



Good Practice Guide

Comparator Management



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Preface

The Purpose of the ISPE Good Practice Guide: Comparator Management is intended to establish strategic and tactical considerations when sourcing and procuring comparators for use in a Clinical Trial.

The information provided in this Guide reflects the cumulative knowledge and experiences of the authors, editors, and reviewers with input from members of the ISPE Investigational Products (IP) Community of Practice (COP) and general membership.

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1 Introduction

1.1 Overview

A comparator drug, also known as a reference drug, is one that is included in a clinical study for the purpose of making comparisons of its performance in a defined population. Comparisons may be made in terms of a combination of factors such as:

- efficacy
- safety
- ease of use
- patient compliance

Comparators should not be confused with placebos. (Placebos are inert representations of an investigational compound designed to eliminate psychosomatic effects from statistical analyses.)

Comparator drugs are usually sought for the purpose of comparing a drug from one organization (the sponsor organization's proprietary investigational drug) with existing marketed products from other organizations. The objective of the comparison is to demonstrate the benefits of the sponsor organization's drug, based on factors such as those listed. This is intended to allow legitimate claims regarding, e.g., greater efficacy or an improved safety profile, for the sponsor organization's drug.

The sourcing of comparator drugs is, therefore, usually conducted confidentially by the sourcing organization based on commercial sensitivity. For example, if Company A learns that Company B is planning to take over the position of their drug within a particular market segment, Company A may change their pipeline strategy or make new plans in response to this information.

There is a global trend regarding the increasing importance of comparative trials. Data from comparative trials have been the focus of healthcare technology appraisal organizations worldwide. Such organizations can provide guidance on the medication that doctors from their country should be prescribing. This can be based on available evidence relative to the benefits, and may be described in terms of functional outcomes and improvements in quality of life versus the comparative costs of the drug and its alternatives.

Comparative effectiveness is expected to help deliver better value and lower costs as part of an overall healthcare reform effort. At the time of publication, a major initiative is underway. The American Recovery and Reinvestment Act of 2009 [1] has invested \$1.1 billion to begin the work of Comparative Effectiveness Research (CER) and the US Department of Health and Human Services has established a new Federal Coordinating Council to help coordinate research and guide investment. Physicians, pharmacists, patients, and purchasers of healthcare, including employers, health plans, and the government, are seeking evidence regarding the comparative effectiveness of drugs in order to make more knowledgeable and informed decisions.

1.2 Scope

1.2.1 Comparator Sourcing Process

The ISPE Good Practice Guide: Comparator Management discusses:

- selection of a comparator: branded or generic version

- identification of the best approach to sourcing
- how to identify the best strength, formulation, and presentation, e.g., regional considerations
- how to establish a preferred supplier or supplier pool
- setting up a comparator sourcing team to obtain the comparator
- consideration of various strategic approaches
- counterfeiting avoidance

1.2.2 **Technical Considerations**

This Guide provides an explanation of the benefits and challenges of blinding of various dosage forms.

1.2.3 **Release of Comparator**

Quality control, product specification, Qualified Person (QP) requirements, and stability testing protocols and methodologies are discussed.

1.3 **Purpose**

The ISPE Good Practice Guide: Comparator Management is intended to establish strategic and tactical considerations when sourcing and procuring comparators for use in a clinical trial. It aims to identify and develop industry good practices for:

- making sourcing decisions
- the technical considerations for blinding
- release for use

Regulatory requirements and their potential impact on sourcing decisions are also considered.

The sourcing and blinding of comparator drugs is a key activity in a clinical study. Making the right strategic decision can ensure costs are kept within budget and study timelines are maintained.

1.4 **Benefits**

One of the main benefits of this Guide is that it provides a unique overview of the management of a sponsor's comparator needs.¹

This Guide is intended to provide a central reference source and provide advice on the considerations that should be taken into account to mitigate risks involved when sourcing comparators.

Clinical trial leaders, their support teams, and other stakeholders (e.g., Quality Assurance (QA), QPs, and technical operations) need to negotiate hazards and obstacles in managing comparators. In addition to sufficient time for planning, this Guide is intended to assist such personnel in making decisions that can help a sponsor to avoid delays and save significant time and costs.

¹ To the knowledge of the authors, this Guide does not exist elsewhere in another form.

1.5 Key Concepts

Comparator

A comparator is a commercially available drug product to be used in a clinical trial in direct comparison with a sponsor's proprietary investigational medicinal product.

