recirculated inside the BSC by means of a vertical downward laminar flow with a downflow rate of 0,36 m/s.[17]

6.5.3 Use of "Closed System Drug-Transfer Device (CSTD)"

To ensure maximum protection of personnel, a needle-free closed transfer system or "Closed System Drug-Transfer Device (CSTD)" is used when preparing GMO-IMP, when authorized by the sponsor. The UZ Leuven hospital pharmacy works with the following products as standard: **ChemoClave™ series** of **ICU Medical**:[18]

• **SpirosTM (closed male luer-connection)**: for use on a syringe to withdraw the solution with GMO-containing IMP from the vial and possibly add this to an infusion bag. The Spiros™ consists of polycarbonate and silicone;

• **Vial spike CH-74 with ClaveTM connector:** for use on a vial with GMO-containing IMP solution. This concerns a "vented" spike, which means that the pressure in the vial is automatically equalized through a filter. The Clave™ consists of silicone, Cyrex® (acrylate/polycarbonate alloy) and Valox® (Polybutylene Terephthalate (PBT) and/or Polyethylene Terephthalate (PET) polymers);

• **Vial spike CH-74S with ClaveTM connector**: for use on a vial that contains GMO-containing IMP solution. This concerns a "vented" spike, which means that the pressure in the vial is automatically equalized through a filter with additional protection against leakage. The Clave™ consists of silicone, Cyrex® (acrylate/ polycarbonate alloy) and Valox® (PBT and/or PET polymers);

• **Vial Spike CH-72 with ClaveTM connector**: for use on a vial with GMO-containing IMP solution. This spike is designed specifically for small vials with a closure of 13 mm. This concerns a "vented" spike, which means that the pressure in the vial is automatically equalized through a filter. The Clave™ consists of silicone, Cyrex® (acrylate/polycarbonate alloy) and Valox® (PBT and/or PET polymers);

• **Infusion line 42 cm with spike and compatible ClaveTM port (without filter) "REF 011-H2504"**: for use on an infusion bag through the spike. The GMO-IMP solution (in the syringe with Spiros™) can be added through the Clave™ connector in a needle-free way. The infusion line consists of polyurethane (PUR);

• **Infusion line 44 cm with spike and compatible ClaveTM port (with 0.2 µm in-line filter) "REF 011-H2862"**: for use on an infusion bag through the spike. The GMO-IMP solution (in the syringe with Spiros™) can be added through the Clave™ connector in a needle-free way. The filter is "low protein binding". The infusion line consists of PUR and the filter consists of polyethersulfone (PES).

As an alternative and in agreement with the clinical trials pharmacy, **the PhaSeal™ system** from **BD** can be opted for.[19]

The sponsor is responsible for evaluating whether any of the above CSTD systems are compatible with the products used in the trial. The sponsor must be aware that the ICU Medical ChemoClave™ system is the preferred choice at UZ Leuven. Only when this system cannot be approved, the BD PhaSeal™ system can be considered as an option (if compatible). If the sponsor rejects both systems and chooses a different system to work without needles, the alternative must be offered in a timely manner in order for the hospital pharmacy to evaluate whether this is a viable option.

6.5.4 Closing schedule

A risk analysis was carried out to evaluate whether a closing schedule and quota for the number of GMO preparations permitted per day in the hospital pharmacy is necessary. The following elements were taken into consideration in this risk analysis: impact on turnaround times of non-GMO preparations, cross contamination, required actions in the event of a spill, properties and storage conditions of the GMO-IMP, etc. Based on this risk analysis, 3 groups of IMP preparations in the hospital pharmacy clinical trials were distinguished, e.g. (1) preparations of monoclonal antibodies preparations, (2) preparations of cytotoxic/ chemotherapeutic agents, and (3) preparations of GMOs. For this latter group, specific time slots ("closing") are provided so that the turnaround time of the two other IMP preparation groups in UZ Leuven can be kept within acceptable limits, the risk of cross-contamination can be minimized, and the highest quality can be offered to these rather complex preparations.

The reconstitution ("preparation") of GMOs in the hospital pharmacy is therefore reserved for **Tuesday afternoons, Thursday afternoons and Friday afternoons (start of GMO reconstitution at 2:00 p.m. at the earliest)**. On each of these afternoons **1 GMO slot** is provided.

The UZ Leuven policy staff is aware that the preparation of GMOs in the afternoon can result in hospitalization, when specific requirements are established in the study protocol with regard to patient follow-up after

administration. The impact of hospitalization was carefully weighed and evaluated compared to the impact on the turnaround time of non-GMO-IMP preparations from other clinical trials (particularly for day ward patients). Given the peak of these preparations between 11:00 a.m. and 1:00 p.m., preparation of GMO-containing IMP in the morning would mean an unmistakable delay of 90% of the IMP preparations with a significant impact on day ward operation, which is not desirable. We rely on the understanding of the implemented time limit and the cooperation of the investigators and Trial Bureaus involved.

