



The Investigator's Brochure: An Insider's Insight

Considered a multidisciplinary document, the Investigator's Brochure provides a summary of research work completed on an investigational medicinal product. It serves several purposes and evolves as the development program progresses. Some Sponsors see and use the Investigator's Brochure as a virtual 'history' of a programme itself.

Here we give a view of what your Investigator's Brochure should look like and the information it should include derived from experience gained over Niche's 20+ years in the business. The information provided here complements our freely available Investigator's Brochure document template [1]. With over 900 downloads, the template is the most accessed document on The Niche Science & Technology Ltd. website.

Before you start

The information in a well-prepared Investigator's Brochure is highly accessible

As the development of a drug progresses details about early development such as pre-clinical methods can be reduced

The content should not be promotional, neither should it draw generalised conclusions about safety or efficacy

Plan for a 80 – 100 page document with internal cross links between section and data sources

Prepare to succeed

Summarise the details of relevant studies in tables at the front of each section

Referencing the scientific literature aids with brevity

Be concise. In-text tables and figures are effective means of reducing text and summarising findings

Don't prepare the summary at the front of the Investigator's Brochure until the main body of the text has been finalised and approved

Key Insights

The Investigator's Brochure is an axis document in any new investigational medicinal product's (IMPs) development programme. Crucial to various processes that regulate clinical research, its content is well defined. The ICH E6 guideline specifies that an Investigator's Brochure should include information on the drug product and its performance in non-clinical and clinical studies along with specific guidance to investigators on the use of an IMP [2]. As such, the Investigator's Brochure is a multidisciplinary document that summarises information from many aspects involved during IMP development.

It is crucial to remember the primary function of the Investigator's Brochure purpose at all times:

To provide information to the Investigator and others involved in a clinical study on such issues as the appropriateness of dose, dose frequency/interval and the characteristics of the IMP – so that it can inform safety considerations and clinical management of study subjects during a clinical trial.

The ICH E6 guidelines little more than general recommendations for the Investigator Brochure's outline and content. Each Sponsor tends to develop its own approach to presenting data. As a result, the quality of Investigator Brochures can vary from company to company. The document should be concise (in practice an Investigator's Brochure should not exceed about 100 pages), clear and focused while remaining balanced and sufficiently complete to communicate what an investigator needs to know when using the IMP. It should serve as the primary reference document for determining whether an adverse event is related to administration of an investigational product (for purposes of reporting to regulatory authorities) and how it may be managed:

In some circumstances, for example if the investigational product already has a marketing authorisation and its pharmacology is widely understood, it is not necessary for the Investigator's Brochure to be an extensive document. The Summary of Product Characteristics or, a package leaflet or labelling may suffice. However, the substitute must provide current, comprehensive, and detailed information on all aspects of the investigational product that could be of importance to the investigator. Where a marketed product is being studied for a new use (a new indication), a brochure should be prepared that is specific to the new indication.

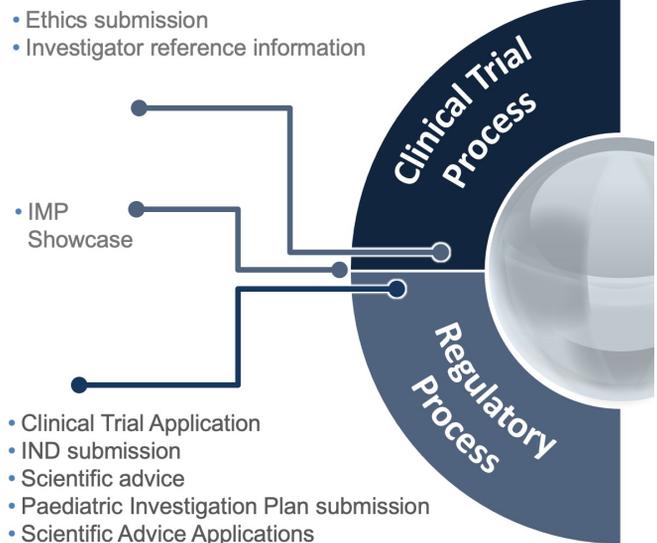
Staying up-to-date

Regulatory authorities and national competent authorities require the Investigator's Brochure for any medicine being studied to be up-to-date– ICH E6 recommends that it is reviewed annually and also 'revised' when necessary – implying that updates follow the introduction of new observations that impact on our understanding of an IMPs clinical actions. Regulatory authorities review updates to ensure that they are accurate, complete, and impartial. Some Sponsors fully re-evaluate the brochures content at each update milestone. However, many simply add new data, which can result in the document becoming both lengthy and disjointed.

