Pharmaceutical Quality Policy

DND*i* Policies

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DNDi
Drugs for Neglected Diseases *initiative*

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I. Introduction and objectives

The mission of DND*i* is to develop safe, effective and affordable new treatments for patients suffering from neglected diseases, and to ensure equitable access to these. The quality of investigational medicinal products (IMPs) is critical to safety and efficacy, as well as successful product development and registration in a highly regulated international environment.

The overall quality objective of DNDi is therefore to establish, implement and maintain a system that assures the supply of IMPs with quality attributes appropriate to the requirements of patients, healthcare providers and regulatory authorities.

The purpose of this policy is to describe the overall intentions and direction of DND*i*'s pharmaceutical quality system (PQS), encompassing the basic principles, management responsibilities and procedural elements that, together with current Good Manufacturing Practices (cGMP), Good Distribution Practice (GDP), product design and risk management, influence product quality assurance, i.e. fitness for intended use.

II. Scope

This policy applies to the development, technology transfer, manufacture, analysis, packaging and distribution of IMPs for clinical trials, including the re-packaging or manipulation of licensed products, these activities and services being subject to cGMP and GDP. The quality principles and requirements established in this policy shall also be applied to Non-Investigational Medicinal Products (NIMPs) used in clinical trials, for example challenge agents, rescue, concomitant or background medications, unless they have a marketing authorisation in the countries concerned. It is the responsibility of all DND*i* staff and consultants managing these activities to read, understand and ensure compliance with this policy.

III. Policy

This policy, along with its associated standard operating procedures, will constitute the quality manual that specifies DND*i*'s pharmaceutical quality system. The basic principles of the PQS are described in section 3.1 below.

3.1 Basic Principles

DND*i* employs a collaborative R&D model to achieve its mission, in which product development and IMP supply are executed entirely through an external network of pharmaceutical company partners, contract development and manufacturing organisations, and expert consultants. DND*i* is ultimately responsible to ensure systems are in place to assure the control of these activities. During the later stages of clinical development, DND*i* seeks partner organisations who, as future license holders, will assume full responsibility for the manufacturing and distribution of the commercial product.

DND*i* will comply fully with international pharmaceutical quality and regulatory requirements. However, DND*i* conducts R&D in a large number of countries, whose cGMP and GDP requirements range from minimal to extensive. Considering DND*i*'s mission and geographical scope, the guidelines published by the World Health Organisation (2007; 2010) represent the most relevant requirements; however specific national and regional regulations (e.g. US Code of Federal Regulations, EC Directives) will also be observed according to the specific project circumstances. In addition, DND*i* will allow alternative, equivalent quality procedures to be used by external partners where scientifically justified and consistent with applicable guidelines.

The design of the PQS will be consistent with cGMP, GDP and the International Conference on Harmonisation (ICH) guideline Pharmaceutical Quality System Q10 (2008), and will be applied in a manner that is proportionate to each of the product lifecycle stages, recognising the different goals and knowledge available at each stage. For example, during the early stages of development, the manufacturing process and product are still evolving and may not be validated to the extent needed for routine commercial production; in this case, the main objectives of the PQS will be to assure the appropriate quality of IMPs and to manage knowledge as an input to commercial product development. During the later stages of development, where the manufacturing process and product are well-defined, it is DND*i*'s intention to utilise the PQS of the commercial manufacturing partner to the fullest extent possible.

These basic principles guide the pragmatic design of the PQS and the fundamental set of standard operating procedures. The critical role of DND*i* senior management in the PQS is now set out in section 3.2 below.

3.2 Management Responsibilities

The R&D Director, as a member of the DND*i* Executive Team, has ultimate responsibility for ensuring that an effective PQS is implemented, and that roles and responsibilities are defined, communicated and realised throughout the organisation. The R&D Director, supported by the Pharmaceutical Development Director, will:

- Define the quality objectives for the organisation needed to implement this policy and the PQS;
- Provide strong and visible support for the PQS in order to create commitment to quality, facilitate communications, advocate continual improvement and allocate appropriate resources (which are human or financial in the case of DNDi);
- Participate in the design, implementation, monitoring and maintenance of the PQS;
- Ensure that an effective escalation process exists to raise quality issues rapidly to the appropriate levels of management;
- Ensure that pharmaceutical quality decisions are made objectively and fulfill the applicable national and international guidelines/regulations;

- Conduct an annual review of product quality issues, as well as regular reviews of the PQS, using suitable performance indicators to measure its effectiveness and progress against quality objectives;
- Review the pharmaceutical quality policy periodically for continuing effectiveness.

