Clinical Trial Unit,

Hospital Pharmacy Central Denmark Region

Letter of Introduction

The aim of this Letter of Introduction is to clarify general guidelines for working with the Hospital Pharmacy Central Denmark Region as a collaborative partner when implementing and managing clinical trials.

Further information can be obtained by contacting:

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1. The Clinical Trial Unit

The Hospital Pharmacy's Clinical Trial Unit (CTU) is the Point of Contact for all initial contacts from investigators, Clinical Research Units, pharmaceutical companies and Clinical Research Organisations (CRO).

The CTU is staffed with employees who represent all production and quality departments of the Hospital Pharmacy.

The CTU can be reached by email on weekdays (Monday-Friday).

2. Hospital Pharmacy Central Denmark Region

The Hospital Pharmacy Central Region Denmark (HRM) possesses the necessary authorisations, qualifications and facilities to serve as a professional clinical trial collaborator.

a. Authorisation

According to The Danish Pharmacy Act, HRM is authorised to manufacture and distribute medicinal products (Section 39 Authorisation) adhering to the following legal requirements:

- The Danish Medicines Act
- The Danish executive order regarding medicinal products
- The Danish executive order regarding the manufacture, import and distribution of active pharmaceutical ingredients (APIs) used in the preparation of medicinal products
- The Danish executive order regarding the manufacture and import of medicinal products and intermediary products.
- The Danish executive order regarding the distribution of medicinal products.
- Eudralex Vol. 4 – Good Manufacturing Practice (GMP guideline)

All handling of components and investigational medicinal products – including receipt, storage and distribution - is conducted according to GMP, GDP and GCP.

HRM is frequently inspected by The Danish Medicines Agency ("Lægemiddelstyrelsen").

Information on date of last inspection can be given upon request

Please see appendix 1a and 1b for HRM's "Authorisation to Manufacture and Distribute".

b. Quality Control System

HRM has a quality control system to ensure that all tasks are carried out in accordance with existing laws.

The computer program "e*D*ok" is used for document management. This program is used to store, distribute and to sign read receipts for HRM's policies, guidelines and SOPs.

e*D*ok is an electronical document management system that continually ensures that only the current version of a document is available. No physical copies are available for distribution.

c. Personnel
HRM employs e.g. pharmacists, pharmaconomists, pharmacy technicians, laboratory technicians and service assistants. Personnel with responsibilities within clinical trials receive specific training when relevant.

Upon request CVs (curriculum vitaes) and documentation for completed GCP training concerning relevant personnel can be handed out. The Hospital pharmacy reserves the right to evaluate who is to be considered relevant. This evaluation is carried out when considering each individual clinical trial.

As a rule Hospital pharmacy employees do not sign documents regarding financial disclosures or confidentiality agreements. Permission to gather, store or distribute personal data is not given either.

d. Services and facilities
HRM provides the following range of services regarding clinical trials:

- Advice and guidance in the planning of clinical Trials – e.g. information necessary for the notification form for the Danish Medicines Agency, information on import of medicinal products, blinding, randomisation as well as suggestions for practical and logistical solutions concerning the handling of investigational medicinal products.
- Formulate the "Katalogiseringsskema" (Investigational Medicinal Product Dossier, IMPD) for the Danish Medicines Agency.
- Assesment of stability data (stability testing and/or risk assessment).
- Order, receive and store active pharmaceutical ingredients, investigational medicinal products and relevant equipment – this includes the documentation on import and storage conditions.
- To manufacture, reconstitute, prepare, repackage and label investigational medicinal products.
- Preparation of randomisation lists.
- Blinding of investigational medicinal products.
- Dispense and distribute investigational medicinal products.
- Accountability logs for investigational medicinal products.
- Availability for monitor visits, audits and inspections.
- Destruction of investigational medicinal products.
- Filing of trial documentation

HRM can provide the following facilities:

- Preparation areas for antibiotics
- Preparation areas for cytotoxics
- Preparation areas monoclonal antibodies
- Sterile and non-sterile preparation areas for other categories of pharmaceutical products
- Storage facilities for room temperature products
- Storage facilities for refrigerated products (2°C-8°C)
- Storage facilities for frozen products (minus18°C)
- Laboratories for physical-chemical and microbiological analysis

Details on monitoring and documentation are described in appendix 2.