Sourcing

Sourcing is the evaluation, selection, and supply of a specific drug based on assessment of factors including:

- dosage forms
- product strength and presentation
- lead-time for acquisition
- importation issues
- blinding complexity
- costs

Investigational Medicinal Product (IMP)

The definition of an Investigational Medicinal Product" (IMP) is provided in Directive 2001/20/EC, Article 2 (d) [2], as "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization, but modified (e.g., change to dosage form or its primary or secondary packaging) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form."

Medicinal products with a Marketing Authorization (MA) are classified as IMPs when they are to be used as the test drug or reference drug in a clinical trial, provided they are used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or used to gain further information about the authorized form. On this basis, provided that the requirement(s) are met, reference products used as comparators should be considered as IMPs.

Manufacturer/Importer of Investigational Medicinal Products

A manufacturer/importer is a person, where required and authorized by a regulatory authority, engaged in manufacturing and/or importation activities.

Sponsor

A sponsor is an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Open-Label Study

An open label study is one in which the investigator and the study participant are aware of the drug therapy received during the study.

Double-Blind Study

A double-blind study is a clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results since the expectations of the doctor and the participant about the experimental drug do not affect the outcome; also called double-masked study.

Single-Blind Study

A single-blind study is one in which the treatment group assignment is not revealed to the study participant, but is known by the investigator.

Blinding

Blinding is a procedure in which one or more parties to the clinical trial (i.e., the subject/patient, investigator, and/or sponsor medical personnel) are kept unaware of the treatment assignment(s) of the clinical trial participants. Blinding is used to remove potential for study bias.

Blind

A randomized trial is “blind” if the participant is not told which arm of the trial they are on. A clinical trial is “blind” if participants are unaware of whether they are in the experimental or control arm of the study; also called masked.

- Phase I Clinical Trial
- Phase II Clinical Trial
- Phase III Clinical Trial
- Phase IV Clinical Trial

Request for Information (RFI)

A request for information is a question or series of questions posed to a supplier or other organization with the purpose of making an assessment. For example, questions relating to sourcing capabilities and resources may be sent to a supplier in order to have data provided to assess their suitability for a particular project.

Master Service Agreement (MSA)

Master service agreements specify generic terms, such as payment terms, product warranties, intellectual property ownership, and dispute resolution.

Key Performance Indicator (KPI)

Key performance indicators are agreed performance measures and metrics that describe the management of the logistics operations between a sponsor and its suppliers.

Non-Disclosure Agreement (NDA)/Confidential Disclosure Agreement (CDA)

Non-Disclosure Agreement (NDA) or Confidential Disclosure Agreement (CDA) is a legal contract that describes confidential information such as specifications, data, documentation, or other technical or business information disclosed between two or more parties.

Participating parties are required to keep all non-public information in confidence and will not, without prior written consent, disclose the information to any person or entity, except those of parties involved such as officers, employees, agents, and representatives.

Technical Agreement

A quality contract/quality agreement/technical agreement is a legal document that establishes a clear definition of cGMP compliance responsibilities between the contract giver and contract acceptor.

2 Comparator Drugs Sourcing Process

2.1 Introduction

Comparators are usually needed once the pharmacokinetics and pharmacodynamics of the investigational drug have been established and it has been determined that the investigational drug is a good candidate for further assessment.

Comparators are only rarely requirements in Phase I studies that are typically run in populations of healthy individuals. Comparators are normally used in later Phase II trials and are required most frequently in Phase III trials.

In many cases, an optimal dose of the investigational drug will have been identified, but there may be more than one strength under investigation. Where there are **several** strengths of investigational drug that could be marketed by an organization, the strength of the comparator should be selected by medical professionals. This should provide a meaningful comparison of the selected strength of investigational drug against existing treatments.

Where one strength of an investigational drug is being studied, but many strengths of comparator exist, the strength of comparator should be given careful consideration in order to determine which strength would provide the most robust comparison of effects.

The choice of a comparator may change in later trials or different trials at the same developmental stage (e.g., Phase IIb), depending on prior results.

The selection of more than one strength of comparator in a cross-over design may be required.

2.2 Stakeholders in the Selection of a Comparator

Numerous stakeholders may be involved in the decision to use a particular comparator. Key stakeholders are listed, along with their responsibilities and involvement in the process:

Medical Affairs/Scientific Professionals

Medical affairs/scientific professionals should make decisions on which specific comparator to use, based on the nature of the investigational compound (e.g., the theoretical potential of the IMP and the results of early clinical trials).