Key elements of the PQS are presented in the following section, organised into groups of closely related activities.

3.3 Pharmaceutical Quality System Elements

3.3.1 Administration

It is DND*i* policy that cGMP and GDP activities will be described in written standard operating procedures; these will be reviewed and approved by relevant, qualified personnel as being fit for purpose and in compliance with regulatory requirements.

All procedures will be available in 'read only' electronic format to all staff and consultants via the DND*i* intranet, and may also form the basis for training.

3.3.2 Contract Services – Chemistry, Manufacturing and Controls (CMC)

CMC service providers will be evaluated prior to use to assure that they have adequate premises, equipment, knowledge, experience and competent personnel to provide the required services, and that they are able to comply with applicable cGMP and GDP standards. The evaluation should take into account a service provider's history and the nature of the services supplied. If an audit is required, it should be conducted on behalf of DND*i* by independent specialists or a team designated by management for this purpose. The audit findings and recommended corrective actions will be documented, along with an effective follow-up plan.

There must be a written quality agreement between DND*i* and the service provider that clearly establishes the quality assurance responsibilities of each party for, inter alia:

- Purchasing of raw materials and components;
- Manufacturing and testing;
- Packaging, labeling, release and distribution;
- Retention of relevant documentation and reference samples; and
- The procedures to be followed in the event of deviations, quality incidents, non-conformance with specifications, suspected product defects and regulatory inspection findings.

The quality agreement should provide for at least one routine quality audit per calendar year, at the discretion of DND*i*, as well as for special cases e.g. product recalls, repeated rejections, or announcement of a regulatory inspection.

3.3.3 Data Integrity and Document Control

Data integrity is a fundamental part of the PQS to ensure product quality. CMC service providers shall have suitable procedures and validated systems in place to ensure that all data, including metadata required to reconstruct GMP activities, is attributable, legible, contemporaneously recorded, original or true copy, accurate, complete, consistent, enduring and available (so-called "ALCOA+"). Data integrity requirements apply equally to both paper records and electronic data throughout the product life cycle.

Comprehensive, accurate and well-controlled documentation is also critical to successful and compliant quality assurance. Consequently, it is DND*i* policy that all documentation relating to cGMP and GDP activities is clearly written, accurate, readily available and stored securely. In this regard, CMC service providers will make all relevant documentation available for review by DND*i* and regulatory authorities, and certified copies of key documents and reports will be provided to DND*i* as set out in the relevant contract or quality agreement. DND*i* will establish a documentation life cycle management process that encompasses document creation, review, approval and notification, as well as change control for revisions, obsolescence and archival. All documentation will be retained for a period not less than that specified in a records retention schedule.

In addition, DND*i* will establish Product Specification Files (PSFs) to support the certification or other assessment of an IMP by authorised personnel e.g. Qualified Person (QP). It will contain detailed information on manufacturing processes, packaging, labeling, quality control testing, batch disposition, storage conditions and shipment for each IMP. However, the existence of a PSF does not exclude the use of any other information that would aid in assessment and decision-making.

3.3.4 Materials

It is DND*i* policy that IMPs used in clinical trials in the EU/EEA, or for export from the EU/EEA, shall be certified by a Qualified Person. Where QP certification is delegated to a CMC service provider, this must be referenced in the pertinent Clinical Trial Application and quality agreement; likewise, where the supply chain contains multiple service providers, certification will be facilitated by the use of QP agreements. A QP declaration must also be submitted as part of EU regulatory filings when a CMC service provider is located outside the EU who would not otherwise require an IMP license. Supplies will only be distributed to investigators when the following two steps have been completed: (i) certification of the IMP after quality control ("technical green light") and (ii) regulatory authorization to use the IMP ("regulatory green light").

DND*i* will initiate suitable stability testing programmes to demonstrate that the quality of an IMP is maintained at its designated storage condition, and for the purpose of assigning appropriate Use Periods/Use by Dates and any special restrictions (e.g. protect from light, do not freeze). The stability testing programmes should employ stability-indicating methods and accelerated/long term storage conditions appropriate to the climatic zone(s) in which use of the product is planned.