Details on the facilities – e.g. room classifications – can be obtained by contacting HRM's Clinical Trial Unit (CTU).

3. Cooperation agreement

HRM will formulate a cooperation agreement for each clinical trial. The agreement is between HRM and the investigator. HRM does not enter into agreements directly with companies (pharmaceutical companies or CROs).

Prior to drawing up the agreement, certain documents and information must be made available to the HRM. These are listed in appendix 3, section 1.

The cooperation agreement contains contact details for all relevant liaisons.

The cooperation agreement defines the services that are to be delivered by HRM. The division of responsibilities between HRM and the investigator (sponsor) is also outlined.

Clinical trials are not part of HRM's basic services and are therefore subject to additional fees. The cooperation agreement defines the price for each service and describes the procedures for invoicing.

The cooperation agreement must be finalised and signed prior to site initiation. In case of substantial amendments during the clinical trials' duration, a new version of the cooperation agreement will be drawn up.

4. Requirements on sponsor/investigator

For HRM to be able to provide a dependable and satisfactory service there are certain requirements asked of the sponsors and investigators.

These requirements concern the availability of necessary documentation and access to essential information. See appendix 3 and 4. This information is necessary to be able to configure the set-up of investigational medicinal products in HRM's production systems.

Please note that it is the responsibility of sponsor/investigator to provide up-to date documentation and information to HRM for the duration of the clinical trial.

If the sponsor chooses to supply a registered drug and refers to the SPC (Summary of Product Characteristics) in stead of referring to an Investigator's Brochure or Pharmacy Manual, it is sponsor's responsibility to monitor changes to the SPC and to guarantee that any updates to the SPC are conveyed to HRM.

HRM must be notified and involved as early as possible when planning and initiating a clinical trial. Please invite HRM to preliminary meetings with sponsor/investigator.

5. Production, preparation, dispensing and distribution of investigational medicinal products

HRM makes use of different validated systems for production, preparation and batch documentation. HRM always uses its own validated systems for production, preparation and batch documentation.

All documentation is in Danish. If there is a requirement for translation to another language, the responsibility and cost lies with the sponsor/investigator.

For each clinical trial the specific production system and the format of batch documentation will be indicated in the cooperation agreement.

If the reports provided by IVRS/IWRS or HRM's production systems are not sufficient, HRM can provide drug accountability. HRM reserves the right to use its own forms. These forms can be adapted to each trial.

HRM does not keep empty or opened packaging. Allocated, used or opened packages are discarded immediately after use. Discarding and disposal follows HRM's standard procedures for waste handling (see section 9 in this document).

HRM reserves the right to make demands concerning utensils, infusion fluids etc. to be used in the preparation of the investigational medicinal products. This in consideration of procurement agreements, workstreams and validation of equipment and procedures.

When dispensing or delivering investigational medicinal products, there might be requirements for the receiving party (typically the clinic) to sign for the receipt. In that case the signed document should be sent, e-mailed or faxed to HRM. This requirement will be described in the cooperation agreement. It is important to fully comply with this procedure. HRM will not dispense further investigational medicinal products if receipt is not confirmed.

6. Monitoring visits

Monitors are welcome to visit HRM - the CTU and the relevant production departments. HRM must be informed of the monitoring plan prior to site initiation. Actual visits are planned on an ad hoc basis with at least 10 working day's notice.

During the monitoring visits the monitor will have access to agreed data, investigational medicinal products and relevant personnel. There is a desk ad a photo copier available, but monitor must bring their own telephone and computer. Wi-fi access is available.