Marketing Professionals

Marketing professionals should conduct market analyses such as competitive landscaping, positioning, the size of the market, and its segmentation. These analyses help them to identify:

- unmet needs in the market
- the presence and effectiveness of therapies already on the market
- the potential current and future competition that the drug may face in being selected by medical professionals to tackle the indication

Depending on the information discovered by these analyses, the investigational drug may be compared against another selected existing medication in order to make the most effective marketing claims. For example, if the investigational drug is believed to be most effective at night time and one of the potential comparators is also known to be most effective at night time, this may be the comparator of choice to help to ensure that the clinical evidence can be compelling.

Clinical Project Professionals (Clinical Project Managers/Study Leaders/Project Directors, etc.)

The clinical team should coordinate the operational conduct of the clinical trial and is responsible for the:

- assimilation of requirements
- setting of relevant study timelines and goals

This includes consideration of the supply of the comparator including the estimated quantities required and the initiation of the process to secure supply. It also may include execution and completion of the acquisition process.

Depending on the size and structure of the sponsor organization, the clinical project professional may be supported by individuals or teams with the responsibility for forecasting volume requirements or specialists in sourcing comparators for many or all of an organization's clinical trials.

Clinical Supply Chain Procurement Professionals (Supply Chain Managers and Coordinators, etc.)

After a comparator is selected, it needs to be sourced, i.e., a supply of suitable materials needs to be identified. Clinical supply chain procurement professionals should identify the optimal source and provide feedback in terms of available options, lead times, and limitations offered by the market.

Regulatory Professionals

Regulatory professionals should be able to advise on the approval of relevant competent authorities and requirement for any documentation to support the use of the selected comparator. Both internal and external regulatory resources can be drawn upon to validate the list of countries to be used in the trial, i.e., can the sponsor obtain the comparator that has been selected in the form and volume needed for use in each of the countries? Either an alternative comparator can be selected or perhaps an alternative country (or countries) to take part in the trial.

Quality Assurance Professionals

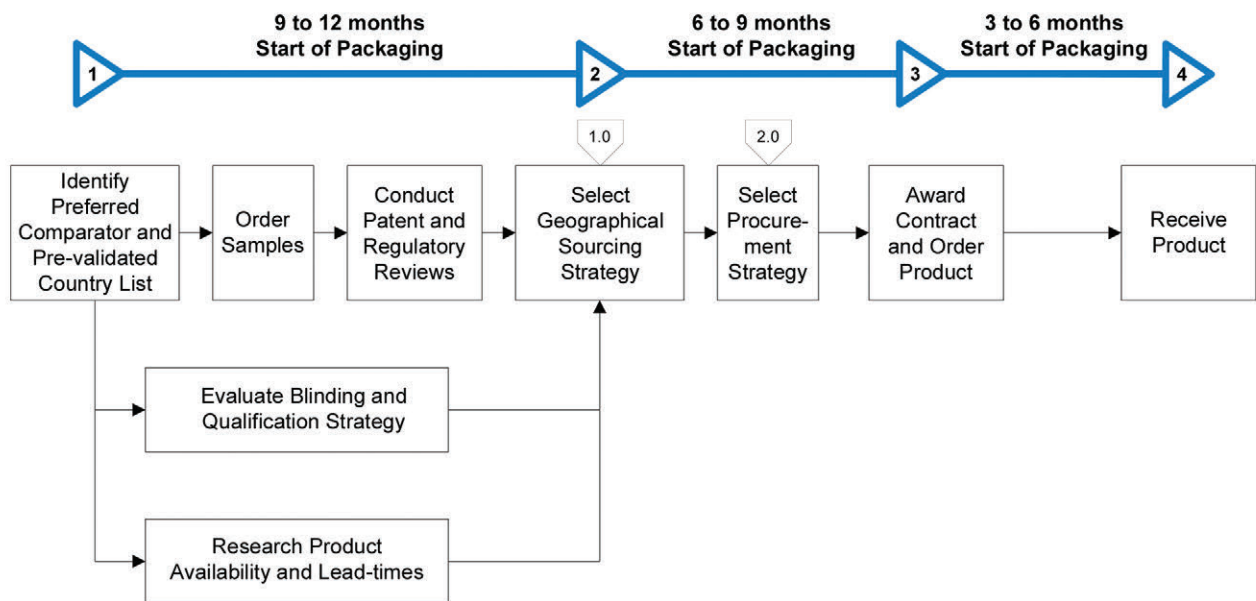
Quality Assurance (QA) professionals should be involved in the sourcing process to ensure that the supplier conforms to the requirements of the sponsor organization and to regulations concerning the quality of the material, e.g., Good Manufacturing Practice (GMP). QA also can assist in the sourcing strategy by evaluating expiry date, supportive stability, and assessing the raw material and packaging material acceptability for each country or region.

