The Investigator's Brochure: A multidisciplinary document

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Abstract

The Investigator's Brochure (IB) is a multidisciplinary document that summarises the main elements of an entire development programme to date. Although the IB also serves other purposes, it is primarily written to enable investigators conducting clinical studies to assess the risks and benefits associated with an investigational product. The ICH E6 guideline specifies that an IB should include information on the investigational product itself as well as on its use in non-clinical and clinical studies, together with a section providing guidance for the investigator on the use of the drug. Beyond a need for good project management skills, the main challenge and responsibility for medical writers is to ensure that the information presented in an IB is as concise and focused as possible while remaining balanced and sufficiently complete to communicate what an investigator needs to know about using the investigational product.

Keywords: Investigator, Brochure, Non-clinical, Clinical, ICH E6, Medical writer

A summary for investigators, but also for other stakeholders

In drug development, the Investigator's Brochure (IB) summarises the main elements of the entire development programme to date, primarily for the benefit of investigators conducting clinical studies. In addition to information on the investigational product itself, the IB provides an overview of non-clinical and clinical findings together with guidance for investigators on the use of the product based on medical interpretation of these findings.

The availability of a current IB is a regulatory prerequisite that sponsors (drug companies) must fulfil when intending to conduct clinical studies, as specified in the ICH E6 Guideline for Good Clinical Practice.[1] Although the IB is primarily targeted at investigators to inform them of the benefits and risks associated with the use of an investigational product, it is also used by independent ethics committees when deciding on ethical approval for conducting a clinical study. An IB also has a number of other regulatory uses, for example, it is a requirement for Investigational New Drug applications in the USA as well as for Investigational Medicinal Product Dossier and Paediatric Investigation Plan submissions in Europe. In addition, an IB can form the basis of some other documents needed for regulatory interactions, such as briefing packages and some of the summaries required when applying for marketing authorisation.

Regulatory guidance on structure and content

Section 7 of ICH E6 provides what is essentially a table of contents that is almost always used unchanged. The highest level sections are:

- Summary
- Introduction
- Physical, chemical, and pharmaceutical properties and formulation
- Non-clinical studies
- Effects in humans
- Summary of data and guidance for the investigator.

An IB is first required when conducting the first clinical study in humans. However, it is a living document and will then need to be updated as the development programme progresses and further information becomes available. ICH E6 specifies that an IB should be 'reviewed at least annually and revised as necessary', and that 'more frequent revision may be appropriate depending on the stage of development and the generation of relevant new information'. By 'relevant new information' the guideline means information that substantially influences what is known about the characteristics of the investigational

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product, especially safety, to the extent that this needs to be communicated to enable reassessment of the benefits and risks. Alternatively, some sponsors issue an addendum to the IB when needing to rapidly communicate 'relevant new information'.

When the investigational product is intended for use in multiple indications, the sponsor will need to decide whether to prepare separate IBs for the different indications, or whether all indications should be covered in a single IB. ICH E6 does not give any specific guidance on this, so the approach taken is often quite subjective. Factors that can influence this decision may include how closely related the different indications are, differences in the product formulation or route of administration, timings of different development programmes, and whether development programmes for different indications are being conducted by different sponsors. With multiple IBs, the extent to which safety information should be included from other indications will need to be appraised on the basis of clinical relevance for the indication in question.

Regarding authoring style, the guideline indicates that the IB should be presented in a 'concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment'. The guideline does not provide any recommendation for the overall length of an IB. As for most documents, a concise and focused presentation style will have the best chances of communicating the necessary messages to the intended audience. In practice, an IB should not need to exceed ~100 pages, and a shorter document can also be sufficient.

The challenges for medical writers

The overarching challenge when preparing an IB is to achieve the concise and focused presentation style, finding an appropriate balance between completeness and readability. Ultimately, of course, the IB should be both complete and readable, but this takes time and effort. Thus, all too often, with time in short supply, an IB can tend to become inflated with information to make it supposedly complete but then the result can often be quite unreadable. This type of situation calls to mind the French philosopher Blaise Pascal, who wrote: 'I have only made this letter longer because I have not had the time to make it shorter'. What all too often happens is that with each subsequent update of the IB new information is simply added. Instead, an IB should ideally be reworked at the time of each update so that the overall length still remains a maximum of ~100 pages.