Monitors are not granted access to production areas. Access to storage facilities can be arranged – if so accompanied by Hospital pharmacy staff.

7. Audits

HRM participates and should be involved in the planning of audits. This is necessary to ensure that the relevant personnel can be present. Notice must be given at least 20 working days prior to the audit. The final agenda for the audit must reach HRM no later than 5 working days prior to the audit.

8. Receipt of supplies for clinical trials (return of shipping containers, loggers etc.)

Investigational medicinal products and other relevant supplies must be shipped directly to the production department as agreed upon in the cooperation agreement.

Shipments can be delivered to HRM within normal opening hours – Monday-Thursday between 08:00 and 15:00 and Friday between 08:00 and 14:30. Each shipment must contain the

documents necessary to perform receipt and import control. Specific documents will be defined in the cooperation agreement.

If the sponsor demands return of shipping containers, temperature loggers or other material, it is the sponsor's responsibility to arrange and pay for their return. This must be agreed upon when negotiating the cooperation agreement and the arrangement must be evident from the cooperation agreement.

9. Transportation

Investigational medicinal product or other clinical trial supplies can be transported in different ways:

1. Investigator or clinical staff collects the supplies from the relevant production department
2. Hospital pharmacy staff delivers the supplies to the clinic/investigator
3. Use of hospital porter to bring the supplies from the hospital pharmacy to the clinic/investigator
4. Clinical trial supplies are transported on the regular conveyances using MidtTransport (Central Denmark Region's in-house carrier company).
5. Specifically ordered (dedicated) transport using MidtTransport
6. Specifically ordered (dedicated) transport using external carrier company
7. Sponsor/investigator has made own arrangements concerning transport. The hospital pharmacy hand over the clinical trial supplies to the appointed carrier.

The chosen solution for transportation will be clearly described in the study specific cooperation agreement.

When solution 1, 2 or 3 is used, temperature is not logged during transport.

When solution 4 or 5 is used, the temperature is logged during transport. MidtTransport is responsible for the logging and notification of HRM in case of temperature deviations. For transports carried out without deviations, HRM is not in possession of the temperature data, given that these data are gathered, monitored and kept by MidtTransport according to the contract between HRM and MidtTransport.

When solution 6 is used, the temperature is logged during transport. The external carrier company is responsible for the logging and notification of HRM in case of temperature deviations. For transports carried out without deviations, HRM is not automatically in possession of the temperature data, but these can be provided against payment.

When using solution 7, it is the sponsor/investigator's responsibility to make arrangements regarding logging of temperature and access to data.

10. Discarding and disposal

a. Unused investigational medicinal product

HRM can take responsibility for the drug inventory and for the shipment of unused investigational medicinal products to be returned to the sponsor or to destruction. This applies to investigational medicinal products that have not been dispensed from the Hospital pharmacy.

The drug inventory and the shipment can be documented.

When shipping waste for disposal the actual destruction by incineration can not be documented. The incineration is performed by an external company.

All medicinal waste from HRM's Aarhus departments is transported by *MidtTransport* directly from HRM and to *Affaldscentret i Lisbjerg under AFFALDVARME AARHUS.* From here it is shipped with *Marius Pedersen A/S* for incineration at *Reno Nord I/S, Troensevej 2, 9220 Aalborg Ø.* This applies to all medicinal waste.

All medicinal waste from HRM's Herning department is transported by *Marius Pedersen A/S* for incineration at *Reno Nord I/S, Troensevej 2, 9220 Aalborg Ø.* This applies to all medicinal waste.

b. Empty or partly used packages

All medicinal waste from HRM's Aarhus departments is transported by *MidtTransport* directly from HRM and to *Affaldscentret i Lisbjerg under AFFALDVARME AARHUS.* From here it is shipped with *Marius Pedersen A/S* for incineration at *Reno Nord I/S, Troensevej 2, 9220 Aalborg Ø.* This applies to all medicinal waste.