Applications

The Investigator's Brochure is a regulatory prerequisite that Sponsor companies must provide when they intend to conduct clinical studies, as specified in the ICH E6 Guideline for Good Clinical Practice [2]. Although the brochure is primarily targeted at investigators taking part in clinical studies (to inform them of the potential benefits and risks associated with exposure to an investigational product, it also several other regulatory uses. These include:

- A regulatory prerequisite for clinical studies, as specified in the ICH E6 Guideline for Good Clinical Practice [2]
- Review by independent ethics committees
- A requirement for Investigational New Drug applications (USA)
- To support Investigational Medicinal Product Dossier Clinical Trial Application and Paediatric Investigation Plan submissions in Europe (and the UK)
- To serve as a source of information for agency briefing packages and summaries required for marketing authorisation



As a multidisciplinary document intended to both teach and communicate, it can be difficult to establish just who the Investigator's Brochure is for: investigator, Sponsor or regulator. It also has an 'unspoken' audience, particularly in small start-up and biotech companies, where can rely on venture capital investment. The Investigator's Brochure is often used as a showcase, underlining key characteristics and summarising proof on concept – summarising how well-advanced a development programme may be. It cannot be emphasised enough that the content and language of the Investigator's Brochure must not be promotional and must not draw generalised conclusions about possible efficacy.

The medical device brochure

Investigator Brochures are not just for pharmaceuticals. As with Investigator Brochures for IMPs, it is required to report clinical and non-clinical information on the investigational device relevant for any proposed investigation [3,4]. Key information should include:

- Identification and description of the device, including information on the intended purpose
- Manufacturer's instructions for installation, maintenance and maintaining hygiene standards
- Pre-clinical evaluation: relevant pre-clinical testing and experimental data, in particular in- design calculations, *in vitro/ex vivo tests*, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation, software verification and validation, performance tests, biocompatibility and biological safety (as applicable)
- Existing clinical data:
 - from relevant scientific literature available relating to the safety, performance, clinical benefits to patients, design and intended purpose and/or of equivalent for similar devices
 - other relevant clinical data available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of equivalent or similar devices, including length of time on the market and a review of performance, clinical benefit and safety issues
- Summary of the benefit-risk analysis and the risk management, including information on known or foreseeable risks, any undesirable effects, contraindications and warnings
- Information for devices incorporating medicinal substances, including blood or plasma derivatives or devices manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives
- The brochure should include a specific set of information or it should otherwise be included in the within other submission documents (more detail provided in Appendix 1).

Structure and 'front end'

The front of an Investigator's Brochure contains housekeeping information such as the Sponsor's details, investigational product(s) identification codes, its chemical or approved generic name, tradename(s) and the document's version and release date. Most Sponsors also include a statement instructing the Investigator/recipient to treat the Investigator's Brochure as a confidential document.

Complex terms used within the document and abbreviated within the text are frequently summarised in a list at the front of the Investigator's Brochure.

The structure of an Investigator's Brochure structure is defined within ICH E6 (Section 7) [2]:

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

Summary

The secret of a well-prepared Investigator's Brochure is accessibility to the information contained therein. To aid this, a summary of the experimental findings are provided at the front of the document.

The summary should provide a high-level overview of the documents content, presenting a profile of physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information. Guidelines suggest that the summary should not exceed two pages (ICH E6) [2]. It is worth noting that providing an informative summary in such a small space becomes more challenging as the development programme for an IMP progresses and the amount of available data to summarise increases. You may need to use more space.

Hint:

When beginning to write a new Investigator's Brochure or updating an existing version, it is generally advised that you should not attempt writing/updating the summary section until the main body of the document has been finalised and approved. This will guard against the introduction of discrepancies between the main content of the Investigator's Brochure and the summary.

Introduction

The Introduction should be 1–2 pages in length and provide a high-level overview of the IMP and the setting of its proposed use. It should provide a background on the therapeutic rationale behind an IMPs use and its target indication. It should include the generic name and the tradename of any drug product, its active ingredient(s). The information should cover details on the pharmacological class an IMP belongs to along with a summary of its position within this class. The content should reference the scientific literature and incorporate aspects of the IMPs clinical development plan and information on any associated briefing packages that may have been conducted.

"The ability to simplify means to eliminate the unnecessary so that the necessary may speak."

Hans Hoffmann

The introduction should include any anticipated prophylactic, therapeutic and/or diagnostic benefits as well as any background on potential risks. Some sponsors also like to include a note on the cut-off date for information incorporated in the document.

Physical, chemical, and pharmaceutical properties

Often called the 'CMC section' by old-timers (standing for Chemistry, Manufacturing and Controls) the text is required to provide a brief description of the chemical, physical and pharmacological properties of the active ingredients or drug product, any additional components (such as the containing capsule) and, where relevant, a quantitative statement of active ingredient for each dosage form of the drug substance and its route of administration. Information should include:

- Product code names, information relating to the chemical structure and physical form/solubility of the drug substance relevant to clinical use/formulation.
- Qualitative list of all excipients without excipient grades and justification for inclusion of the excipients in the formulation if clinically relevant.
- Details of any matching placebos (if relevant).
- Recommendations on storage and handling of the dosage form. This may be by reference to the product label.