So, when preparing an IB, it is essential from the outset to bear in mind the need for conciseness. Often, pushback can be encountered from team members when confronted with a need to reduce the length of their contributions, and here it is important for the writer to remember (and argue) that it is almost always possible to retain key messages while reducing length. It can help to quote Rabbi Hillel, whose recommendation for how the bible could be summarised in one sentence was: '*What you yourself hate, don't do to your neighbour*. The rest is commentary'. This is a nice way to persuade teams that no matter how much starting material you have, it can inevitably be condensed further.

A consequence of the pursuit for conciseness is that, at each update, the contents of the entire IB should be revisited not only in terms of what should be added, but also in terms of how much of the existing content can be reduced or omitted. Logically, the first edition will contain an emphasis on non-clinical information, with no clinical information at all. At each subsequent update, the proportion of clinical information in the IB will increase (bearing in mind that ideally the overall length of the IB should not increase), starting with pharmacokinetics and pharmacodynamics and then progressing to safety and efficacy information from the target population. At the same time, as more clinical information becomes available, the amount of detail may be decreased for the non-clinical information as the clinical performance of the investigational product becomes better understood.

The six main sections of an IB

Summary

The first main section of an IB is the 'Summary', which should provide a high-level overview of all the subsequent sections, providing a profile of 'physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information'. ICH E6 recommends that the Summary should 'preferably' not exceed two pages. In reality, this is rarely achieved, especially with later versions of an IB that may, for reasons explained above, already contain a large amount of information. It is often easiest for a writer to ensure that the Summary is brief if he or she is already involved in preparing the first edition of an IB. When a writer inherits a later version with an already lengthy summary, it can often be a challenge to convince the team that what has 'worked' in previous editions now needs to be substantially revised. But it is certainly worth a try!

Introduction

The Introduction should aim to provide a high-level overview of the investigational product and the setting in which it is being investigated. Information to be covered includes the generic and trade names of the drug product, its active ingredient(s), and the pharmacological class and position of the product being investigated within this class, especially potential advantages over other products within the class. This section should also summarise the rationale for investigating the investigational product, identifying anticipated prophylactic, therapeutic, or diagnostic indications, and provide an overview of the investigational approach as already conducted or intended.

While some or all of the subsequent sections of an IB may be provided in some form by various team members (more on this later), the Introduction is one section of an IB that the writer inevitably will be required to draft *de novo*. Typical sources of information may include the clinical development plan and presentations and briefing packages that may have been prepared previously.

Physical, chemical, and pharmaceutical properties and formulation

This is a brief section describing the chemical, physical, and pharmacological properties of the investigational product, in terms of the drug product and, where relevant, also the drug substance. The section should aim to provide the investigator with sufficient information on the investigational product so that potential risks associated with either the drug itself or any excipients can be assessed. This section should also provide information on storage and handling, including preparation steps needed prior to administration, such as reconstitution or dilution.

Typically, the information for this section will be provided by the Sponsor's Chemistry, Manufacturing, and Controls (CMC) department, but the writer may need to adapt the material provided to the required format for the IB.

Non-clinical studies

Non-clinical studies have a key function in the first edition of an IB as they provide the sole evidence upon which benefits and risks can be assessed before first administering the investigational product in humans. A complete summary of the non-clinical profile is required, although sometimes details of exploratory studies may be omitted if they have been superseded by more complete studies providing the same type of information.

The basic structure of this section is provided by ICH E6, and includes major subsections on non-clinical pharmacology, pharmacokinetics and metabolism, and toxicology. In turn, the Toxicology section should be subdivided according to the topics of single and multiple dose toxicology studies, carcinogenicity studies, 'special studies' (studies specific to the type of product being investigated, e.g. irritancy studies on a product applied topically), reproductive toxicity studies, and mutagenicity studies. The amount of non-clinical information to be summarised will vary between programmes, and may, for example, be less extensive for a human plasma protein (for which only limited testing in animals is possible) than for a new chemical entity intended for an oncology indication (with a high potential for toxicity).