2.3 Identification of the Supply Strategy to be Used

2.3.1 Selection and Communication of a Comparator for a Clinical Trial

An abbreviated process flow is shown in Figure 2.1.

Figure 2.1: Abbreviated Comparator Sourcing Process



The timeline for the abbreviated comparator sourcing process is illustrated at the top of Figure 2.1. The comparator sourcing process should begin approximately 9 to 12 months before the comparator is received, i.e., before the comparator reaches its destination in preparation for any onward testing or blinding and packaging. This should allow for contingency and to identify the best strategic option for the complete duration of the trial.

Identifying the Preferred Comparator and Pre-Validated Country List

Typically, identifying the preferred comparator and pre-validated country list is the responsibility of clinical researchers and medical affairs specialists, but marketing departments also can be involved. Individuals from these departments should work together to identify the target comparator. The comparator sourcing department should collate and feedback data to enable an informed decision to be made on the best comparator.

The factors involved in making a decision about the comparator are not limited to, but include the following important considerations:

- the **consistency** of comparator across markets in which the IMP will be compared (and potentially marketed)
- the **availability** and **access** to the product
- the supply **risks**
- the **cost**
- ease of blinding (see Chapter 3 of this Guide)
- compliance with regulatory requirements (see Chapter 4 of this Guide)

In a controlled experiment, variables should be kept the same, except for the one variable that is being tested. The consistency of the comparator should be considered, particularly when making any claims against the comparator, which is frequently the objective of such trials. For example, if there is a range of strengths of comparator available in various markets, the purchasing organization may select the strength of comparator that occurs most frequently, or it may choose to drop a “problem” country from the study, depending on the study’s objectives and the importance of that market.

Large, single lots of product can help to maintain consistency and to create efficiencies (e.g., less use of QA resources, fewer shipments). Sourcing multiple lots from one or multiple suppliers to accrue sufficient material (e.g., in flexible dosing studies) should be avoided.

A purchasing organization can construct a representation of what is available in each territory by identifying the different strengths, formulations, presentations, and brands that are available. An early indication can be established of how easily available each option may be, allowing the formulation of a strategy.

Availability (lead time, licensing, and expiry dating) and access should be considered. Availability and access both contribute to the risks involved in sourcing comparators.

Once several potential candidates have been identified samples should be ordered so that they can be examined. The potential for any modifications, e.g., over-encapsulation or repackaging, that may be required can be assessed. For further information on modification and stability considerations, see Chapter 4 of this Guide.

The final consideration is the potential costs of a sourcing strategy and to balance these with the risks identified and options available.

Choosing Branded or Generic Comparators

The choice of whether to use a branded or generic product may be a cost consideration. It also can be determined based on factors such as:

- presence and status of the best in class drugs on the market
- unmet needs and market segmentation
- pricing of the comparator on the market
- perceived, distinct advantages of the investigational drug in terms of efficacy and/or safety profile

The selection of a generic product as a comparator may be excluded before the cost advantage can be taken into a consideration. Use of the branded product could be necessary to meet the commercial objectives of a study.

Table 2.1

Option:	Branded (Innovator)	Generic
Pros	Usually best for making marketing claims	Cheaper than branded
	May be the only option as standard of care	Can be easier to access documentation
	Proven with clinical/non-clinical data available	Generic manufacturers may be willing to provide active product plus placebos
Cons	More expensive	Must be certain of a bona fide source (although this applies to branded product as well)
	May be more commercially sensitive, i.e., accessing large volumes could draw attention to trial activity	Quality of product may not be recognized in all territories (quality also may be an issue with branded products)
	Can be more difficult to access large volumes in all study territories	Strength, presentation, or formulation less likely to be available in all study territories

Ordering Samples

Once the comparator has been selected, the purchasing organization can order a sample of the product for internal review. The samples can provide an opportunity to study the label and patient information leaflet and to conduct stability testing.

Labels for products approved in Europe can be found on the EMA website [3], which can help to expedite the process of information gathering.

