MIND YOUR LANGUAGE!

Requirements for Local Language Labeling in Clinical Trials

A white paper from Prisym ID

PRISYM ID

MIND YOUR LANGUAGE!

Requirements for Local Language Labeling in Clinical Trials

THE LABELING LANDSCAPE

Global clinical trials labeling is a complex subject and an integral part of clinical trials supplies management. The landscape is varied in terms of the systems and processes employed in designing, populating and printing labels (including booklets and IFUs). To control clinical trials labeling on a global scale a number of key functions need to be managed.

The three main functions are:

- Complexities around local language labeling
- Managing source data for labels, booklets and IFUs
- Customizing labels for country specific requirements

There are a number of stakeholders using a range of solutions and standard operating procedures to produce clinical supplies, including those responsible for the regulatory submissions, defining the protocols and the various approvals that take place throughout the complete lifecycle; typically involving qualified persons, regulatory affairs and other specialists.

All parties come with their own unique set of skills and objectives, but have one overall goal for the creation of the required labels and booklets and need to work closely together in sharing the information, designs and data in order to provide a sound and secure process.

The three main parties involved in clinical trials labeling include:

- Pharmaceutical R&D (discovery company)
- Clinical supplies organizations
- Booklet and label printing companies

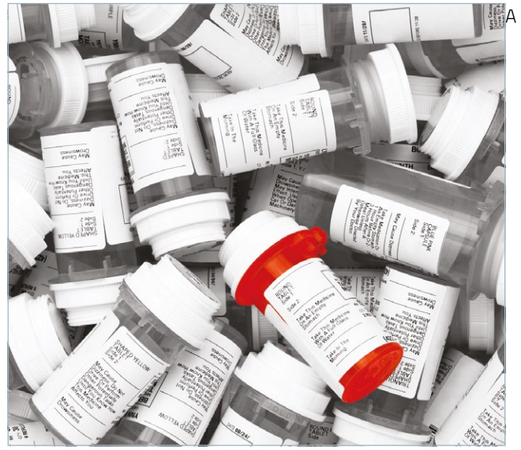
The discovery companies that wish to trial the drugs adopt a range of approaches to the packaging and labeling of supplies, ranging from in-house management of the whole process to an outsourced model where clinical supplies companies take on the complete job, to an approach where only part of the task is subcontracted.

Also, the production of the booklets is a very specialized area so there are also companies employed that focus solely on the aspects of booklet production, overprinting and labeling.

THE FUNDAMENTALS

The definition for the label, the booklet and the IFU might seem very basic, but the creation of these various assets is subtly different. Whereas a label can be printed 'on-demand' or truly 'Just in Time' (JIT), as can an IFU, the booklet is a little more complicated.

LABELS



A 'single panel label' is essentially a single panel adhesive backed paper or synthetic label that contains information relating to the product. When designing a label there are specific elements that need to be addressed, including UNICODE text (with sophisticated copy fit and formatting functionality), images (products and logos), line art and barcodes (plus new developments in 2D codes and RFID).

It is not just single language labels that are printed on single panel labels. If there is enough room on the label, multiple languages can be printed.

A single panel label is usually printed on a thermal transfer printer such as Zebra, SATO or Intermec, where labels are on rolls and printed in either 'on-demand' or in a 'batch process' mode. In addition, desktop laser printers will also suffice where sheets of paper rather than rolls are used; however this tends to be more of a batch process due to the number of labels per page being printed.

Single panel labels are the approach to printing on-demand with the possibility to join-up all systems to provide a highly efficient JIT approach.

BOOKLETS

Booklets are multi-page, complex documents with a lead-time to their production, requiring an inventory to support a trial.

- A booklet is generally made up of:
- A back page that carries the glue for adhering to a surface
- A front cover that is often overprinted with patient specific and product data at time of dispatch/pack
- A spine which is sometimes the area where overprinting is placed
- An index to identify the country specific pages - usually the first page in the booklet
- Country specific pages in local language and design specific requirements

Booklets require highly specialist printing and production technology to be produced. Therefore this dictates that their production is almost exclusively outsourced to specialist booklet manufacturers.

Consideration must be given to how a booklet is designed and what the actual output from the system or process is that will be supplied to the manufacturing company.