Until the writer has some experience with summarising non-clinical studies, this section can often be daunting. Depending on the sponsor's process, the writer may be provided with more-or-less complete sections, including tables and figures, and in this case the writer's main task may be limited to addressing language and formatting issues to ensure consistency with the rest of the IB as well as any style conventions. At the opposite end of the scale, the writer may be asked to generate text and tables *de novo* on the basis of anything from final reports (best-case scenario) through to sometimes non-validated information of varying quality contained in PowerPoint slides or *ad hoc* documents produced previously for any number of reasons (worst-case scenario, rare but known to happen).

ICH E6 lists the type of information to be summarised for non-clinical studies. Beyond the aspects of study design and the animal species or tests systems used, the summaries should include, as applicable, information on the nature, frequency, and intensity of pharmacological or toxic effects, time to onset and duration of these effects, and reversibility of the effects. When a large number of non-clinical studies are available, it can be beneficial to provide the details of each study in a tabulated format, often in an Appendix, and then provide focused summaries of results and interpretations, supported by tables and figures, within the non-clinical section.

Effects in humans

This section should summarise the results obtained in all clinical studies conducted with the investigational product to date. ICH E6 specifies that information should be summarised on the 'pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities', and this list in effect

provides subheadings that may be suitable for this section.

The earlier clinical studies (Phase 1) are focused on pharmacokinetics, pharmacodynamics, and product metabolism, usually in healthy subjects, whereas the later studies (Phases 2 and 3) provide efficacy data from the target population of patients for which the investigational product is intended. All clinical studies report safety, with the most comprehensive safety information being derived from longer-term use in Phases 2 and 3 studies.

ICH E6 specifies that 'where possible, a summary of each completed clinical trial should be provided'. However, while it is often easiest just to include self-contained summaries of each clinical study, adding new summaries with each update of the IB, this should not be the only approach. Instead, keeping them as concise as possible, the summaries should ideally be supplemented by a synthesis of the overall picture that has emerged from the sum of the information provided by individual studies.

In the case of pharmacokinetics, such a synthesis should be structured from information obtained in single and multiple dose studies that provide information on absorption, plasma protein binding, metabolism, distribution, and elimination. As appropriate, pharmacokinetic information may be analysed for specific subgroups as well as for the population as a whole, at a minimum typically by sex, age, and hepatic and/or renal impairment. Further aspects of the pharmacokinetic profile to be presented are potential effects of other drugs and food on the pharmacokinetics of the investigational product (and potential effects of the investigational product on other drugs), and population pharmacokinetic analyses.

In the case of efficacy and safety, wherever study designs permit, a pooled analysis of data can provide a suitable synthesis based on information from a larger number of subjects than available in individual studies. For efficacy, this may not always be possible due to differences in study design, in which case the synthesis should then be an integrating discussion of the efficacy findings drawn from across the range of studies conducted. For safety, a pooled analysis is almost always meaningful for eliciting potential safety signals. However, such a pooled analysis is often logistically not possible for an IB, due to resourcing and prioritisation issues, in which case a side-by-side analysis (as a tabular summary) of safety data from different studies can also provide insight. Because pooled analyses are rarely conducted specifically for IBs, this is the situation that is generally encountered by writers unless such an analysis happens to be available close to the time of preparing the IB, for example, for a regulatory submission. Irrespective of the approach taken, the aim is to summarise safety information in such a way that the investigator can readily understand the types of safety issues that may be encountered by patients treated with the investigational product.

As for the non-clinical section of the IB, the writer may be provided with text, tables, and figures that then only need to be revised for language and consistency. Alternatively, the writer may be provided with clinical study reports and be asked to write the clinical section *de novo*. In this case, it is important to work closely with the sponsor to ensure that the desired messages are synthesised from the various clinical studies contributing information to the IB, including the interpretation of efficacy and safety analyses across population subgroups.