The samples also enable the assessment the comparator's packaging and a **blinding and qualification strategy** can start to be developed. For further information, see Chapter 3 of this Guide.

Counterfeit Avoidance

Counterfeit medication represents a risk to patient safety by:

- not containing the right amount or quality of active product
- not containing any active product
- possibly containing an agent that could be directly harmful to a patient

When sourcing a comparator, the traceability of the product should be known. The purchasing organization or their direct supplier should be able to trace the medication back to the manufacturer and minimize the risk of any counterfeit medication entering the supply chain.

Security in the supply chain could be achieved by obtaining comparator directly from a manufacturer, but this is rarely possible due to a lack of supply infrastructure and concerns about confidentiality. The objective should be to keep the supply chain as short as possible; preferably there should be only one link in the chain (i.e., one supplier) between the purchasing organization and the organization manufacturing the comparator. Where possible, audited suppliers should be used that:

- can provide documentation to establish the quality of the medication being supplied
- have a robust process in place for documenting the traceability of a comparator

Researching Product Availability and Costs

The sample does **not** usually provide an opportunity for the assessment of the availability or the lead time involved for obtaining the product. Ordering one or two packs as samples differs significantly to ordering several hundreds or thousands of packs.

In territories where there is tight control over inventories (e.g., Europe), a reliable estimation of the lead-time required to provide larger volumes is required to avoid unexpected delays. The cost of delaying the launch of a product by just one day is estimated at up to \$8 million in lost sales (http://www.ciscrp.org/professional/facts_pat.html [4]). Market intelligence such as this should be known.

Market intelligence can be achieved to some extent early in the process by canvassing the experience of preferred suppliers or by asking for a preliminary quote. Manufacturers may not provide a quote (e.g., an indication of lead time or pricing) without confirmation that the quote is for a genuine clinical trial. Manufacturers may request information such as:

- a list of countries
- a trial reference number, such as the EudraCT [5] number in the EU (currently conveying no further information about the trial)
- study ID number

A request for such information may confirm that supply is coming directly from the manufacturer.

