Good Practice Guide

Harmonizing the Definition and Use of Non-Investigational Medicinal Products (NIMPs)



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This Guide aims to address relevant approaches to support the regulatory, manufacturing, and clinical site aspects related to NIMPs as well as exploring the importance of the initial sourcing strategy. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

A Non-Investigational Medicinal Product (NIMP) is a medicinal product not defined within the description of an IMP and may be considered a background, challenge, concomitant, endpoint, escape, or rescue medication dosed for preventive, diagnosis, or therapeutic reasons. NIMP is EU terminology, but has been accepted globally within the pharmaceutical industry.

Currently there are no complete regulations or practical guidelines for NIMPs and pharmaceutical organizations may overcomplicate their clinical trials by submitting products as IMPs when they could have been managed as NIMPs. The ISPE Good Practice Guide: Harmonizing the Definition and Use of Non-Investigational Medicinal Products (NIMPs) is intended to provide an overview of regulatory requirements and to help to alleviate regulatory and operational ambiguity surrounding NIMPs.

Definitions of key terms are provided and the Guide summarizes current consensus on what the pharmaceutical industry and regulations/guidelines define as NIMPs. In addition, an appendix is provided that categorizes regions or countries according to regulations and practices related to NIMPs. Current approaches to supply chain management of NIMPs are also considered.

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1 Introduction

1.1 Background

In 2011, the ISPE Investigational Product Community of Practice (IP COP) Non-Investigational Medicinal Product Task Team, with the help of ISPE, issued an on-line survey with the goal of understanding how the pharmaceutical industry manages Non-Investigational Medicinal Products (NIMPs). The survey was distributed to the ISPE IP COP, as well as several pharmaceutical groups within LinkedIn™. The survey was completed by 57 participants [1].

Overall, the results from the survey suggest that the pharmaceutical industry is conservative with its use of NIMPs. This seems to originate from the regulatory and operational ambiguity that surrounds the use of NIMPs. This Guide aims to shed some light on this relatively grey area of the pharmaceutical industry.

The EU guidance [2], lists five categories of NIMPs:

1. Background Medication
2. Challenge Agent
3. Concomitant Medication
4. End-Point Medication
5. Rescue Medication

Although the survey indicated some degree of confusion and misunderstanding surrounding practical and operational aspects of NIMP management, three key findings from the survey data were selected and have been elaborated upon:

1. Which NIMP category is most often utilized?
2. Which NIMP category is most commonly challenged by the local competent authorities?
3. Which functional area of the clinical trial sponsor organization determines if a medicinal product should be categorized as an Investigational Medicinal Product (IMP) or as a NIMP?

Out of these European Union (EU) guidance categories, the Background Medication was utilized most often among the survey responders. Concomitant and Rescue Medication followed closely. No additional categories were identified suggesting that these categories were sufficient to capture the practical need within the pharmaceutical industry.

Background Medication was indicated as the most regulatory challenged NIMP categorization followed by End-point Medication and Rescue Medication. The higher incidence of challenges associated with Background Medication compared to other NIMP categories may be explained by considering how it is defined. The Background Medication is the standard of care to treat an indication that is the object of a clinical study, and therefore, may be under greater scrutiny by local competent authorities. This is supported by information from several countries whose local regulations require that Background Medication is used strictly in accordance with its market authorization; otherwise, it is considered an IMP (see Appendix 1).

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Another trend from the survey results was which Sponsor department or functional area is considered responsible for the classification of a clinical trial material as a NIMP. The most common response was that a combination of functional areas (e.g., Clinical Supply, Regulatory, Quality, and Clinical (internal Medical Sponsor/Clinical Operations)) is consulted in order to make the determination. A discussion involving several functional areas with all stakeholders present can help to ensure that all points of view are considered. In some cases, a NIMP classification process had been added to an organization's standard operating procedures.

Where organizations allocated the decision to a single functional area, there was a relatively even split between Clinical Supply, Regulatory, and Quality. The Clinical functional area was seemingly under-represented. The Clinical team can provide expert opinion on determining if the clinical trial material is considered a "standard of care" or "background therapy" as defined in the clinical protocol as they are most acquainted with the therapeutic area. It may be contended that a clinical trial material could be used off-label as a NIMP if a Scientific Advisory Committee (SAC) supports that its off-label use is well established (see Section 2.3 of this Guide). However, there is a risk that local competent authorities will not accept this claim (see Appendix 1). The pharmaceutical industry may feel the risk is too high and mitigate that risk by following a more conventional approach; one that treats the material in question as an IMP rather than a NIMP.

The results of this survey confirm the ambiguity concerning many facets of NIMP management. This Guide, the ISPE Good Practice Guide: Harmonizing the Definition and Use of Non-Investigational Medicinal Products aims to address this ambiguity.