Finally, if the investigational product has already been marketed anywhere at the time of preparing the IB, then the post-marketing safety information obtained by the sponsor will also need to be summarised. Although such safety data are generally not collected as rigorously as in clinical studies, the post-marketing safety database will often include data from a larger number of subjects than can be obtained from clinical studies conducted prior to marketing. Typically, this section will be provided by the sponsor's Pharmacovigilance department.

Summary of data and guidance for the investigator

The guidance for the investigator can be viewed as a kind of discussion section in which the totality of the non-clinical and clinical experience is summarised and interpreted so that inferences for the use of the investigational product in future studies can be drawn. Thus, any non-clinical findings of potential concern will need to be discussed in terms of either what has been observed in clinical studies conducted to date or what may be anticipated in future clinical studies.

This section should also provide practical information for the management of subjects being treated with the investigational product. If applicable, information should also be drawn from published knowledge on other drugs in the same class. This section of the IB will generally contain subheadings that are also used in prescribing information, such as 'Therapeutic indications', 'Contraindications', and 'Warnings and precautions for use'. Thus, this section may be viewed as a precursor of the prescribing information that is prepared when marketing approval is applied for.

Unless writers are medically qualified, they are unlikely to be asked to prepare the guidance for

the investigator *de novo*. Instead, this section is likely to be provided by the sponsor, with the writer then conducting a linguistic and consistency check versus the rest of the IB.

The project management aspect

In addition to writing the IB, or parts of an IB, the writer also needs to be a good project manager to ensure preparation to the required specification and availability on time. While this principle also holds true when writing almost any type of document, the IB can be among the more challenging in this respect because it covers the entire development programme and therefore the writer often has to interact with team members from a range of functions to obtain the information needed. Sometimes members from non-clinical and CMC departments are less familiar with the document standards required for writing an IB and are less sensitive to the often tight timelines involved. The writer is therefore often the person who needs to address these issues by interacting directly with team members to ensure that they understand which material is required, and by when.

Depending on the sponsor's approach to preparing IBs, the process may start with the writer having to identify the people to interact with for each section. If they are going to provide text and table or figure contributions, then it can help to be proactive by ensuring that the correct IB template is available to the team, either by distributing the file or by supplying a link to where the document is located. In the case of IB updates, the final version of the previous edition of the IB will usually serve as the template for the next edition. While it is unrealistic to expect perfect formatting and consistency when team members submit their contributions (it is the writer's job to ensure this!), providing a template or document in the correct format nevertheless increases the chances of receiving material in a useable format.

Another project management challenge is the need to track the reviewing and revision of individual sections. If no one else is responsible, then the writer is well advised to draw up timelines for writing, reviewing, revision, and finalising the IB and distribute these to the team so that everyone is aware by when the approved document is required. Ideally the writing, reviewing, and revision steps should be planned for the IB as a whole so that team members from different functions can consider the totality of the information being presented. In practice, some contributions may be provided later than others, forming rate-limiting steps for the IB as a whole, and this needs to be planned for accordingly, for example, with truncated review cycles that are separate from those for the main document. There can be a number of permutations for this type of situation, and the writer should develop strategies for minimising the chances of the overall timelines being threatened.

Conclusions

The IB is a living document, needing regular updating, that presents writers with an interesting opportunity to interact with a diverse team drawn from a range of functions contributing to the development of the investigational product. This diversity can increase the logistical challenges involved in obtaining the material needed for preparing the IB. Depending on the process foreseen for preparing the IB, the writer may be involved in coordinating and revising text contributions received from various team members, or the writer may be required to write some or all of the IB based on reports and other material received as source information. Whichever process is involved, the main challenge and responsibility is to ensure that the information presented in the IB is as concise, complete, and focused as possible, and that the IB is appropriately structured to enable it to effectively communicate what an investigator needs to know for evaluating the benefits and risks of using the investigational product.

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Reference

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Author information

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