The GMO preparations must be requested in advance, in a timely manner and in accordance with the **closing schedule** system. The hospital pharmacy clinical trials makes use of an **electronic calendar tool (Appoint) using programmed open time slots** through the external website of UZ Leuven - hospital pharmacy - clinical trials - schedule an appointment. On Tuesdays, Thursdays and Fridays, there will be 1 slot opened for a GMO preparation in the Appoint calendar, which can be booked by the study coordinator when the administration of GMO-IMP is scheduled in consultation with the treating physician. The patient study number must always be stated when scheduling a time slot. Upon start-up/enrollment of a patient, the study coordinator will be prompted to immediately record the slots for the next administration times.

6.5.5 Materials required for GMO-IMP reconstitution

6.5.5.1 Personal Protective Equipment (PPE)

Below you will find an overview of the PPE used at the UZ Leuven hospital pharmacy.

- Apron: Medline apron 'Prevention^{TM} Plus' (REF. DYNJPE2301P)
  - It offers optimal protection against both cytotoxic/chemotherapeutical agents and biological agents (e.g. bacteria and viruses)
  - Certified in accordance with legislation to meet the following safety standards:

  → EN 14605:2005 + A1:2009 **Type PB[4]**, which provides protection against spray-tight compounds

  → EN 14126:2003 **Type PB[4]-B** for certified protection against pathogens, including viruses. See Figure 2.

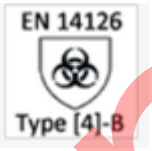

Figure 2. Symbol EN 14126 standard. Necessary required operational practice for manipulation of GMO products.

- Gloves: For safety considerations two pairs of gloves are put on during reconstitution/preparation of GMO products: one non-sterile pair of gloves and one sterile pair of gloves.

→ Non-sterile gloves: Microflex® 93-853 long cuff[21] or Honeywell KCL SivoChem® 759 (including 40 cm long manchet).

→ Sterile gloves: TouchNTuff® DermaShieldTM 73-701.[22]

-Certified in accordance with legislation to meet the following safety standards:

→ **EN ISO 374-5:2016** (tested against virus penetration).[20]

→ **16523-1:2015** (tested against chemicals in general). (For your information: this stricter standard replaces the obsolete EN 374-3 test standard against cytotoxic/chemotherapeutical penetration.)

- Mask: Surgical mouth mask.

- Safety glasses: (available, if requested by Sponsor).

6.5.5.2 Cleaning and disinfection

The area and work surface in the BSC must be cleaned and disinfected after carrying out activities with GMO-containing IMP to prevent exposure of such to employees as well as the subsequent preparations (cross-contamination), through potentially contaminated surfaces and possible aerosol formation. As with the cleaning of areas and surfaces where activities with cytotoxic/chemotherapeutical agents and other potentially toxic substances (PTS) are being carried out, the same cleaning detergent and disinfectant, respectively **Klercide® Neutral Detergent** and **ethanol (70%),** are used by applying these consecutively and allowing them to act for at least 10 seconds. Ethanol (70%) is chosen in consideration of its rapid, short-acting effect and strong activitity against (myco)bacteria, fungi and enveloped viruses (and to a lesser extent naked viruses). Although isopropyl alcohol (IPA) (60%) has an even faster effect and would leave less residue, it is not active against naked viruses and is therefore not used in the hospital pharmacy.

To kill off GMO-IMP, additional disinfectants are commonly required based on their spectrum. The choice of the disinfectant and the corresponding contact time during which the disinfectant must act, depends on the GMO-containing IMP itself (e.g. the microorganism from which the vector is derived). The UZ Leuven formulary stocks two sterile, stable and easily manageable disinfectants with good virucidal activity:

(1) **Klercide® Sporocidal Active Chlorine** based on sodium hypochlorite with 0.5% available chlorine (5000 ppm av Cl). This Klercide® has a high virucidal activity with proven effectiveness against the Human Adenovirus C;[23]

(2) **Spor-Klenz® Cold Sterilant** based on hydrogen peroxide (and peracetic acid and acetic acid) with a minimum contact time of 10-30 minutes at room temperature (depending on the microorganism used). Spor-Klenz® Cold Sterilant has not been tested for adenoviruses or AdenoAssociated Virus (AAV) but has been tested for (even more difficult to kill) naked viruses such as the norovirus and has demonstrated an effect against this naked viruses with a contact time of 10 minutes at room temperature.[24]

As an additional disinfectant in the case of GMO-IMP preparations the UZ Leuven hospital pharmacy clinical trials prefers using **Klercide® Sporicidal Active Chlorine.** For GMO-IMP derived from adenoviruses or AAVs, a standard contact time of **10 minutes** at room temperature has been established. Depending on the microorganism used, this contact time will be revised and possibly extended. In consideration of the limited shelf life (relatively short stability) of chlorine compounds, the standard recommendation is to replace the chlorine solution once a week.[13] Nevertheless, Ecolab Life Sciences® guarantees a durable shelf life during the use of Klercide® Sporicidal Active Chlorine in 1 L packages, since this acts as a closed system (SteriShield Delivery System) that also ensures permanent sterility.[23] From a “best practice” perspective, we prioritize a shelf life of up to **3 months** in the hospital pharmacy, after which the solution will be replaced.