An area that brings together booklets and label printing is what is termed as 'overprinting'. The technology of choice used to overprint booklets tends to be dictated by the size, or thickness of the booklet.

For smaller booklets thermal transfer printers can be used and for larger booklets the technology employed tends to be inkjet.

INSTRUCTIONS FOR USE (IFU)

An IFU is the instruction leaflet within a container that provides instructions to the patient. IFU leaflets are not used much in clinical trials due to the use of booklets, although it is worth inclusion as a laser printed documentation that can be printed on-demand or JIT.

The fact that IFUs can include variable data is a capability that should not be overlooked and with the use of readily available and affordable technology IFUs can be easily printed in-house.

CRITICAL ELEMENTS

There are many different elements that need to be considered when designing a label whether it's for a single panel label, booklet or IFU. These include a combination of text, phrases, variables, barcodes and graphics.

Some of the regulatory requirements that need to be printed include:

- Name of the sponsor, clinical research organization or investigator
- Trial reference code to allow identification of clinical trial
- Trial subject identification number/treatment number
- "For clinical trial use only" or similar wording
- Quantity of dosage units
- Route of administration
- In case of open trials the name/identifier and strength/potency
- Batch or code number to identify the contents and packaging operation
- Storage conditions
- Period of use to allow return of IMP after expiry
- "Keep out of the reach and sight of children"

Generally, the industry requires text formatting to use Windows fonts with the ability to resize individual blocks or individual characters (i.e. using bold, italics, underlining and UNICODE).

A number of languages may be needed per label. Due to this dependency, it makes the decision on whether the data fits on a single panel being produced rather than a booklet. The ability to toggle from any foreign language to English is a common requirement so that the English equivalent can be viewed.

Variables on a format allow values to be added to a label when it is designed and then added to the label at time of print. In essence, a value may or may not be known when the format is being designed and instead can be decided when the label is physically printed.

All linear and 2D barcodes must be available as part of the design tool; 2D symbologies are becoming more commonly used as the use of e-labeling increases.

Additionally, in the same way that phrases are approved, icons, logos and pictures need to have an approval process before being added to a label.

CHALLENGES FACING CLINICAL SUPPLIES LABELING

As clinical trials are run in many countries, there is an obvious need for translated instructions; within a particular language spoken in different countries there can also be small differences that need to be catered for at a very local level.

At the time of print, data can come from a range of systems - trial data, randomization data and production data. This requires solid and secure management to bring version controlled information from all systems together to print at the point of dispatch.

Also to be considered are 'country specific regulatory issues' which means the design of a label is different dependent upon the destination country.

This can be relatively straightforward to address for single panel labels and an 'on-demand' printing approach but more of a challenge for booklet design where a large amount of information needs to be managed plus multiple page formats.

In essence, once a stock of booklets has been printed there is little chance to make changes to the booklet itself.

Some of the problems faced by global clinical trials label printers include:

Language problems -

- There is a need to know early on which countries the trial will run - especially for booklets
- Phrases need to be translated quickly and efficiently – using in-house resources or a third party
- All phrases need to be approved and ready in good time
- Plurals need to be managed with confidence
- It is necessary to determine whether or not text will fit in an area when printed in different languages
- Local language differences need to be managed

Data problems -

- Data needs to be brought into one place to be managed (including external supplier data)
- The same data needs to be used to populate all assets (labels, booklets, IFUs)
- Data needs to be maintained and managed independent of asset design
- Correct version of the data needs to be available at time of print

Design problems -

- A knowledge of how the drug will be packaged
- An understanding of the country specific requirements
- Whether the labels will be produced in-house or outsourced
- Which label material will be used - stock labels or custom designed consumables
- Available room on the label for all information
- Ideally all systems used in the process will be joined-up as re-entry of data or 'cut-and-paste' is not desirable

The more automated and robust the systems the better, and if run efficiently they can provide the company with a competitive advantage.

THE PERCEIVED COMPLEXITIES OF LANGUAGE LABELING

The approach to language labeling across the clinical supplies industry varies from centrally administered phrase libraries that cover many languages and are common to all trials that are labeled, through to organizations that prefer to administer a set of phrases specific to each trial and limited to only the languages required.