Substance versus Product

Potentially confusing terms in the CMC section relate to the use of drug 'Substance' and drug 'Product'. The term drug substance describes an active ingredient that is intended to furnish pharmacological activity or other direct effect. In contrast, drug product relates to a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Non-clinical studies

The structure of this complex section is described within ICH E6 [2]. It should report on all relevant non-clinical pharmacology, toxicology, pharmacokinetic and investigational product metabolism studies, detailing the nature and frequency of any effects the IMP may have. In addition to summarising the time of onset and duration of any effects and any dose response findings, the summary for each investigation should include information on:

- Animal species tested
- Number and sex in each test group
- Unit dose (e.g., mg/kg)
- Dosing intervals
- Route of administration
- Duration of dosing

Referencing the scientific literature can aid brevity when describing the use of standard methodology. Use of tables and figures is a good way of summarising study findings. These should be placed and clearly referenced at appropriate places within the text.

Klimisch score

Data quality is important for chemical risk assessment and regulatory decision-making. The Klimisch score was developed to rank the reliability of data from toxicological and ecotoxicological studies [5]. The system has been extended to physico-chemical studies and is recognised by many regulatory authorities.

The non-clinical data is reported in specific sections detailed below. Early pre-clinical studies characterising an IMPs profile tend to be conducted under 'experimental' conditions whereas drug toxicity, genotoxicity and safety pharmacology need to be conducted under Good Laboratory Practice (GLP) conditions. You should report whether or not a study was conducted under GLP conditions and may consider providing the Klimisch score [5].

Non-clinical test material

Experiments conducted in the early stages of development may involve an IMP prepared using small-scale manufacturing methods that may differ from those eventually used to produce clinical batches. This can have relevance to observations and therefore should be summarised. It can be useful to include information on the batches used, any information on the impurity profile and how it compares to the profile of the material proposed for clinical investigations. A description of how dosages are expressed should also be provided, i.e., in terms of free form base or acid or in terms of salt etc.

Non-clinical studies (cont.)

Non-clinical pharmacology

During the process of development a broad variety of experiments are conducted in a variety of *in vivo* and *in vitro* settings. They tend to be identified as primary, secondary or safety pharmacology studies. Primary studies relate to the targeted actions of the product and secondary studies usually involve efforts to characterise the general pharmacodynamic profile beyond the IMPs primary indication. Safety pharmacology reports on studies that provide data possibly relevant later in development in terms of potential safety implications. Studies should be reported in a hierarchical fashion (primary, secondary, safety) with *in vitro* studies reported before *in vivo* studies. A table is often used at the front of this section to summarise the types of studies being reported (Example 1).

Example 1

A range of *in vitro* and *in vivo* studies were conducted to investigate the primary and secondary pharmacology of NST001. In addition, safety pharmacology studies have been conducted in rats and dogs. A listing of these studies is provided in Table 1.

Table 1. Studies investigating the pharmacology of NST001

Phase	Type of Study
Primary Pharmacology:	In vitro binding affinity Gerbil foot tapping model Anti-emetic activity in shrews and ferrets Marmoset human threat test
Secondary Pharmacology:	Receptogram screen
Safety Pharmacology:	Overt central and peripheral pharmacodynamic effects in Han Wistar rats Overt central and peripheral pharmacodynamic effects in beagle dogs Cardiovascular, electrocardiographic and respiratory effects in Han Wistar rats Cardiovascular effects in beagle dogs (oral administration) Cardiovascular effects in beagle dogs (iv administration) Dog Purkinje fibre assay

Early development study summaries should contain details on the methods used, the study findings and a conclusion on the relevance of any findings relative to the proposed effects. As the clinical development programme progresses, details on the materials and methods can be condensed and results put in context with any reported findings in humans. For example, if there are human studies showing blood pressure lowering effect of an antihypertensive drug, it might be considered no longer necessary to show data-rich tables and/or graphs of blood pressure lowering effects in animals. A statement to the effect that the blood pressure lowering (possibly with an average lowering effect) in a test species was predictive of the blood pressure lowering effect observed in humans (cross referencing where the human data can be found in Investigator's Brochure).

As a product enters the later stages of development a brief (1 – 3 pages) summary of the key non-clinical findings may be sufficient. At this stage, the nonclinical pharmacology section should summarise the pharmacologic activity substantiated in humans. Often a table of the key findings will suffice.

Non-clinical studies (cont.)

Pharmacokinetics and product metabolism in animals

Describe succinctly the analytical methods that have been used to measure IMP levels in blood, urine and tissue, outlining assay validation.

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product should be reported in all species studied. The start of this section often summarises the types of studies that have been conducted in tabular format as detailed in Example 2. As development progresses, detail you provide relating to the materials and methods used can be condensed. Findings should be put in context with the known behaviour in humans.

Example 2

The pharmacokinetics, distribution, metabolism and elimination of NST001 have been investigated through a series of oral, intravenous and *in vitro* studies in the rat, dog and monkey using unlabelled and [¹⁴C]-labelled drug. A summary of the studies conducted is provided in Table 2.

