Guide on Medical Information
ABOUT INTERFARMA

Interfarma - The Pharmaceutical Research Industry Association - is a non-profit industry group, representing national and foreign companies and researchers responsible for promoting and encouraging the development of scientific and technological research in Brazil, focused on production of pharmaceutical raw materials, inputs, medications and health products.

Founded in 1990, Interfarma currently has 55 member companies. Today, these laboratories are responsible, in the pharmaceutical chain, for sales of 80% of the leading market medications and also for 33% of generics, produced by companies controlled by member laboratories. Interfarma sees research and innovation as factors in economic development and ethics as a fundamental principle of its activities.

The organization encourages debates on topics of interest to society such as clinical trials, healthcare funding and access, combating informality, as well as biotechnology and regulatory system. Among the institutional actions are interaction and closer relations with the various agents, through a frank and open dialogue, especially with health authorities, industry leaders, opinion makers and other stakeholders who can assist in creating a new healthcare scenario, with the main objectives of increasing access and strengthening innovation in Brazil.
The pharmaceutical industry is constantly looking for innovations that turn into therapeutic options for the growing challenges of public health, giving dynamism to a sector that at all times recycles its concepts and opens new horizons for patients and healthcare professionals.

Preamble

In line with the legitimate expectations of Brazilian society, many healthcare professionals have sought technical and scientific information on products and related diseases within the pharmaceutical industry in order to have grounds for clinical practice. Thus, this guide aims at addressing the main topics in the Medical Information area, Department of the pharmaceutical industry responsible for ensuring unification/alignment of answers to scientific and spontaneous questions of the scientific community, thus allowing the balanced, updated and not biased scientific discussion, between the company and healthcare professionals.
Definitions

For the definitions of healthcare professional, those contained in CNS Resolution No. 287/98 should be considered.

- **Unsolicited requests**: scientific spontaneous questions made by healthcare professionals and consumers to the pharmaceutical company, directly or indirectly through company employees.

- **Solicited requests**: questions somehow induced by employee of the pharmaceutical company, either of the Commercial or Medical area.

- **Department of Medical Information**: Department of the company which, in reactive approach, has as main role to meet unsolicited requests of healthcare professionals on products and related diseases, according to the internal procedures of each company. The Medical Information area may have proactive approach within the company, in support of different areas. The nomenclature of the department may differ between pharmaceutical companies, since the name is an internal decision of the company. It is strongly recommended that the Department of Medical Information, due to its scientific and unbiased character, is completely detached from the commercial area, and may be within the technical and scientific structure (medical, research and development areas etc.) of pharmaceutical companies, so there is no conflict of interest between areas.

- **Leaflet**: Health legal document containing technical and scientific and guiding information on medicinal products for their rational use.

- **On-label Information**: information approved by Anvisa on registration or post-registration, or that is consistent with or complementary to approved data, not bringing information different of that approved by the Agency. This information is recognized by the Agency because they have technical and scientific evidence of efficacy and safety for use by the population.

- **Off-label information**: any information not consistent with that approved by Anvisa on registration or post-registration, including, but not limited to indications under investigation, use in not approved population or use form not provided for in the registration.
Main activity

In general, the main activity of the department of Medical Information is to answer unsolicited requests. This kind of request may be done in two ways:

**Non-public questions**

Questions sent to the department in charge of Medical Information through different contact channels (for example, but not limited to telephone, email, fax, mail, request form) or through company employees.

In case of non-public questions received by employees of the commercial area of the pharmaceutical company, the company is responsible for ensuring that the question is unsolicited, in accordance with its internal procedures. The sending of notice of answer to employees of the commercial area is optional to pharmaceutical companies, according to internal procedures. Employees of the commercial area can have access to the content of answers to non-public unsolicited requests, according to internal procedures of companies or can only be notified about what kind of information was sent (e.g. scientific article, medical letter).

The involvement of the medical area in the answer to off-label unsolicited requests is allowed. Only employees of the department of Medical Information should be involved in the delivery of the content of answers to non-public questions containing off-label information.

