Good Practice Guide

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

Connecting a World of Pharmaceutical Knowledge

Good Practice Guide

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

Disclaimer:
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.

Limitation of Liability
In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, or the authors, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

© Copyright ISPE 2013. All rights reserved.

No part of this document may be reproduced or copied in any form or by any means – graphic, electronic, or mechanical, including photocopying, taping, or information storage and retrieval systems – without written permission of ISPE.

All trademarks used are acknowledged.

ISBN 978-1-936379-57-6

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.

Acknowledgements

This Good Practice Guide was produced by a Task Team led by Esther Sadler-Williams of Catalent Pharma Solutions and Lee Miller of Merck & Co., Inc. The work was supported by the ISPE Investigational Products Community of Practice (COP).

Good Practice Guide Core Task Team

Ajay Acharya	Merck & Co., Inc.	USA
Anneli Bergqvist	AstraZeneca	Sweden
Ann Calnan	GlaxoSmithKline (GSK)	United Kingdom
Miriam Cruz	Eisai	USA
Fran Degennaro-Culver	Merck & Co., Inc.	USA
Kristen DeVito	Catalent Pharma Solutions	USA
Lisa Falzone	Bayer Healthcare Pharmaceuticals	USA
Beth Gardner	Takeda	USA
Christine Harloff	Bayer Pharma AG	Germany
Kay-Christian Karstadt	Multipharma GmbH	Germany
Peter Kulmburg	Roche	Switzerland
Dawn Lundin	Merck & Co., Inc.	USA
Karen Main	Astra Zeneca	USA
Lee Miller	Merck & Co., Inc.	USA
Lars Muller	Novo Nordisk A/S	Denmark
Peter Orosz	Boehringer Ingelheim	Germany
Sarbari Roy	AstraZeneca	Sweden
Esther Sadler-Williams	Catalent Pharma Solutions	United Kingdom
Hans von Steiger	Pfizer Inc.	USA
Andrea Zobel	Marken Ltd.	Germany

Special Acknowledgement

The Task Team would like to give particular thanks to Chris Parkinson (GSK) and Mike Arnold (Pfizer) for their general support and professional insights.

Many other individuals reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

The Document Task Team also wishes to thank ISPE for technical writing and editing support by Gail Evans (ISPE Guidance Documents Writer/Editor).

Connecting a World of Pharmaceutical Knowledge

ISPE Headquarters
600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

ISPE Asia Pacific Office
73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office
Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

Table of Contents

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).

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.

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.

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.

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.