1.2 Overview

Currently, there are no complete regulations or practical guidelines for NIMPs. Many Good Manufacturing Practice (GMP)/Good Clinical Practice (GCP) guidance documents and regulations simply "allude" to management of NIMPs within their scope. As a result, organizations may overcomplicate their clinical trials by submitting products as IMPs when they could have been managed as NIMPs. Alternatively, organizations may file clinical trial products as NIMPs only to be denied approval by a health authority later in the process.

The European Commission (EC) has issued a guidance document on the requirements (content) for clinical trial submissions (dossiers) regarding NIMPs, but it does not include "practical operational guidance."

This Guide is intended to provide an overview of regulatory requirements and to help to alleviate regulatory and operational ambiguity surrounding NIMPs.

On 17 July 2012, the EC commission adopted a proposal to issue regulations repealing directive 2001/20/EU [3 and 4] which suggests the new regulations will include standards for "auxiliary medicinal products." These regulations are expected to come into force around 2016.

1.3 Scope

This Guide aims to address regulatory, manufacturing, and clinical site aspects related to NIMPs.

Definitions of key terms are provided and the Guide summarizes current consensus on what the pharmaceutical industry and regulations/guidelines define as NIMPs. In addition, an appendix, based on currently available information, is provided that categorizes regions or countries according to regulations and practices related to NIMPs.

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Current approaches to supply chain management of NIMPs are considered in order to create guidance and schematics around:

- Sourcing strategies
- Approaches to packaging and labeling
- Recommendations for storage and distribution
- Approaches to clinical site re-imbursement
- Approaches to management of drug accountability, traceability, complaints and recalls with reference to the original sourcing strategy

Throughout this Guide, the standard industry term “subject” (applicable to all phases of clinical trials) is used synonymously for “patients” or “CT participants.” For the purposes of this Guide, “ancillary” items including infusion solutions, water for injection, saline, and medical devices such as syringes, needles, etc., are considered out of scope.

Adjuvants are outside the scope of this Guide. “Blinded” supplies including “comparators,” see the ISPE Good Practice Guide: Comparator Management [5], are also outside the scope of this Guide as blinded drug supplies and comparators are defined as IMPs.

Organizations usually have their own nomenclature to describe the use of study drugs within a protocol. Therefore, it is not possible for this Guide to reference all possible drug descriptors and users of this Guide need to examine each drug in their protocol based on protocol design and objectives.

1.4 Purpose

This Guide aims to provide practical guidance based on industry experience and to support to personnel, organizations, and clinical sites which manage NIMPs.

1.5 Benefits

This document is intended to provide support so those in Clinical Supplies, Quality, or Clinical Operations who may have a need to include NIMPs within their clinical protocols. A benefit of this document is that it summarizes the current regulatory guidelines and incorporates a practical operational guidance for use of NIMPs. By combining these main areas of interest, it is intended to alleviate a perceived gap within the pharmaceutical industry.

1.6 Key Concepts

Approved Label

The information contained on the label for the products, which is defined as part of the marketing authorization.

Background Medication

A medicinal product that is administered to each of the subjects (independent of treatment assignment) to treat the indication that is the object of the study. This therapy is generally considered the current standard of care [2]. All subjects receive the product. Background medication is considered a NIMP as no data or information regarding the effectiveness of these products to itself or relative to another medicinal product is collected.

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Comparator Product

An investigational or marketed product (i.e., active control) or placebo used as a reference in a clinical trial [6]. Regulations define comparators as IMPs (i.e., not NIMPs) because during the clinical trial, one gains information concerning the effectiveness of the comparator to its self or relative to another medicinal product. For further information, see the ISPE Good Practice Guide: Comparator Management [5].

Competent Authorities

This Guide uses the term competent authorities and also may be considered synonymous with regional regulatory agencies.

Concomitant Medication

A medicinal product that is administered to a subject as part of their standard of care for a condition that is not the indication for which the IMP is being tested [2]. The concomitant medication is not the object of the study. All subjects receive the product and concomitant medication is considered a NIMP as no data or information regarding the effectiveness of these products to itself or relative to another medicinal product is collected.

End-point Medication

A medicinal product that is administered to a clinical trial participant to measure the effect of the IMP or other relevant clinical endpoint.

Extemporaneously

Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula). Also, any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the official formula), see 2001/83/EC article 3(1) and (2) [7].

Investigational Medicinal Product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization, but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form [7].

Non-Investigational Medicinal Product (NIMP)

A medicinal product not defined within the description of an IMP and may be considered a background, challenge, concomitant, endpoint, escape, or rescue medication dosed for preventive, diagnosis, or therapeutic reasons. The medicinal product can be provided by the study sponsor or the clinical site. NIMP is EU terminology, but has been accepted globally within the pharmaceutical industry

Off-label Use

Use of a medicinal product in a way other than what is defined in its marketing authorization.