The sponsor is responsible to evaluate whether Klercide® Sporicidal Active Chlorine (or possibly SporKlenz® Cold Sterilant) is sufficient in killing off the relevant GMO-containing IMP and to provide its written approval for use as confirmation. It is also the responsibility of the sponsor to determine the minimum contact time (at room temperature) in function of the microorganism used. **In other words, the UZ Leuven hospital pharmacy clinical trials requires written approval from the sponsor for the disinfectant proposed above, stating the minimum contact time required before the trial with GMO-IMP can start.**

If the aforementioned disinfectants are not conclusive in killing off the relevant GMO-IMP and/or cannot be approved by the sponsor, the **supply of an “suitable”* disinfectant as described in the protocol is the responsibility of the sponsor,** in consideration of the specificity of GMO-containing IMP. The sponsor has the most expertise and knowledge on the characteristics of the studied microorganism (and possibly the vector derived from it) and thus knows how to combat such. This procedure is different from the non-GMO trials in

which standard Klercide® Neutral Detergent and ethanol (70%) are used in disinfection. This is a necessary condition for the approval of the start-up of the trial.

*Requirements for a disinfectant to be "suitable" for use within the UZ Leuven hospital pharmacy clinical trials:

1. Proven **effective** against the GMO or against the microorganism from which the GMO vector was derived (e.g. lipid vs. non-lipid virucidal) tested in 3 phases according to the NBN EN 14476+A1 guidelines following the European Committee for Standardization (CEN) standards25 or according to equivalent standards

2. **Irreversible** killing off of the microorganism

3. **Sterile** (0.2 micron filtered), i.e. no growth of bacteria in the solution being used (particularly, non-fermenters e.g. B. cepacia)

4. **Stable** solution (possibly established per unit of time)

5. **Low aggressive/corrosive** vs. stainless steel in BSC

6. **Manageable** (small) packaging of up to 1 L

7. Solution (> powder) in **spray form**

8. Realistic and pre-established **contact time at room temperature** in function of the concentration of the product and the microorganism being used with a maximum of 30 minutes

9. Obtained authorization on the **Belgian biocide market** and subsequent inclusion in the list of authorized biocides from the FOD. For this, we refer to https://www.health.belgium.be/, after which we proceed to Environmental - Chemicals - Pesticides and Biocides - List of permitted biocides.26 For information purposes: the list of biocides authorized as medical materials falls outside this scope.

6.5.5.3 Rinse time in the BSC

To ensure that any aerosol build-up (formed during the preparation of GMO-IMP and/or cleaning of the BSC) has been completely removed after cleaning and disinfecting the BSC, a rinse time is established before any subsequent preparation can be initiated to reduce the chances of inactivating or contaminating the new IMP (cross-contamination). During this time, the BSC is not used so that an undisturbed laminar air flow can change the air in the BSC ("flushing" of the BSC). The rinsing time is only timed after the end of the contact time (once the effect of the disinfectant is activated) and cleaning of the residue of the disinfectant in the BSC. **A rinse time of 10 minutes is applied by standard**, corresponding to a minimum of 660 air changes in the BSC (hereby referring to the specific aforementioned BSCs available in the pharmacy) after disinfection with Klercide® Sporicidal Active Chlorine or Spor-Klenz® Cold Sterilant. If the rinse time is longer in the function of the GMO-IMP or a specific disinfectant, it is the sponsor's responsibility to inform the pharmacy staff members of such.

6.5.5.4 Spill case in the event of incidents

The following hospital-specific (internal) guidelines for incidents with cytotoxic/chemotherapeutical agents and potentially toxic substances - spill case are applicable:

See Muzlidoc [internal]: Incidents with cytotoxic agents and potentially toxic substances – spill case

6.6 Release of GMO therapy

In the event of a GMO-containing IMP preparation in the pharmacy, the GMO-IMP will finally be released by a pharmacist after preparation. The release process is described in a step-by-step way in a checklist in the study-specific preparation worksheet (which is based on an internal pharmacy-specific template). Drafting the study-specific preparation worksheet before the site opens to the relevant trial is the responsibility of a staff member within the hospital pharmacy clinical trials team. In-process controls are included in the preparation worksheet.