All medicinal waste from HRM's Herning department is transported by *Marius Pedersen A/S* for incineration at *Reno Nord I/S, Troensevej 2, 9220 Aalborg Ø.* This applies to all medicinal waste.

c. Unused investigational medicinal product / Empty or partly used packages discarded by the clinic (investigator)

Investigational medicinal products and packaging that are to be discarded and disposed of by the clinic (investigator) are handled the same way as the rest of the clinic's clinical waste. That means according to local procedures valid for the site.

11. Archiving

Documentation is archived for at least 5 years after completion of the clinical trial.

12. Log of changes

Dato	***Version***	***Ændring***
Januar 2019	3.0	Log of changes added. Details concerning temperature registration during transport added. Appendix 1a (statement from the Danish Medicines Agency added.

Bilag 1a – Hospitalsapotekets fremstiller og distributionstilladelse

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

3 September 2018

Statement concerning manufacturing authorization

Danish hospital pharmacies have according to the Danish law a license to prepare drugs.

Hospital pharmacies have therefore not an official certificate from The Danish Medicines Agency.

This statement confirms that the Hospital Pharmacy Central Denmark Region according to the Danish Pharmacy Law, Decree No 801of 12/06/2018 is allowed to produce medicinal products for clinical trials. The hospital pharmacy is also allowed to import compassionate use medicinal products and medicinal products for clinical trials.

Claus Mortensen
Medicines Inspector
CMO@DKMA.DK
Telephone: +20939054

Appendix 1b – Manufacturing and distribution authorisation

Hospitalsapoteket
Region Midtjylland
Nørrebrogade 44
8000 Aarhus C
Phone. +45 7846 3641
Hospitalsapoteket@auh.rm.dk
www.regionmidtjylland.dk

Date 20.06.2018
Charlotte Bjørn
Phone +45 2327 7042
chabjoer@.rm.dk

Statement concerning manufacturing and distribution authorisation

This statement confirms that Danish hospital pharmacies by law are licensed to manufacture and distribute drugs.

The Hospital Pharmacy operates in accordance with Danish legislation and EU GMD/GDP guidelines and is regularly inspected by the Danish Medicines Agency, but licenses are not issued.

Date 20.06.2018
Director of Pharmacy
Anette Thomsen

Date 20.06.2018
Head of Quality, Qualified Person
Charlotte Bjørn

Authorisation number for Hospital Pharmacy Central Denmark Region: 395

Afdeling Herning
Gl. Landevej 61
7400 Herning

Afdeling Viborg
Erik Glippings Vej 3
8800 Viborg

Afdeling Skejby
Palle Juul-Jensens Boulevard 99
8200 Aarhus N

Afdeling Aarhus
Nørrebrogade 44
bygning 17
8000 Aarhus C

Afdeling Horsens
Sundvej 30
8700 Horsens

Afdeling Randers
Skovlyvej 1
8930 Randers NØ

Administration
Nørrebrogade 44
bygning 14b
8000 Aarhus C

Kvalitet
Nørrebrogade 44
bygning 14b
8000 Aarhus C

Appendix 2 – Hospital pharmacy facilities – monitoring and documentation

a. Temperature monitoring

In all locations (storage rooms, cold rooms, refrigerators) where medicinal products are stored the temperature is logged.

Where possible this is done by using CTS (CTS = BMS = Building Management System).

In locations where CTS is not an option external loggers ("MicroLite" and "Testo") are used.

CTS sensors and external loggers are re-validated yearly.

The departments of HRM are each responsible for the temperature monitoring. In each department one person has been appointed responsible for the task.

Temperature monitoring using CTS

CTS-sensors register and log the temperature at least every 10 minutes.

If 3 successive readings from the same sensor are out of the acceptable temperature range, an alarm is triggered in the technical support department.

During HRM's opening hours the technical support department contacts the department where the alarm has been activated. The department is responsible for corrective measures, relocating and quarantining the stock if necessary and the casework regarding the temperature deviation.