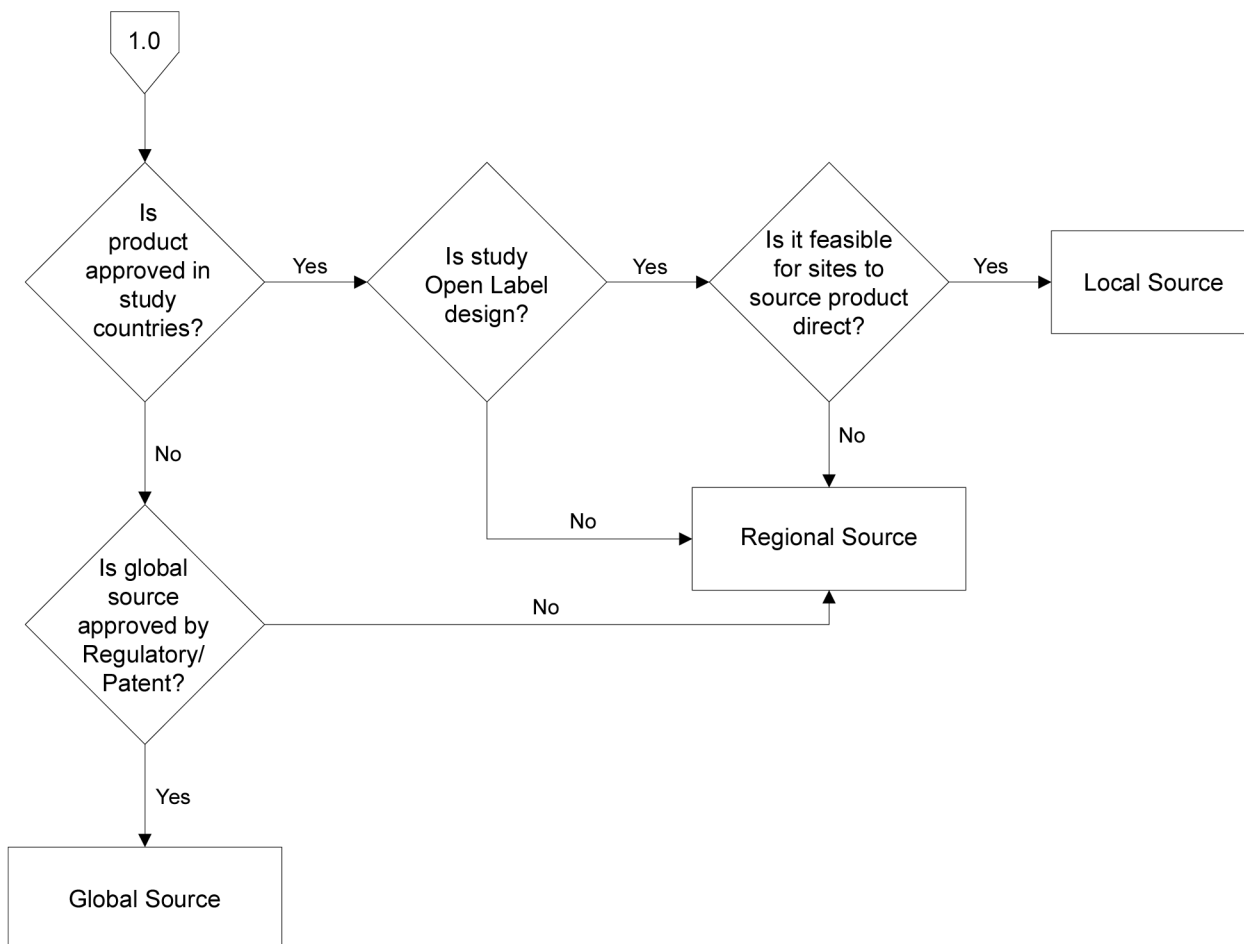
Regulatory Review

A review of the licensing status and the requirements of competent authorities in the selected trial countries can be performed simultaneously with the assessment of availability and lead times and review of the samples by the purchasing organization's regulatory team and that of the preferred supplier. This should help to identify any potential supply issues at an early stage. Where a decision is taken to source the comparator locally, but it is not licensed in one or more of the countries participating in the trial, the sponsor may need to reconsider the inclusion of that country in the trial. Alternatively the comparator may be changed, depending on the number or importance of countries affected.

Once this research is complete and the target comparator and list of countries has been confirmed, a geographical strategy should be selected.

2.3.2 *Choosing a Geographical Strategy*

When considering the geographical sourcing options, the process map shown in Figure 2.2 can be referred to as a guide. **Note:** purchasing organizations may follow different process maps depending on the specific situation.

Figure 2.2: Process for Selecting a Geographical Source

A determination should be made as to whether the comparator being sourced is approved or licensed for use in each trial country.

Where a comparator is approved or licensed for use in each trial country, QA should confirm whether a global source is available. The source should be approved by QA in terms of the quality of the source and material. A review of any potential patent issues should be performed.

Where the comparator is not licensed in each trial country, the design of the study should be considered before proceeding.

2.3.3 Open Label Trials

If a trial is to be conducted with an open label, there will be no requirement to modify the comparator. Where a comparator can be sourced locally, this may be the preferred route, as there may be no need to change the language of the label. In addition, this should result in minimal wastage with local investigators being able to order the drug as needed by the patients in the trial.

Several requirements should be considered before an open label trial:

1. Local investigators should have the facility to pay for the medication required. They may hold a budget or a way of submitting invoices for the sponsor in order to pay directly or indirectly for the comparator.

2. Inventories for the comparator should be sufficiently stocked to ensure that the volumes required in the trial are available for the duration of the trial.
3. The suppliers of the medication should be known to the sponsor and their information should be verifiable:
 - control over the suppliers used should be maintained
 - investigators should be required to provide the details of each supplier to minimize risk of counterfeit entering the supply chain

Where possible, each supplier should be reviewed and audited by the sponsor. The extent of an audit should be sufficient to satisfy the sponsor that appropriate rigor is being exercised in supply of the product. Depending on the severity of any negative findings, alterations may be proposed or the sponsor may choose not to work with the supplier. Sponsors may consider the holding of appropriate licenses and GDP awareness to be sufficient.

Where feasible, the comparator should be procured locally for simplicity and low wastage. It also may be possible to supply the comparator regionally for an open label trial with potential benefits of clinical consistency, a lower regional price, and mitigated risk of counterfeit drugs entering the supply chain.

2.3.4 Blinded Trials

A blinded trial is one in which the comparator will need to be modified in order to obscure its identity. The non-distinct clinical image may be designed to match the investigational product or a placebo to match the comparator. This is intended to remove any psychosomatic effects of the patient knowing which treatment group they are in, or in other words, what drug they are taking as part of the clinical trial.