**Public questions**

Unsolicited requests made during a public scientific forum that can be directed either to a company specifically or to event participants. For example, during a lecture, a healthcare professional asks the
company employee something about a product, but the request is heard by other participants. This request is characterized as public. Likewise, the answer given can be public (in case of on-label and off-label questions) in accordance with what is internally defined in each pharmaceutical company. In scientific forums, with controlled attendance and intended solely for healthcare professionals, where there is opportunity for discussion of off-label information in order to make clear separation between promotion and scientific exchange, it is recommended that when providing the answer the off-label character of the request is clearly disclosed, and the participation of employees of the commercial area is limited.

If the request is made through websites restricted to healthcare professionals and viewed by a large number of people, the answer to the request can be directed to the company that owns the website/forum, or posted there, so that all participants of the website/forum can view/see it (only for on-label questions). In the event of off-label questions, the answer should be sent to the requester only.

It is important to stress that if the representative only discloses the service of Medical Information without inducing the healthcare professional to specifically request any information, this is not considered a solicited request. For example, the sales representative delivers a card with the contact channels of the area of Medical Information and advises that if the healthcare professional has some scientific doubt, he can get in touch through the channels. This scientific doubt would be characterized as an unsolicited request.

All questions addressed to the department of Medical Information should be recorded through a database that can be traced in order to keep track of the questions. In addition to the request addressed, the records should contain the answer sent to the requester.

Other support activities for the company internal areas will be addressed in Chapter 4.
General Recommendations

Non-Promotional and Informative Character

Answers to scientific questions should be based on updated technical and scientific information (cited or wholly or partially provided in accordance with the procedures of each company), balanced in its content, accurate as for the benefits and risks of treatment without promotional character and in specific reference to the subject requested. It is recommended that the internal approval process for answers to scientific questions does not involve the commercial area of the company.

Answers to scientific request provided by the department of Medical Information do not necessarily represent the position and/or recommendation of the pharmaceutical company on certain issue, but represent the updated scientific information available in the literature and/or database of the company on the topic asked. Thus, the decision of the therapeutic approach lies with the requesting healthcare professional.

Audience

Questions about technical and scientific information should be answered only to healthcare professionals. It is recommended that in such cases the number of registration with the Union Council should be requested.

Answers to healthcare students are optional to pharmaceutical companies, according to internal procedures, provided that only related to on-label information.

Levels of Evidence and Unpublished Information

According to ANVISA Resolution RDC 96/2008, where possible, the use of information cited in publications with levels of evidence I and II (ANNEX 1) is recommended. However, in view of absence and/or limited availability of information published
in studies of evidence levels I and II, the department of Medical Information should send the material available to the requester, always considering indexed journals. Internal information of the company (data on file) can be used in response to scientific questions. However, it is recommended it is only used when such questions cannot be answered by published evidence.

**Types of Materials**

The format of the answers to scientific questions varies according to the internal procedures of each pharmaceutical company, which may be, but not limited to medical letters, scientific papers, presentations/scientific lessons etc.

It is important that the company informs that the sent material is intended for individual use, and may not be reproduced, being forbidden the reproduction, transfer and/or commercial activities involving the materials such as resale of articles, provided that the pharmaceutical company complied with the copyright laws.

**Questions about Comparing Products**

If the question is related to comparative data of different products, it is recommended to send information extracted from studies disseminated in scientific publications, preferably with levels of evidence I or II. In the absence of available studies that directly compare the medicines, it is also possible to send systematic reviews or studies that describe the general characteristics of drugs in the same therapeutic class or used for the same indication. Information provided about comparing products should be based on an objective analysis of evidence already published.

**Off-Label Questions**

According to the request, the company should answer specifically to off-label unsolicited requests, explaining this condition and informing the indication contained in the package leaflet approved by Anvisa, if applicable. It is essential that the department of Medical Information emphasizes that the pharmaceutical company does not recommend the use of its products out of specifications described on package leaflet approved by Anvisa.