Table 2. Pharmacokinetic and metabolism studies conducted with NST001

Type of Study	Dose Route	Salt Form	Dose (mg/kg) or Concentration	Species	No. /Group
Toxicokinetics: 14-day study	Oral	B	10, 50, 300	Mouse	3M
Toxicokinetics: 13-week study	Oral	B	25, 50, 100	Mouse	3M/3F
Pharmacokinetics	Oral	A	5	Rat	5M
	iv		2		3M
Toxicokinetics: 14- and 21-day studies	Oral	B	3–80	Rabbit	3–4F
Pharmacokinetics	Oral	A	5	Dog	3F
	iv		2		3F
Toxicokinetics: 4- and 13-week studies	Oral	B	0.5–30	Dog	3–9M/ 3–9F
Pharmacokinetics	Oral	A	3	Monkey	2M/2F
	iv		1		2M/2F
Permeability	<i>In vitro</i>	B	0.5–200 µM	NA	NA
Tissue distribution	Oral	G	5	Rat	1–3M
Red blood cell association	Oral	G	10	Mice	3M/3F
	Oral	G	5	Rat	3M/3F
	iv	G	1	Rat	6M
	Oral	G	3	Dog	3M/3F
	Oral	G	3	Rabbit	4F
Metabolism	<i>In vitro</i>	F, B	0.5–50 µM	Rat, Human	NA
Cytochrome P450 enzyme induction	<i>In vitro</i>	A	0.5–25 µM	Rat	NA
Metabolite profiling	Oral	G	10	Mouse	3M/3F
		B	50–600	Rat	d
	iv	G	3	Rabbit	4F
		B	3, 10–50	Dog	3M/3F
		G	1	Rat	6M
Elimination (intact and bile duct cannulated)	Oral	G	5	Rat	3M/3F
	Oral	G	3	Dog	3M/3F
	Oral	G	3	Rabbit	4F

M = Male; F = Female

Toxicokinetic studies provide a critical evaluation of drug disposition at toxicologic doses while investigating possible associations between drug levels and the occurrence and time course of adverse effects indicative of toxicity. Objectives are different from pharmacological challenges which aim to determine factors such as solubility, stability, absorption etc., they look for biological changes that are affected by the dose size [6].

Non-clinical studies (cont.)

Pharmacokinetics and product metabolism in animals (cont.)

During the early stages of development summaries are expected to contain details on the methods used, the results and relevance of any findings to the proposed effects. Discussion of the findings for this section should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, in addition to their relationship to the pharmacological and toxicological findings.

Focus	Content
Distribution	Information from whole body autoradiography studies should be presented along with observation from <i>in vitro</i> protein binding (all species including human) and any milk and placental transfer studies.
Metabolism	Metabolic profiling and identification should be provided for all toxicological species together with <i>in vitro</i> data from multispecies microsomes, hepatocytes or liver slices.
Balance Excretion	Quantitative information on the amount of drug-related material excreted in urine, faeces, expired air and/or remaining in the carcass should be provided together with any data generated in bile-cannulated animals.
Interactions	Information on potential pharmacokinetic drug interactions should be provided. Normally, data generated in <i>in vitro</i> studies using human microsomes and <i>in vivo</i> studies looking at enzyme induction (generally derived from the 1-month toxicological investigations) would be included and other relevant data such as protein binding or renal excretion may also be discussed on a case-by-case basis.
Other Studies	This section is included when needed to cover information from special studies performed to investigate effects specific to the IMP and/or its administration.

Toxicology

As with the pharmacokinetics section, data on the various studies should be provided in tabular format including details on the animals studied and dose (see Example 3). Information should follow a hierarchical structure: single dose, repeated dose, carcinogenicity, special studies (irritancy, sensitisation etc.), reproductive toxicology and genotoxicity (mutagenicity) studies. Data on *in vitro* and *in vivo* studies conducted in mammalian and non-mammalian species should be presented separately

Summaries should describe the rationale and results as well as commenting on the relevance of the findings to the proposed clinical usage while discussing exposure cover at toxicological no-effect dosages. Where reproductive toxicity studies have been conducted effects on fertility, reproductive performance, foetal organogenesis, and peri- and post-natal development should be discussed. Special studies might involve assessment of irritancy and sensitisation tests and studies done to evaluate haemolytic potential for intravascular study drugs.

This section may provide cross-references to the section detailing guidance to the investigator, where an integrated discussion of the non-clinical data will be provided including discussion of its relevance to the use of the study drug in human subjects (emphasising any key safety issues).

Non-clinical studies (cont.)

Toxicology (cont.)

Example 3

Single and repeat administration studies have been conducted in mice, rats, dogs and monkeys. Fertility and embryofetal development studies have been conducted in rats and rabbits. Local tolerability (intravenous) studies in dogs and *in vitro* haemolysis evaluations have also been conducted. A battery of *in vitro* and *in vivo* genetic toxicity studies were also performed. A listing of studies conducted is presented in Table 3.