In blinded trials, the preferred order for sourcing a drug would be:

1. globally
2. regionally
3. locally

As a minimum requirement, locally procured medication would need to be relabeled and further modification may be required.

Re-labeling can be achieved locally, but may not be an option or may not meet the “standards” of consistency required.

Blinding strategies are discussed in Chapter 3 of this Guide.

2.3.5 Hybrid Option

Where there is a potential global supply strategy that can be accessed, but there is also concern regarding the importation of material into one or more particular countries, a hybrid approach could be used. In a hybrid approach, global supply is used for most territories, but selected countries may be supplied locally. This may present the same challenges as those encountered with local supply (the potential need for quality over-labeling and mitigation of risk in the supply chain), but these challenges could be restricted to one or a few countries.

This approach could be used both as a long term or a short term solution (until assurance was in place that a country could join the global supply chain).

This approach also can offer a “utility player” function or “contingency plan” should any issues arise with the primary option and researching local supply options may be beneficial.

2.3.6 Distribution

When considering the geographic strategy, the method for moving the comparator product to site should be considered.

If sourcing locally for open label studies, this may be relatively uncomplicated. Each local supplier should be audited to ensure that the supply chain to that point has been secure and that any documentation needed for submissions can be obtained. A sourcing partner or supplier may provide a service where they purchase centrally (regionally or globally) and then store and distribute directly to site when needed. Where this service is being offered, these capabilities also should be audited.

For blinded trials, where modification of the comparator is required, this should be performed by:

- the sourcing supplier (if they have the capability)
- an organization with the capability (this may be the sponsor)

Selected suppliers may be able to store and distribute to the organizations that will modify the comparator for distribution.

The Request for Information (RFI) process should consider the logistics capabilities and experience. Specific storage capabilities, licenses for handling material, and couriers used by suppliers as they relate to the needs of the purchasing pharmaceutical organization should be confirmed, e.g., cold chain products usually need special consideration. Other considerations may include:

- the avoidance of temperature excursions, where possible, through the use of specialized shipping containers
- a process for review and release of any product temperature deviations
- temperature monitoring during transit
- the ability to check with the manufacturer that the comparator can be used in the event of an excursion (e.g., how will the selected supplier achieve this?)

Agreement should be made with the supplier concerning responsibility for transport so that the transfer of Qualified Person (QP) responsibility is clearly defined. In addition, for cold chain product reducing the travel distance may reduce the probability of a temperature deviation.

2.3.7 Summary Table

Table 2.2 considers sourcing from a geographical perspective and outlines some of the advantages and disadvantages which should be considered.

Table 2.2: Key Advantages and Disadvantages of Different Geographical Sourcing Strategies for Comparators

Strategy:	Local	Regionally Centralized	Globally Centralized
Description	Sites must source and supply the comparator within each country.	All comparator is sourced from one central location to supply all countries within a region, e.g., EU.	All comparator is sourced from one central location to supply all countries globally.
Positives	Simple solution for small studies or open label studies. No need for central storage, no import issues, minimized distribution/IVRS.	Efficiencies can be gained from procuring drug through a centralized process and using centralized expert resource.	
	Drug will be ready-labeled with local country language.	Quality documentation, such as CofA, CofC, TSE, should be accessible.	
	Reduces perceived risk of being challenged at the time of submission.	Accesses large single lots of clinically consistent material with maximum expiry.	
	Minimal wastage in open label trials. Drug can be ordered as needed.	Reduces wastage as drug can potentially be moved between regions to meet demand.	
	Leverage patient insurance for SoC therapies.	Close control can be maintained of stock levels and finances handled centrally.	
	Mitigates risk of storage excursions.	A supply agreement can be put in place to cover the duration of the trial.	
		Recall of product is easier.	
Negatives	Formulation may vary between countries.	May need to create a labeling strategy to support all countries.	
	Comparator may not be licensed or on local formulary.	Longer lead times would be expected for the production of large, single lots.	
	Takes local human resources away from their key tasks.	Different countries may have different licensing specifications.	
	More appropriate for rescue, SoC, or concomitant medication.	May require testing to demonstrate equivalence across regions.	
	Only really a good solution for open label studies.	Problem countries may prevent coverage of all regions.	
	Site must have sufficient budget for up-front purchase.	Requires central storage and distribution or possibly IVRS.	
	Doesn't take advantage of less expensive price in other region.	Potential for storage excursions, e.g., temperature.	
	More stability work may be needed due to multiple sources being used.		

Acronyms used in Table 2.2 (also see Appendix 6.)