IMP stability shall also be re-evaluated following any significant change in the active pharmaceutical ingredient, manufacturing process, formulation or packaging.

Concerning the return of unused IMP supplies, this shall be conducted in accordance with written instructions provided by DND*i*. Unused supplies will not be sent to DND*i* and will normally be destroyed, and reissue or reuse of such supplies will only be considered in exceptional circumstances when satisfactory quality can be assured (e.g. well-controlled storage by manufacturers or depots, complete documentation). Adequate records should be maintained to enable the reconciliation of returned supplies versus subsequent destruction or reuse. Destruction operations shall not be carried out without prior authorization by DND*i*.

In order to assure the safety of patients and the quality of its products, DND*i* will thoroughly investigate any complaints it receives, whether verbally or in writing, concerning potentially defective IMPs and take appropriate corrective action based on the results of the investigation. Complaints shall also be subjected periodically to trend analysis. For defects which, if confirmed, could pose a serious health risk or lead to regulatory action (e.g. labeling error, sterility failure, tampering, counterfeiting), DND*i* will establish a recall system to ensure that affected IMPs are removed promptly from use and are fully accounted for.

3.3.5 Personnel

Establishment and maintenance of a satisfactory system of quality assurance relies on sufficient numbers of suitably qualified and trained personnel. Their individual responsibilities should be clearly defined, understood and recorded in job descriptions. In addition, key staff at DND*i* responsible for supervising CMC activities should possess relevant and recognised scientific qualifications (e.g. chemistry, pharmacy), as well as adequate practical experience and understanding of the manufacture and quality control of IMPs, in order to exercise independent professional judgment.

All DND*i* staff engaged in CMC activities should be aware of the principles of cGMP and GDP that affect them and receive training in the procedures relevant to their activities; training records should be kept.

Consultants and contract staff should be qualified for the services they provide, and evidence of this should be included in the training records.

3.3.6 Quality Management

Continued assurance and improvement of pharmaceutical quality also relies on the following elements. The responsibility for notification, review and approval of these items will be defined in the quality agreement with the CMC service provider (see section 3.3.2).

- All changes potentially impacting quality, e.g. relating to facilities, equipment, materials, manufacturing processes, test methods, storage or packaging, shall be carefully controlled by the use of a formal change control system. This ensures that all potential benefits and

risks are systematically assessed before implementation, and are tracked and communicated to relevant parties.

- All deviations, quality alerts or incidents, non-conformance with specifications, suspected product defects, complaints or regulatory inspection findings shall be fully investigated in order to determine root causes. Emerging or systematic trends may be identified during the course of this assessment that require additional investigation. Investigations should, if necessary, extend to other batches of the same IMP or other products that may be associated with the specific observation or failure. A written record of the investigation will be prepared, and should include the conclusion and any recommended corrective and preventative actions (CAPA).

In addition, DND*i* will:

- Proactively use quality risk management tools to identify, scientifically evaluate and control potential quality issues during development and manufacturing. The level of effort and formality of evaluation should be commensurate with the level of risk.
- Maintain effective procedures to manage IMP recall and perform mock recall exercises periodically.
- Using a system of tracking tools, undertake monitoring and periodic management reviews of quality, including:
    - The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities;
    - Quality performance measures, including product quality monitoring, trending, complaints and recalls, effectiveness of CAPA;
    - Improvements to manufacturing processes and products;
    - Improvements to the PQS and related processes;
    - Provision of training and the allocation of resources;
    - Knowledge capture and dissemination;
    - Escalation of important issues for discussion with senior management.

3.3.7 Regulatory

CMC information represents an integral component of regulatory submissions for clinical trial applications, regulatory agency meetings, product registration and post-approval changes/variations.

The accuracy of CMC data presented in regulatory submissions will be verified against its primary source, while the content will be reviewed to ensure that it is clear, supported scientifically by the data, is suitably formatted and fulfills the applicable regulatory requirements. When DND*i* is the sponsor of the clinical trial(s), the CMC submission and any subsequent responses to regulatory questions will be approved by a duly authorised member of DND*i* staff. In the case of market authorisation applications, the license applicant will have final responsibility for approval of the CMC submission.

IV. References

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