Table 3 Toxicology Studies Conducted with NST001

Study Type/ Duration	Dose Route	Salt Form	Dose (mg/kg) or Concentration	Species	No. /Group
Single Dose					
Acute toxicity	Oral	B	1000-1500	Mouse	2-7M/0-6F
Repeat Dose					
14 day	Oral	B	10, 50, 300	Mouse	6M/6F
13 weeks	Oral	B	25, 50, 100	Mouse	12M/12F
31 days	Oral	B	5, 15, 50	Rat	12M/12F
4 weeks	Oral	B	1.5, 20	Dog	3M/3F
13 weeks	Oral (tablet)	B	1, 3, 10	Dog	3M/3F
3 months	Oral	B	2.5, 10	Monkey	3M/3F
4 day	<i>iv</i>	B	2.5, 5, 10	Rat	4M/4F
Reproductive Toxicity					
Fertility	Oral	B	5, 15, 50	Rat	24M/24F
Embryofetal development	Oral	B	5, 15, 50	Rat	30F
Genotoxicity					
Ames assay	<i>In vitro</i>	B	0.1 - 2500 µg/plate	NA	NA
Micronucleus test	Oral	B	150, 300, 600	Rat	7M
Special Toxicology					
Haemolysis	<i>In vitro</i>	B	0.17 mg/mL	Dog, Human	NA
Local tolerability	<i>iv</i>	B	10 mg/dog	Dog	3M
4-week investigative	Oral	B	5, 50	Rat	10M/10F
12-day investigative	Oral	B	50	Rat	6M

NA: not applicable.

Non-clinical assessment of safety

This important section serves to interpret the findings of the non-clinical programme in the form of a brief description (1-2 pages) of the scope of the work conducted and the extent to which the IMP has been shown not to cause abnormalities and/or toxicities.

A summary is also provided on observations that could be considered adverse findings, non-adverse toxicological findings and findings of unknown significance. Levels of exposure to the IMP and no adverse event levels are also provided along with effect reversibility and possible clinical significance. This section usually includes an estimate of the levels of exposure (in terms of dose and time) that would be considered acceptable in humans.

Key terms

Describing the no-observed-adverse-effect-level (NOAEL) is an important part of the non-clinical risk assessment. It is a professional opinion based on the design of the study, indication of the drug, expected pharmacology and spectrum of off-target effects. There is no consistent standard definition of NOAEL. It is based, in part, on the varied definitions of what constitutes an adverse effect. Toxicologists, either investigating or reviewing available data, have not been consistent in defining an effect as either adverse or acceptable. The common definition of NOAEL, 'the highest experimental point that is without adverse effect,' serves us well in general discussions. It does not, however, address the interpretation of risk based on toxicologically relevant effects, nor does it consider the progression of effect with respect to duration and/or dose [7].

The maximum tolerated dose (MTD), also known as the maximum tolerable dose or maximally tolerated dose, is defined as the dose that produces an 'acceptable' level of toxicity or a dose that, if exceeded, would put animals (or patients) at 'unacceptable' risk for toxicity [8].

Effects in Humans

This section should be left blank if the Investigator's Brochure is intended to support a first-time-in-human study and no clinical studies have yet been conducted.

Introduction

Where clinical studies have been conducted this section should start by noting the stage of development for the IMP and summarise the studies that have been conducted. A description of each completed clinical trial should be provided (see Example 6); ICH E6 states available information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities should be included [2].

As recommended for the non-clinical studies, a table of the investigational studies performed to date can be informative (see Example 4). The summary may also provide data on doses used (including placebo) and a total for the number of subjects included in clinical studies as well as information on which studies were conducted in healthy volunteers and which patients. Data collected during early clinical development should only be included in the Investigator's Brochure once the source study has been formerly reported.

Example 4

Table 4. Clinical studies performed (Clinical cutoff – 12 Dec 2007)

Study Design	Population	Doses	Main Result
Single dose, rising dose	16 M volunteers	1 to 100 mg	Well tolerated; QT prolongation at 25 mg
Repeat dose, rising dose	24 M volunteers	25, 50, 75 and 100 mg bid x 7 days	Well tolerated; dose related prolongation of QT
PK in the elderly volunteers	12 M/F 24-40 yo 12 M/F 65-80 yo	100 mg bid x7 days	No difference in tolerability
PK in renally impaired	12 M/F >18 yo	acutely and then 100 mg bid x7 days	No change in GFR or RBF
Effect of food	16 M volunteers	100 mg	No effect

Key: M = male; F = female; PK = pharmacokinetics; GFR = glomerular filtration rate, QT = electrocardiogram time interval between the Q and T waves

This section's introduction may include statements about frequently observed adverse events, changes (or lack of) in ECGs, vital signs or laboratory values and general statements regarding any safety consensus that may not be covered elsewhere.

Investigator Brochures written during early development, when perhaps only one or two clinical studies have been reported, it is possible to summarise the clinical data by individual study. However, as more studies are completed (and reported) data should be compiled according to specific sections: pharmacokinetics and metabolism, safety and pharmacodynamics/efficacy.