**Questions on Products of another Company/Competitor**

If the question is related to another company product, it is recommended that the requester is instructed to get in touch with the manufacturer of the competing product to obtain the requested information.

**Questions Related to Adverse Events/Technical Complaint**

The department of Medical Information should follow the reporting criteria of Pharmacovigilance and Technical Complaint in accordance with the internal policies of each company.
This chapter aims at mentioning activities with internal partners of the department of Medical Information, but is not intended to exhaust all its interactions with other areas.

**Interface with Customer Service (SAC)**

Customer Service (SAC) is one of the communication channels of pharmaceutical companies, and the main mode of receiving technical and scientific questions. According to the structure of each pharmaceutical company, SAC may be the first level of service the department of Medical Information.

In case of receiving scientific questions through SAC, it is recommended that internal procedures are followed to collect general information about the request and requester, and address them to the second level of service, if necessary. In the case of contact of employees of the commercial area at SAC, it is recommended that SAC follows the internal procedures of each company to prove the indirect request of healthcare professionals and spontaneity in questions, ensuring that this evidence is documented.
Interface with Areas of the Company (Commercial, Medical and Regulatory teams)

In support of the Commercial, Medical and Regulatory areas, the department of Medical Information may act in accordance with the internal procedures of each pharmaceutical company in:

• Revision/Approval of promotional and non-promotional materials;
• Conducting literature search in response to questions from regulatory agencies;
• Mapping of key publications about products, competitors and associated pathologies;
• Provide training sessions for Medical and Commercial areas;
• Among other activities related to Medical Information.

Interface with Pharmacovigilance

Besides the subject mentioned in chapter 2, item "Questions Related to Adverse Events/Technical Complaint", in support of Pharmacovigilance and in accordance with the internal procedures of each company, the department of Medical Information can conduct bibliographical research for monitoring of adverse events in literature.

Chapter Four

Participation in Scientific Events

Scope

In order to answer questions of healthcare professionals, the department of Medical Information can attend events involving healthcare professionals, including but not limited to national or regional conferences and Satellite Symposia.

Recommendations on Booths

It is recommended that there is clear distinction between the commercial area booth and that for the department of Medical Information, according to the internal procedures of each pharmaceutical company. The area intended for the department of Medical Information should not contain logo of products or any commercial reference.

Disclosure of contacts of the department of Medical Information at the booth is allowed.
# Annex 1

## Levels of Evidence

For classification of Levels of Evidence it is recommended to use the Oxford Centre for Evidence-Based Medicine (OCEBM).

The complete reference to find the table of Levels of Evidence and a glossary of terms used for classifications can be accessed at OCEBM website (http://www.cebm.net/ocebm-levels-of-evidence/).

### Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 1*)</th>
<th>Step 2 (Level 2*)</th>
<th>Step 3 (Level 3*)</th>
<th>Step 4 (Level 4*)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>n/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standards**</td>
<td>Case-control studies, or &quot;poor or non-independent reference standard&quot;**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort study**</td>
<td>n/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.


* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, IvanMoschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodkinson
Indexing

Indexing refers to previous verification and analysis of a material so that its main elements are highlighted, and it enables it to become a material liable to identification and search.

By saying that a journal is indexed it is understood that it is part of a database having criteria for evaluation and indexing. Considering that the database is a product, the sponsoring institution establishes such criteria. There are several criteria ranging from the content originality of (i.e., the journal cannot contain republications, the content has to be original) up to the regulation.

So for Medical Information, indexing or indexed material consists of scientific articles and/or scientific journals that are indexed in databases having rules for accepting journals in its scope.

Types of Scientific Publications

It is possible to classify scientific publications in the following way:

a. Annals of Conferences
b. Scientific Articles (newspapers and journals)
c. Monograph, dissertation and thesis;
d. Report;
e. Critical Review.