Standard of Care

See Background Medication and Concomitant Medication.

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Rescue Medication

A medicinal product used to manage the subject's treatment when the efficacy of the IMP is either over expressed or under expressed resulting in a safety concern to the subject.

Further definitions are included in Appendix 3.

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2 Regulatory Framework and Considerations

2.1 Summary and Interpretation of Current Regulations Related to NIMPs

This section provides a detailed overview of EU and US regulations related to NIMPs, which are current at time of publication. Interpretation of the regulations and reference to country specific requirements is presented. The section concludes with a discussion on the use of NIMPs without a market authorization and off-label use. A practical and straightforward method to determine if a medicinal product should be considered a NIMP or an IMP is provided, along with illustrative examples.

When making a designation of a NIMP versus an IMP, study drugs should be considered on a case by case basis. Study drugs can be grouped into different categories, such as standard of care or rescue medication. Although these designations can provide insight into a study drug classification, individual drug attributes, e.g., source and presentation, are key factors that also should be examined as part of the classification. The attributes of the individual drugs selected and the use of the drugs within the protocol are the determining factors when making a NIMP versus IMP designation. How a specific drug regimen is selected for a subject, e.g., randomized by Interactive Response Technology (IRT) or physician selected, is not a determining factor when making a NIMP versus IMP designation.

2.1.1 EU Guidance and Regulations

The most recent guidance on NIMPs was produced by the Health and Consumer Protection Directorate-General of the European Commission. The document is part of Chapter 3 – *Quality of Investigational Medicinal Products* of Volume 10 Clinical Trials Guidelines. It is entitled *Guidance on Investigational Medicinal Products (IMPs) and "Non-Investigational Medicinal Products" (NIMPs)* [2]. The EU guidance helps to clarify and distinguish an IMP from an NIMP in accordance with applicable EU legislation. It discusses safety and traceability of NIMPs, as well as implications for sourcing, dependent on the status of the Marketing Authorization (MA) of a NIMP.

A NIMP, while considered a medicinal product, is outside the definition of an IMP; However, many of the requirements set forth for IMPs are also requirements for NIMPs. For example, it is the responsibility of the sponsor to ensure that the NIMP is of suitable quality and that the safety of the clinical trial subject is not jeopardized (see Section 3.2.2 of this Guide). The EU guidance [2] states that "the same level of quality and safety should be ensured for the NIMPs as for the IMPs." In addition, the sponsor must adhere to Good Clinical Practices during the clinical trial. One must be able to "adequately reconstruct the movement and administration of the NIMP [2]." Furthermore, traceability at the subject level and when required by the clinical trial protocol, evaluation of compliance are expected.

"The Detailed guidance on the request to the local Competent Authorities for authorization of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)" [8] contains stipulations on where NIMPs should be sourced from and the requirements of the NIMP dossier. These stipulations and requirements are expanded upon in *"The Rules Governing Medicinal Products in the European Union, Volume 10"* [2].

Possible scenarios for sourcing of NIMPs, in order of preference by the EU include:

- NIMP with an MA in the country that is involved in the CT
- NIMP with an MA in another Member State (MS)
- NIMP with an MA in an International Conference on Harmonisation (ICH) country (e.g., EU, US, and Japan) or in a country having a Mutual Recognized Agreement (MRA) with the EU (e.g., Australia, Canada, New Zealand, and Switzerland)
- NIMP with an MA in another country not previously noted

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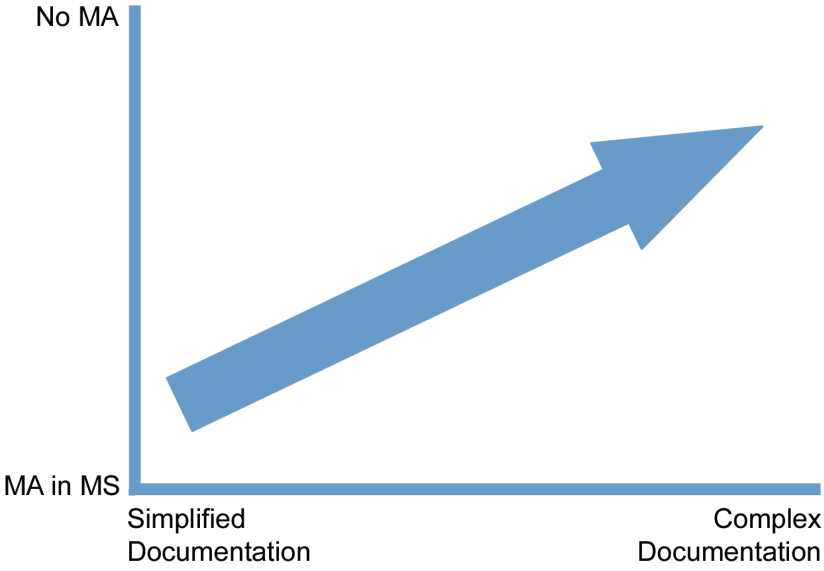
- NIMP without an MA.