Information on early phase studies becomes less relevant as development progresses. As focus switches to observations in patients, data on healthy volunteers becomes less relevant and can simply be reported in a brief (separate) textual summary. Content may change again as development progresses further; as patient data increases with large Phase III trials it may be advisable to adopt a more inclusive approach to data from on going studies. When adopting this approach the writer should first provide information on observations in completed studies and then (blinded) data from on going studies.

Effects in Humans (cont.)

Pharmacokinetics and metabolism

The extent of information to provide is dictated by the IMP's stage of development. Observations in healthy subjects and patients should be reported separately. A synthesis of information from single and multiple dose studies should inform on the IMPs pharmacokinetic profile (including information on absorption, plasma protein binding, metabolism, distribution and elimination) and bioavailability (where available). Information should be given on specific subject subgroups – typically by sex, age and hepatic and renal impairment. Additional aspects may include effects of other drugs and food on the IMPs pharmacokinetic profile and its potential effects on other drugs. Subheadings can be added to guide navigation.

Safety

This section must include data detailing the extent of exposure (doses used) and the number of subjects included in the studies, active doses investigated and the number of trial subjects receiving placebo. In summarising safety observations, it is recommended that authors contextualise observations in terms of the study population by providing information on their demography (age, gender, ethnicity) and health, identifying healthy subjects of early phase investigations and the target disease population.

During early development it is beneficial to combine healthy volunteer data, as long as it is indicated clearly whether events occurred following single or multiple dose exposures. Data from drug-drug interaction studies should be presented separately as the potential for interaction creates its own unique safety considerations. Similarly, studies in specialist populations such as renal or hepatic patients should be reported separately.

Suggested safety data subheadings are: single-dose studies, repeat-dose studies and drug-drug interaction studies. Each section should include information on the most frequently experienced adverse events along with a summary of the incidence of events and how they relate to IMP exposure. Serious adverse events should be clearly described along with any data implying effects on vital signs, ECG and/or laboratory measures. In some cases it is appropriate to provide information on individual subjects with emphasis placed on describing how any issue was resolved.

One issue that frequently arises with Investigator's Brochures is the assumption, by some investigators that the information it provides is the most up-to-date and relevant for the study population they happen to be investigating. However, the focus of the brochure only on reported outcomes means that it is unlikely to include information relevant to testing in a novel setting – such as a new patient sub-population, updated dosing requirements or population-specific adverse event information. Such information is likely to be better covered in the risk assessment statements of the Study Protocol or the Investigational Medicinal Product Dossier.

Pharmacodynamics and efficacy

In early phase clinical development focus is often placed on monitoring pharmacodynamic markers identified as providing some indication of a novel drugs clinical potential. For example, a study may include 24 hour blood pressure monitoring when assessing a new treatment for hypertension. Investigator's Brochures written for Phase I/ II studies may have their own section reporting on the pharmacodynamic profile of an IMP. As an IMP enters the later phases of development and investigations begin to determine clinical efficacy (in our current example that might be the potential to lower blood pressure below a certain threshold). At this point pharmacodynamic data becomes less relevant, the data may be combined with the pharmacokinetic contribution or be omitted completely.

When reporting the efficacy findings it can be difficult to pool clinical observations when there are differences in the design of the studies that have been conducted, particularly differences between the Phase II and Phase III programmes. Studies can be reported individually; however, an attempt should be made to summarise efficacy findings across the range of studies and relating effects with any safety signals.

Marketing experience

Information should be provided on countries where an IMP has been marketed or approved as well as any relevant history of use and, if possible, an estimate of patient exposure. Countries where an IMP applications for marketing approval/registration was rejected or withdrawn should also be recorded. Any post-marketing safety information available to the sponsor will also need to be summarized along with information from any pharmacovigilance databases. When the product is not marketed this section is left blank with a statement that the product is not yet marketed.

Reference Safety Information (EU)

Regulatory requirements stipulate that the Investigator's Brochure should include a clearly identifiable section called the Reference Safety Information (RSI), which must summarise available information on the IMP, how to determine whether adverse reactions should be considered as 'expected', and on the expected frequency and nature of such adverse reactions [9, 10]. The sponsor's informed opinion on the expectedness of an adverse reaction must be provided from the perspective of previously observed events rather than the basis of what might be anticipated from the IMP's pharmacological properties [9].

Specific guidance was recently issued in the form of a Q&A publication by the Clinical Trial Facilitation Group [11]. It highlighted how the RSI should be used by the Sponsor for the assessment of the expectedness of all suspected serious adverse reactions (SARs) in clinical trials to assess the need for expedited safety reporting [12]. It noted that RSI content should include a clear list of 'expected SARs', i.e. SARs that could be expected following exposure to the IMP (see Example 5).

The list should be restricted to previously observed 'suspected' SARs where, after a thorough Sponsor assessment, reasonable evidence of a causal relationship had been established between the event and IMP [13]. By implication, each 'expected SAR' should already have been reported as a 'suspected' SAR more than once. Where SARs turned out to be fatal and/or life-threatening, they would be considered to be unexpected even if the fatal or life-threatening SARs had been reported previously [13].