It is recommended that when the use of a primary source of information is requested one should check if it not already published in its complete form (scientific articles).
About Databases

Databases, specifically, are the selection of part or total of another collection of data, constituted of at least one file, and designed for a particular purpose or a particular data processing system.

It is worth highlighting that there are databases that do not have solid evaluation criteria, accepting any type of journals. The most important databases are located in universities/academic centers such as Bethesda (NLM), Philadelphia (ISI), Amsterdam (Elsevier), Ipswitch (EBSCO), Geneva (WHO), Moscow (RAS), Shiraz (ISC), Warsaw (CI), among others.

Major sponsoring entities:
• Thomson Reuters
• Wolters Kluwer
• NLM – National Library of Medicine Databases.
• Elsevier – Excerpta Medica/Embase, Scopus, Scirus.
• EBESCO
• DOAJ - Directory of Open Access Journals - Database of periodic publications (all titles have free access to the full text)

Where to find information in Brazil:

In Brazil, BVS (Biblioteca Virtual em Saúde - http://www.bireme.br/php/index.php) is a database that aggregates other databases and performs searches simultaneously in all of them, bringing the results of various sources at a time. In its scope of scientific and technical literature BVS has information about:
• General Health Sciences
• Evidence Portal
• Specialized Areas
• International Organizations
• LIS - Health Information Locator
• DeCS - Health Terminology

In addition to the Ministry of Health itself, professional associations are sources of reliable information.
Impact Factor (IF)

Impact Factor (IF) measures the number of citations attributed by the scientific community to articles of journals. IF is not related to Evidence Levels.

It is a measure that reflects the average number of citations of articles published in a given journal. In a given year, IF of a journal is the average number of citations per article of all articles published in that journal in the last two years.

Below the example of how to calculate the Impact Factor of 2013:

A = the number of times that the articles published in 2011 and 2012 by that journal were cited in indexed journals during 2013

B = the total number of "citable items" published by that journal in 2011 and 2012 ("citable items" are not only articles but also reviews, notes, etc.).

2013 IF = A/B.

It is possible to get the impact factor of a journal from Journal Citation Reports (JCR), an annual publication of "Instituto de Informação Científica" [Institute of Scientific Information], a Thomson Reuters division. Another international evaluation system is SJR - SCOPUS SCImago Journal & Country Rank: http://www.scimagojr.com/index.php

In Brazil, there is a similar system called Qualis (http://www.capes.gov.br/avaliacao/qualis), which evaluates the most important journals within each area.

Strata range from A to C with subdivisions. From A to B2, journals also have associations with an impact factor as below:

- A1 - Impact factor equal to or greater than 3,800
- A2 - Impact Factor between 3,799 and 2,500
- B1 - Impact Factor between 2,499 and 1,300
- B2 - Impact Factor between 1,299 and 0,001
- B3 - Periodicals in Pubmed
- B4 - Periodicals in Scielo
- B5 - Periodicals in other indicators
annex III

Examples of Materials of Medical Information

This annex aims at mentioning some of the materials prepared by the department of Medical Information, but is not intended to exhaust them.

Preparation of Medical Letters

Prepared from scientific materials science, it is a compilation of key information about products and/or molecules under study. It answers specific questions from healthcare professionals, as defined in Chapter 1. These documents should be based on the concept of Evidence-Based Medicine, considering the Evidence levels (ANNEX 1), and should be properly referenced, thus allowing the location of the source of information.

Preparation and/or distribution of presentations/medical classes

Information of the presentations/medical classes should be properly referenced, allowing the audience to locate the source of information. Verification of copyrights and inclusion of appropriate disclaimers in the material use (e.g. off-label disclaimer “Declaração de Conflito de Interesses” [Conflict of Interest Statement] etc.) are required as well.

Preparation of FAQs (Frequently Asked Questions)

Tool to answer specific questions relating to clinical trials, adverse events and/or issues associated by healthcare professionals and/or general public. It is usually developed in format of "Questions and Answers" to provide verbal answers to the requester; however, depending on the subject matter addressed and/or target audience it can be a written answer.