Outside opening hours the technical support department contacts the pharmaconomist on duty or the relevant supervisor, who will then see to the corrective measures, relocating and quarantining of stock if necessary as well as assigning the casework regarding the deviation to the relevant party on the next work day.

Once weekly the technical support department sends data files from the CTS system to HRM. This data shows temperature logs for the past 7 days.

If any readings are outside the acceptable temperature range, the person responsible makes an assessment of the data. If the duration of the temperature excursion is less than 30 min, the excursion is documented on the print-out by recording the cause (e.g. when medicinal products are put into stock), signing and dating the document. In the case of temperature excursions longer than 30 minutes, a deviation report will be completed.

Temperature monitoring using external "MicroLite" logger

- Data is logged every 15 minutes
- The logger is manually checked (no printing) at least once a week to see, if there have been any excursions since the last check.
- If the outside temperature exceeds 25 ºC, the check is performed daily during the working week.
- Data from the logger is downloaded to a computer and the temperature logger is reset every 3 months. Data is filed on HRM's network drive.

If temperature excursions are observed during the weekly check, the data from the logger is downloaded and the logger is reset. The observed excursion is assessed by the person responsible for the department's temperature monitoring. A deviation report is drawn up and relevant corrective measures are implemented.

Temperature monitoring using external "Testo 174 Termologger"

- This type of logger is only used as a back up system in case of CTS failure in the Herning department

Temperature monitoring documentation (CTS and external loggers)

Documentation consists of printed graphs. These are filed by the individual departments for 5 years.

It can be obligatory for some clinical trials to file the temperature records for up to 15 years. In that case it is the responsibility of the clinical trial monitor to make paper copies of the documentation and file these in the study files.

b. Environmental monitoring

In compliance with GMP and HRM's standard operation procedures the work environment is monitored at fixed intervals using validated methods.

The following methods are used in HRM's environmental monitoring program.

Microbiological testing:

- Agar plates with disinhibitor for gloves/hands
- Agar plate (settle plates) with disinhibitor for air. Passive sampling.
- Contact plates with disinhibitor for surfaces, equipment and clothing
- Swab sampling for surfaces and equipment
- Volumetric air sampling

Other methods:

- Particle counting

GMP guidelines do not specify any special requirements for rooms used to manufacture non-sterile medicinal products and thus no special requirements for the environmental monitoring. Based on the GMP guidelines definition of grade D rooms, HRM has composed a programme for monitoring the environment in rooms where the preparation of non-sterile medicinal products is carried out.

c. Access

Access to buildings, rooms and storage facilities is limited according to the standard operating procedures of HRM. Only employees have access to production rooms, storerooms, cold room and refrigerators.

Appendix 3 – Check list

SECTION 1

The following documents and information (Section 1) must be forwarded to HRM (Hospital Pharmacy Central Denmark Region) prior to the negotiation and drawing up of the cooperation agreement.

Protocol	
Current version of the trial protocol (Please specify number and attach document)	
Amendments if relevant (Please specify number and attach document)	
Protocol summary in Danish	
Documents/information regarding investigational medicinal products (IMP)	
List of all IMPs supplied by sponsor (Please state all trade names, generic names, administration form and pack size.)	
List of all IMPs where HRM must use registered medicinal products from stock (Please state all trade names, generic names, administration form and pack size.)	
Investigator's Brochure/SPC for all IMPs (Please specify version/date for last update and attach the documents*.)	
Procedure for ordering IMP (E.g. IWRS/IVRS, Hospital pharmacy to manage stock and place orders through usual vendor, order by fax or e-mail to monitor/sponsor?)	
List of all equipment, labels and/or other materials supplied by sponsor (Please specify what is supplied and where/when it is to be used)	
List of all equipment, labels and/or other materials where Hospital pharmacy must use goods from own stock (Please state all trade names, specifications and where/when it is to be used.)	
From which country is the IMP shipped?	
How must receipt be acknowledged? IWRS/IVRS, fax, e-mail?	
Will IVRS/IWRS be used for allocation of IMP to patients? (If "Yes", please specify version of User Guide and attach document. Specify what activities the Hospital pharmacy is to carry out in the IWRS)	
How often will IMP be delivered?	
How many packages does each shipment contain?	
How many parcels (eg cool boxes) will each shipment consist of?	
Authority approvals	
Approval from The Danish Medicines Agency (all approvals – with and without conditions) (Please specify "Case no." and date and attach the documents.)	
Approval from the relevant Ethics Commitee (all approvals – with and without conditions) (Please specify "Case no." and date and attach the documents.)	