Local language labeling is concerned with how to manage phrases in different languages and to drill down to a highly local language level to ensure the instructions and information provided are understood precisely. For example, in South America several versions of Spanish may be required. The need for a local person to understand these subtleties is important and the use of technology to assist in this process is essential, yet difficult to achieve.

'The complexities of local language labeling' can include:

- Management and control independent of the language
- Translation of individual phrases
- Bulk translations import
- Specific local language differences
- Country specific requirements
- Trial specific language management
- Centralized language management plus mandatory phrases
- Use of internal translation people and/or third party translation companies
- Secure access to the system by all stakeholders
- Management of plurals
- Printing labels 'on-demand'
- Multiple page booklets and the associated 'lead times'

Regardless of the differences in the approach to the management of phrases and local language labeling there are a number of key aspects that need to be addressed.

PHRASE CREATION, APPROVAL AND VERSION CONTROL

The key objective is to ensure that the phrases used on a particular piece of design work are correct and remain correct throughout the trial. Once the phrases have been created and approved, it is a requirement that the content be used across a variety of final patient facing assets (labels, booklets and IFUs). Also, language experts must be able to efficiently manage all the phrases in their language and must be able to monitor the impact of any changes proposed or implemented to a phrase library. Therefore, 'Approved Phrases' and 'Sets of Phrases' need to be managed outside of a specific trial and held independent of the trial.

One of the goals of a phrase library is to allow native speakers to contribute. This is where the access to a system must be managed by rigorous security features and user rights. A contributor may have the rights to view but not physically change anything.

Creating sets of phrases and grouped phrases is a logical approach (such as 'dosage phrases'). Phrases need to be version controlled and managed and mass imported to a phrase database. The ability for the user to designate the source language that is used as the original basis for a translation must be accommodated.

It is useful to be able to Import and export source phrases. The ability to be able to bulk input all phrases that have already been translated in a controlled and auditable manner are especially useful when a system or trial is being set up.

The import of phrases into a management tool might include the common import cases:

- The phrase in the import file has no existing record
- The phrase in the import file can map to an existing record that is able to be modified
- The phrase in the import file can map to an existing record that is locked or not able to be modified

The handling of plural cases as a process requires specific consideration. While in 'UK English' there is a well understood convention of singular and plural, this is not the case in other written languages, where there are multiple different plurals that need to be managed for the same singular form.

LANGUAGE DATA CONFIGURATION

Language data configuration can be structured and managed in a number of ways. A system that is flexible and configurable should provide the capabilities for:

- Central administration
- A set of phrases specific to a trial
- Limited to only the languages required for a particular trial
- Grouped phrases

There are phrases that are common to all companies and trials, phrases that could be translated once and used many times by all companies in the industry. It is worth considering a set or pack of phrases that the industry adopts. The same could be said for images as there are some common type images but these are not extensively used.

The set of phrases shared by many is an interesting concept and an approach that has been adopted in other industries such as the transport of hazardous material across Europe, commonly known as the Global Harmonization Standard (GHS). In this instance, the risk and safety phrases and pictograms are standard and common and various companies maintain a commercial set of the phrases that they sell, support and maintain.

PHRASE MANAGEMENT USING THE DICTIONARY CONCEPT

The 'dictionary' concept is one that isolates a particular phrase from its translations. This approach is used to utilize the security, version control and audit trail to control and manage the dictionary itself.

The concept of a version controlled dictionary is a robust approach and means the dictionary can be managed independently to the translations.

For instance, the 'Dictionary' may well be defined in English but the translation of the dictionary into English means that a totally independent translated database will exist in all required languages.

In essence, you can have someone that manages the dictionary and a different person that creates the actual translations.

Another approach can be organized as a set of 'regulatory terms' and then divided into the terms used in a specific trial. The same is true for packaging specific terms again divided and used in a specific trial.

The terms and phrases to populate a label design, booklet or IFU could be easily sourced from any of these repositories.

In summary, although the management of language data can be complex, by using the right principles and approach for configuration the task can be controlled and well managed by various stakeholders in different locations.