- The RSI is a list of expected serious adverse reactions, which are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA).
- It is used for the assessment of the expectedness of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials.
- An expectedness assessment is required to be conducted by the sponsor on each 'suspected' SAR to determine expedited reporting of Suspected Unexpected Serious Adverse Reaction (SUSARs).
- It is not a simple list of SAR occurred in clinical trials, but it includes only the SAR considered expected and therefore with no need to be transferred to the national competent authorities

Example 5

Table X: Serious Adverse Reaction for the IMP considered as 'expected' for safety reporting purposes

System Organ Class	SARs	Number of subjects exposed (N) = 125		
		All SARs	Fatal SARs	Life-threatening SARs
		n (%)	n (%)	n (%)
Cardiac Disorders	Tachycardia	25 (20.0)	0 (0.0)	4 (3.2)
Nervous System Disorders	Headache	15 (12.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	Diarrhoea	10 (8.0)	0 (0.0)	0 (0.0)
Hepatobiliary Disorders	Elevated AST	5 (4.0)	0 (0.0)	0 (0.0)

n = number of subjects who have experiences a SAR; SAR = serious adverse reaction

Summary of data and guidance for the investigator

Note: The main purpose of this section is to provide any investigator with a clear and readily accessible understanding of the possible risks and adverse reactions they may encounter, and of the specific tests, observations, and precautions that may be needed during a clinical trial.

Guidance should also be provided on the identification and treatment of possible overdose and adverse drug reactions, based on previous human experience and on the pharmacology of the investigational product. Where there has not been any human exposure it should be stated that no data are available. For IMPs in early phase development it should be stated that limited data are available. In this case, the text should state that any guidance is based on nonclinical data and any known class effects.

Based on the IMPs nonclinical and clinical data, this section should provide an overview of its characteristics so as to provide any investigator with the most informative interpretation of the available data along with an assessment of the possible clinical implications. A structure for the section is provided in Example 6. Published reports on related products should be discussed where appropriate. This information should be presented in a way that will help an investigator to anticipate adverse drug reactions or other issues that may arise during a clinical trial and their management.

Information may also be drawn from published knowledge on other drugs in the same class. The information should be provided with clearly labelled subheadings, which often include: 'Therapeutic indications', 'Contraindications' and 'Warnings and precautions for use'. Possible subheadings are provided in the our Investigator's Brochure document template [1].

Example 6

Enter Sponsor logo

Investigator's Brochure	Compound No.:
	Version:

- 7. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR**
- 7.1. Development Core Safety Information**
- 7.2. Posology and Method of Administration**
- 7.3. Contraindications**
- 7.4. Special Warnings and Special Precautions for Use**
- 7.5. Interactions**
- 7.6. Use during Pregnancy and Lactation**
- 7.7. Undesirable Effects**
- 7.8. Overdose**
- 7.9. Drug Abuse and Dependency**
- 7.10. Other Potentially Clinically Relevant Information for the Investigator**

References, Supplements and Appendices

The text within the brochure will likely refer to the scientific literature from time-to-time. A Sponsor templates usually have standard styles for citing the literature. References may be provided at the end of each section or be given in a combined list at the end of the Investigator's Brochure. References should not be made to internal Sponsor documents (as these may not be readily available to an investigator or regulatory body).

Investigator Brochures tend to be updated annually. However, during the early stages of development studies can be completed and reported in weeks or months, generating significant new safety data. This information may be provided in the form of a supplement. Supplements should be considered as separate, standalone documents and not a revision or an appendix. A supplement should adopt the format of the parent Investigator's Brochure. Information provided in a supplement should be fully incorporated into the next revision of the Investigator's Brochure.

Appendices can be provided where additional information to supporting the observations summarised in the Investigator's Brochure may be helpful. For example, appendices can include descriptions on how key efficacy measurements are made, lists of additional clinical studies or lengthy data tables (such as listings of adverse events).

An interview with our Head of Medical Writing

Q What is so different about writing an Investigator's Brochure?

A When you are working on an Investigator's Brochure you need to be a talented project manager and politician. You often have to gather contributions from representatives involved in every aspect of the drug development programme. You need to manage each of their 'requirements' while ensuring that the document remains fit-for-purpose

Q What is the main challenge when writing an Investigator's Brochure?

A To ensure that the information presented in the document is as accessible and concise as possible and its focus is relevant to the IMP's stage of development. All the while you want the information you provide to remain balanced and sufficiently complete in terms of all the data that an investigator could possibly need. For this reason I would always suggest it is only attempted by an appropriately trained writer.

Q What is your #1 tip for working on an Investigator's Brochure?

A I would say that it is to remember that the IB is a living document and so changes with each iteration – changes can be minor in some cases but they are often significant. I would advise a writer to be aware of this and rather than focusing on what can be added with each new revision they should be thinking about the overall structure and what could be taken out.