Manufacturing Authorisation or Wholesale Dealer Authorisation for the manufacturer/distributor of IMP (Please attach copy of current authorisation)	
Contact details	
Investigator (sub-investigator). State title, name, clinic, address, phone no. and e-mail address.	
Study nurse. State title, name, clinic, address, phone no. and e-mail address.	
Sponsor. State company, title, name, address, phone no. and e-mail address.	
Person responsible for finance. State title, name, address, phone no. and e-mail address.	
Monitor. State company, title, name, address, phone no. and e-mail address.	
Payment data (debtor no. and FAS no. if relevant)	
Monitoring	
Monitoring plan (Be as detailed as possible on monitoring interval, expected duration of visits, which hospital pharmacy personnel should be present and specify what data/documentation the monitor needs access to.)	
Miscellaneous	
Are there other tasks which HRM is expected to fulfill? (If "Yes", please specify/describe in detail)	

* PLEASE NOTE!

Regarding investigational medicinal products supplied from sponsor, it is the responsibility of the sponsor to guarantee that all documents required are the up-to-date versions and that they are made readily available for HRM for the duration of the clinical trial.

The sponsor is responsible for monitoring any changes to the published SPC and for informing HRM of any changes concerning the investigational medicinal products in use.

Regarding investigational medicinal products where HRM uses registered products from stock, monitoring changes of SPC's is part of the standard procedures undertaken by HRM.

SECTION 2

The following documents and information (Section 2) is required by HRM no later than 20 working days prior to dispensing of the first dose to the first patient (provided that terms of cooperation have been finalised and agreed upon in the cooperation agreement).

Protocol (if amended after SECTION 1 was completed)	
Current version of the trial protocol (Please specify number and attach document)	
Amendments if relevant (Please specify number and attach document)	
Information regarding handling of IMP	
Investigator's Brochure/SPC for all IMPs (Please specify version/date for last update and attach the documents if amended after SECTION 1 was completed *.)	
"Pharmacy Manual" or other detailed description of the handling of IMP (Please specify version and attach document.)	
Specifications for equipment such as filters, syringes etc. (List relevant equipment and its specifications)	

* PLEASE NOTE!

Regarding investigational medicinal products supplied from sponsor, it is the responsibility of the sponsor to guarantee that all documents required are the up-to-date versions and that they are made readily available for HRM for the duration of the clinical trial.

The sponsor is responsible for monitoring any changes to the published SPC and for informing HRM of any changes concerning the investigational medicinal products in use.

Regarding investigational medicinal products where HRM uses registered products from stock, monitoring changes of SPC's is part of the standard procedures undertaken by HRM.

Appendix 4 – Master data in addition to Investigator's Brochure, SPC or Pharmacy Manual

If required by HRM, the data listed below must be made available to HRM no later than 20 working days prior to dispensing of first dose to the first patient.

Master data	
Specific density of liquid formulations (stated in g/ml and valid for the temperature that the IMP must be stored and handled at)	
Surplus of active substance (solid/lyophilize)	
Amount (weight) of excipients (solid/lyophilize)	
Concentration of active substance after reconstitution	
Stability after opening	
ATC-code (if known)	

PLEASE NOTE!

It is the responsibility of the sponsor to guarantee that the up-to-date data are made readily available to HRM for the duration of the clinical trial.