Figure 2.1 illustrates that the level of information required in a NIMP dossier varies relative to how a NIMP is sourced, i.e.:

- For a NIMP sourced from an MS, the dossier could be considered simplified.
- For a NIMP with an MA in a non-ICH or non-MRA country or a NIMP that does not have an MA, the dossier requirements become significantly more rigorous [2].

The level of detail contained in the NIMP dossier is commensurate with the perceived risk associated with the status and source of the MA of the NIMP.

Figure 2.1: NIMP Dossier Requirements Relative to Marketing Authorization Status



2.1.2 US Regulations

There are no distinct Investigational New Drug (IND) regulations surrounding the use of NIMPs in the US. Regulations pertaining to INDs are focused on the exemptions allowed for use of a drug in an investigational setting.

The use of a drug in a clinical trial as per approved label does not usually require the filing of an IND; however, an unapproved drug used as a NIMP could require an IND filing. This IND filing would be for the drug under study rather than for the NIMP, but should include information on the NIMP.

Where NIMPs are used in several different studies (similar to a Drug Master File reference), an IND could be filed separately for the NIMP (although this would be considered unusual).

Where a NIMP is a US-approved medicinal product, it may be disclosed in the clinical protocol only as “included in the dosing regimen.”

2.2 Interpretation of the Regulations

EU regulations define NIMPs as well as the requirements for the dossier, traceability, quality, and safety of NIMPs. There are no comparable specific regulations available in the US.

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Key aspects of the European regulations, which consider both GMPs and GCPs, include:

- Dedicated regulations in terms of manufacturing of IMPs do not apply to NIMPs
- The quality and safety of NIMPs should be ensured in the same way that they are for IMPs
- Traceability of NIMPs should be ensured
- Documents for a Clinical Trial Application Dossier may by simplified depending on the marketing authorization status
- Safety reporting

NIMPs used in clinical trials should be safe and in compliance with the EU GMPs for medicinal products for human use. Clinical data should be generated in accordance with GCP.

The manufacturing of NIMPs falls outside those GMPs which define requirements for manufacturing of IMPs [6]; however, aspects of the general EU requirements for human medicinal products should be considered, including importation, release, labeling and package inserts, and distribution.

Information to be included on IMP labels (see Annex 13 to the EU GMPs [6]) is not a requirement for NIMPs; however, local competent authorities may recommend an additional sticker listing, e.g., Trial Number, Sponsor Name, and the term “For clinical trial use only.” Examples of local recommendations are provided in Appendix 1. The table demonstrates the level of variability between countries.

Sponsors of clinical trials are considered responsible for ensuring that additional labeling processes at packaging and labeling suppliers or on site are performed in compliance with applicable GMPs and GCPs. Appropriate agreements and procedures explaining the roles and responsibility of all parties involved should be established.

An important aspect in deciding whether a commercially available NIMP may be used without additional labeling depends on its intended use according to its MA. For example, a background treatment may be used without any additional labeling if the intended use of the medicinal product is in accordance with the MA. As long as the trial protocol defines the use of a NIMP as in compliance with the MA (especially its indication), there is less likelihood that an additional label will be needed. Proprietary (brand names) should not be defined in the protocol. Collection of data about the background treatment should not be an objective of the trial; however, the definition of use of a NIMP in accordance with the MA may be challenging in some therapeutic areas, e.g., oncology. Some therapy schemes are not covered exactly by an MA, as state of the art combination treatments (standard of care) may be updated based on publications of leading oncology groups. Standard of care is usually based on national and international consensus, and may vary from country to country. This can lead to different recommendations on the label requirements of a NIMP by local competent authorities. For example, a local commercial product given as background treatment to all subjects within a trial independently of their randomization to a treatment group may need:

- Full IMP label
- An additional sticker with some IMP information

In addition, there may not be any requirements to modify the local commercial product.

It is usually mandatory for multinational trials to check labeling requirements with local competent authorities in each participating country on a case-by-case basis. The sponsor should provide information to justify the classification of a NIMP as a standard of care (see Section 3.3 of this Guide). Alternatively, centrally procured NIMPs labeled in accordance with international IMP labeling requirements [6] maybe provided. In this case, the sponsor should consider supply chain resources, costs, and impact on other planned packaging jobs.

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