CofA – Certificate of Analysis

CofC – Certificate of Confidentiality

EU – European Union

IVRS – Interactive Voice Recognition System

SoC – Standard of Care

TSE – Transmissible Spongiform Encephalopathy



2.4 The Planning Stage

2.4.1 *Choosing to Work Transactionally or Strategically*

The acquisition of the comparator can be achieved either transactionally or strategically.

A transactional approach means that each time a batch of drug is required, a request could be made of several suppliers to provide a quote for the product. A supplier selection can then be made based on factors such as the available documentation, lead-time, or the cost of the drug. This “snapshot” approach would be repeated each time a new requirement arises.

A strategic approach can mean several things, including a purchasing organization’s strategy to operate a repeated transactional approach.

For the purposes of this Guide, strategic comparator sourcing means that several options are reviewed, possibly in partnership with a specialist, before selecting the optimum option for a given trial or series of trials.

The selection of a strategy is usually a consideration that is longer term than the duration of a trial (or trials). The selection may be determined by which strategy offers the greatest security of supply, the best pricing, or the greatest flexibility and control, e.g., it is based on more than accessing what is available at a given point in time for a current need.

A more strategic approach to comparator sourcing can help organizations to reduce risk and access more meaningful cost reductions concurrently.

Two key elements facilitate a strategic approach to comparator sourcing:

1. providing the greatest length of time for the procurement team to identify and secure the best sourcing strategy
2. sourcing directly from the comparator’s manufacturer through partnership with a sourcing specialist that has an established relationship with that manufacturer

There should be a direct interface between procurement and the clinical teams in order to increase the length of time available for sourcing. This can allow procurement greater visibility of the trial protocol and create a feedback mechanism for the discussion of any difficulties that the selected comparator may bring to the trial, in addition to providing an opportunity to highlight any alternatives.

A forecast for the initial exact volume requirements and future estimated volume requirements should be provided to the procurement team. This should allow the supply of the comparator and the purchase terms to be determined as soon as possible.

Generally, in order to adopt a strategic approach, organizations should start the process about six to nine months before the delivery date of the comparator.

Once a sourcing procedure with an adequate timeline is established, more sourcing options may become available than would be possible at the “last minute,” including access to the comparator from the manufacturer. Trial sponsors can leverage this direct sourcing route while preserving anonymity by partnering with a proven sourcing specialist that maintains extensive relationships with manufacturers and can negotiate on the sponsor’s behalf. This route allows access to:

- comparators with full documentation
- long expiration dates

- large single batches
- a secure supply chain

Agreements may be established with the comparator's manufacturer to schedule production runs to ensure reliability of supply throughout a trial, while maintaining the confidentiality of the sponsor.

Allowing time to identify a source that can reliably provide the comparator can help to avoid unseen costs of delays that could result from lack of supply during the trial.

In some circumstances, both transactional and strategic approaches to sourcing may be required.

A transactional approach may be the only option if the procurement and clinical teams do not communicate sufficiently. This can carry a greater risk than the strategic approach and such risks and adaptive processes should be considered.

Comparators that are sought at the "last minute" can leave an organization vulnerable to regulatory, operational, and financial risks. The following risks are examples of those that can be exacerbated when locating comparator at the last minute:

- Regulatory and QA Risks:
 - lack of understanding and experience of import/export requirements
 - cannot account for e-pedigree/backward traceability
 - Inability to return all packs in the event of a recall
- Operational Risks:
 - supply restrictions may be put in place by manufacturers when the next requirement comes along
 - dealing with errors caused by suppliers, manufacturers, or sponsors
 - unaudited suppliers may not provide documentation, as previously agreed
- Financial/Commercial Risks:
 - Delays when sourcing subsequent requirements to match a quickly sourced comparator can be costly and could halt a trial.

2.4.2 Establishing the Scope for Flexibility

Forecasting supply requirements for a clinical trial can be a complex and expensive operation. Organizations may plan to have a specific level of overage² because of the unpredictable nature of patient recruitment. Competition for patients within a market and an indication can be fierce and can add to this variability.

Flexibility is considered to be beneficial and two options, depending on the selected strategy, are:

1. Having contingency to supply higher volumes than anticipated for each trial location. If sourcing locally, this may require identifying a back up supplier or a supplier in an alternative region along with an acceptable level of certainty that importation would be achievable, if needed.

² Overage means excess stock, i.e., more than the amount that would have been required to satisfy the demands of the trial.