When GMO-IMP is reconstituted in a decentralized way (i.e. in the nursing unit/hospital ward where it will also be administered) by a Trial Bureau employee involved, the Trial Bureau itself is responsible for compliance with the basic guidelines (and any additional guidelines) on biosafety, microbiological safety and microbial practices, and thereby guarantees the proper outcome of the preparation and for the continued administration of the GMO therapy.

6.7 Accountability

The pharmacy is responsible for carrying out general accountability, also referred to as “Drug Inventory”, of GMO-containing IMP in accordance with the requirements as described in the study protocol. Carrying out the patient-specific accountability is delegated by the pharmacy to the Trial Bureau involved. The study coordinator of the Trial Bureau implements these in accordance with the specific requirements as described in the study protocol.

6.8 Transport of GMO-IMP

Whether the GMO-IMP has been prepared, released and dispensed by a pharmacist in advance or only been dispensed, it is further placed in the appropriate transport container for transport to the Trial Bureau/nursing unit/hospital ward involved. The sponsor is responsible for providing a suitable transport container since there is none available at the UZ Leuven hospital pharmacy. The pharmacy is responsible for placing the study medication under suitable conditions in the transport container as specified in the study protocol. The container can then be collected by the study coordinator at the hospital pharmacy counter. The study coordinator is responsible for returning and disinfecting the transport container after administration at a pre-scheduled time.

6.9 Administration of GMO-IMP

The GMO therapy administration will take place based on the guidelines described by the protocol.

Locations classified as L1 or L2 must comply with the following [internal] guidelines when administering GMO-IMP with RN 1 or RN 2, respectively:

https://wiki.uz.kuleuven.ac.be/display/preventie/Bioveiligheid

The standard [internal] guidelines for administration of medicines also apply here and are as follows:

http://wiki/display/public/muzlidoc/Toediening+van+geneesmiddelen

The nursing unit is responsible for having rescue-medication available that must be administered in the event of an adverse event as well as supportive medication.

Adverse drug reactions are reported according to the established [internal] guidelines: http://wiki/display/public/muzlidoc/Medicatiegerelateerde+incidenten+-+definities

6.10 Removal of GMO-IMP

Our internal procedures also apply to GMO-containing IMP and materials (see SOP "STU-APO-08 Destructie[10] [Destruction]") with regard to the removal of study medication. The remainder of the administered medication will be removed through the "hazardous medical waste (HMW)" circuit. For safety reasons, it is not possible to have the used vials or other GMO-IMP residues collected for destruction by the sponsor. Used vials are destroyed immediately after preparation due to safety reasons. We will, therefore, not wait until the accountability logs are completed to destroy the used vials.

See [internal]: http://wiki/display/public/muzlidoc/Verwijderen+en+vernietigen+van+geneesmiddelen

10 https://wiki.uz.kuleuven.ac.be/x/PhnJHw

7. Revision History

Version N°	Reason for the change	Description of the change
2	Harmonization GSOP template	Addition of references and history. Modification of layout in accordance with GSOPS.
	In accordance with regulation 'contained use'	Addition: no involvement of the Department of Prevention & Environment (including the biosafety coordinator) as a support service if the GMO in the context of a trial is already on EU/Belgian market as a medicine.
	In accordance with regulation 'containment levels'	Correction of applicable containment levels: The operational practices regarding patient stay and care on the hospital ward in the case of a trial with GMO-IMP must meet the requirements of containment level HR1/HR2. Operational practices concerning activities on the hospital ward beyond patient stay and care (e.g. reconstitution and administration of GMO-IMP) must meet the requirements of containment level L1/L2. Correction of applicable containment levels in Figure 1 (Flowchart). Addition of note that a varying containment level within a room is allowed provided prior to lowering/rating the containment level the room is 'released'.
	In accordance with SOP STU-APO-05 'Distribution of study medication' - part CSTD	Deletion of explanation and availability PhaSeal™ system from BD. Can only be opted for as an alternative (instead of fixed 2nd choice) in agreement with clinical trials pharmacy.
	Change of material PPE	PPE change: Berner short Z+B+ replaced by Medline short 'Prevention™ Plus'. Required EN standards added. Figure 2 added. PPE change: Gloves section updated. Non-sterile gloves updated with alternative Microtouch Nitra-Tex or Honeywell KCL SivoChem® 759. Required legislation EN ISO standards updated. PPE change: Addition of safety glasses. Addition of abbreviation GTMP.
	Clarification of GMO-based drug definition and exclusion of CAR-T cell therapy	Clarification of definition of GMO-based drug to domain in vivo GTMP. Clarification that ex vivo GTMP, such as CAR-T cell therapy, is not within the scope of this SOP.

8. Annexes

Annex #	Annex name
/	/