Q You clearly enjoy working on Investigator's Brochures – why?

A The Investigator's Brochure offers a unique set of opportunities. First, you get to work with a broad range of scientists. Second, you get to learn about every aspect of an IMPs development. By serving as the central point of contact you can contribute to the overall interpretation of the pharmacokinetic, toxicology and pharmacology data. Finally, you get to practice a host of skills – medical writing, project and people management.

And finally...

The Investigator's Brochure is a compilation of an IMPs clinical and nonclinical data relevant to its study in human subjects. The information provided here will complement the Investigator's Brochure template provided on the Niche Science & Technology website [1]. Together the documents delineate the minimum information to be included and provide useful suggestions for its layout. Additional guidance on the process of development is provided by Freberg [14].

It should be emphasised that the document is intended to provide the investigators and others involved in a clinical trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. Although it is often used as a 'promotional' document for an IMP, it is intended to provide insight to support the clinical management of the study subjects during the course of the clinical trial. Thus, the information 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 their own unbiased risk-benefit assessment. For this reason sponsors should resist turning it into the repository of everything that is known about the IMP.

Considering the important safety function this document serves, it is highly recommended that a medically qualified person and trial-experienced team member participate in the preparation of the text and that individual sections be approved by the disciplines responsible for providing the data that are described. They should also vouch for the accessibility of the information they have provided. Writing an Investigator's Brochure is easy enough, interpreting one correctly is a completely different matter [15].

References

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Next Steps

We created this Insider's Insight to provide a few key learnings and share some helpful pointers we have acquired over the years. We hope you found it useful. We also point you to our ICH-compliant template, which is a great start to writing your own Investigator's Brochure [1]. However, it is a complex and important document and for that reason I would always suggest it is only attempted by an appropriately trained writer.

If you would like advice on your own Investigator's Brochure challenge you can contact us at the email address below. We also run training sessions on how to write Investigator's Brochures from time to time, so please contact me if you would like to know when we will next be running one of these ever-popular training courses.

Get in touch

Info@niche.org.uk



+44 (0)20 8332 2588
www.niche.org.uk

Appendix 1: The Medical Device Clinical Investigator's Brochure

The content of an Investigator's Brochure for a medical device should be in line with requirements stated in ISO14155:2020. This information should either be included in the Investigator's Brochure itself or clearly indicated within other submitted documents.

- Reference to important relevant clinical and non-clinical information reported in the scientific literature (if any) with an analysis and bibliography
- Classification of device with supporting rationale for its classification.
- Brief description of device and its intended use (together with any other devices designed or expected to be used in combination with it).
- Design drawings including components, sub-assemblies, circuits and diagrams of operation with appropriate descriptions and necessary explanations/instructions, such as storage and handling requirements.
- A photograph of the device (preferably in colour).
- Details of any comparable device on the market
- Identification of any features of design that are different from a previously similar marketed product (if relevant).
- Details of any new or previously untested features of the device including where applicable, function and principles of operation with emphasis on information on any required deviation from normal clinical practices.
- Summary of experience with any similar devices manufactured by the company including length of time on the market and a review of performance related complaints.
- Information to be placed on the label, and instructions for use to be provided with the device when placed on the market.

Any available clinical and non-clinical information based on relevant pre-clinical testing and experimental data, in particular regarding in-design calculations, in vitro tests, ex vivo tests, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation, software verification and validation, performance tests, evaluation of biocompatibility and biological safety, as applicable. Clinical data should include information relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of the

device and/or of equivalent or similar devices (if from the same manufacturer, including length of time on the market and a review of performance, clinical benefit and safety-related issues and any corrective actions taken).

Summary of the risk benefit analysis to include identification of hazards and estimated risks associated with the manufacture (including factors relating to device design, choice of materials, software) and the use of the device (ISO 14971:2019), together with a description of what actions have been taken to minimise or eliminate the identified risk.

- Description of materials coming into contact with the body, why such materials have been chosen, and which standards apply (if relevant).
- Identification of any special manufacturing conditions required and if so, how such requirements have been met
- A description of the methods of manufacturer, in particular as regards sterilisation and identification of packaging used for sterilisation of device
- A summary of the relevant standards applied in full or in part, and where standards have not been applied, descriptions of the solutions adopted to satisfy the essential requirements or general safety and performance requirements
- The results of the design calculations and of the inspections and technical tests carried out, etc.
- What provisions, if any, have been made by the manufacturer for the recovery of the device (if applicable) and subsequent prevention of unauthorised use? Including procedures for analysis of implantable devices following explant.
- Identification of any tissues of animal origin
- Identification of a substance (medicinal product), human blood derivative or non-viable human tissues and cells incorporated with the device as an integral part.
- Details of training for users (both healthcare professionals and patients)

For more detail see:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/989414/Guidance_for_mfrs_-_compiling_a_submission_to_MHRA_-_May_2021.pdf

<https://www.medical-device-regulation.eu/tag/clinical-investigations/>