CUSTOMIZING LABELS FOR COUNTRY SPECIFIC REQUIREMENTS

There are country specific regulatory requirements that need to be adhered to. A mechanism to advise, remind or guide content authors of the specific requirements that individual countries have in place for artwork design is required.

From the perspective of certain phrases that must be used on labels for specific countries, this is a relatively trivial problem to overcome.

The more complex scenario is that of conditional requirements. These requirements are of the 'this must be used' but also cover conditional situations where one asset is required based upon the presence or absence of another asset on the artwork.

MANAGING SOURCE DATA FOR LABELS, BOOKLETS AND IFU'S

Language information and its management should be totally integrated with an 'on-demand' label printing approach. However, when booklets are considered there is a need for them to be designed and printed early and in good time to be used within the actual trial. Therefore, In the case of booklets, when the bringing together of information and data is considered the approach is to 'overprint' an already printed booklet available from stock, an area we considered in some detail earlier.

When printing labels 'on-demand' there is a need to bring all information and data together into one place this includes the language specific information plus:

- The trial data
- Randomization data
- Production data

All this information needs to be brought together to populate all label formats on-demand at point of dispatch.

There are in essence two main scenarios when considering the management of source data. Interestingly, the scenario adopted is not so much to do with the data itself but the way in which the data is to be handled because of the organization that will undertake the actual printing and packaging.

The two areas to consider are data management in-house by the pharmaceutical companies and clinical supplies organization that undertake the printing for a range of clients.

It is probably fair to say that because the pharmaceutical company owns the data then the use of this data and integration into internal systems is more straightforward. Whereas, a third party clinical supplies company needs to accept data in various formats from its clients and there is no single format or approach, therefore the solutions and processes they need to employ must be flexible and robust.

The data that a clinical supplies organization receives can be provided in various formats including PDF, CSV files or as a direct link.

The clinical supplies companies need to ensure that the data received has not and cannot be changed. This means that the data needs to be locked and robust operating procedures are in place so that the data is in a secure location; locking the file and restricting access.

Solutions do exist for clinical trials labeling data management that provide specific features for the generation and management of trial data. The systems securely and accurately manage clinical trials data for supplies and complete patient kit/patient pack labeling.

There are a number of pieces of information that need to be managed, stored and easily updated, these include:

- Patient stratifications
- Multiple center management
- Visit and treatment logging management
- Complete randomization based on treatments and stratification

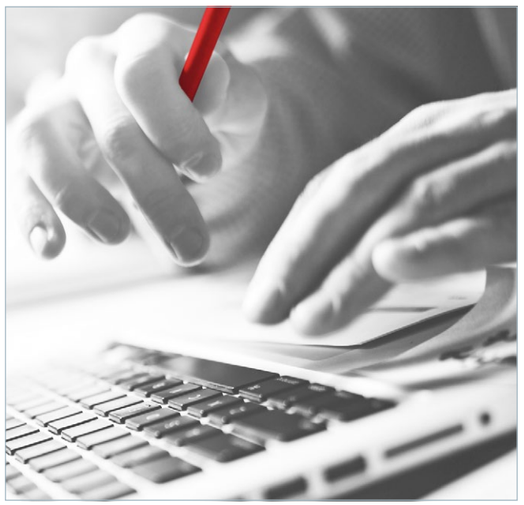
In the case of the pharmaceutical companies the data management issues are the same. However, there is much more opportunity for a tight integration into existing and future systems, including Enterprise Resource Planning (ERP), inventory management systems, and manufacturing execution and packaging systems.

RANDOMIZATION

The generation of randomized data can either be an in-house exercise or one where the data is received externally for use in a particular trial. Typically, a large pharmaceutical company will generate their own randomized data and either use this themselves for printing the labels or overprinting or send it to the company that they have outsourced the clinical trials supply job to.

If however you are the clinical trials supply organization, you may do jobs for a vast range of companies and some smaller pharmaceutical companies do not have their own randomization tools. In this instance, the clinical trials supply organization will need to use a solution that manages the randomization as part of the trial.

The creation of randomized data needs to follow the same processes as all other parts of the trial in terms of approval and version control.



ENTERPRISE RESOURCE PLANNING PRODUCTION DATA AND INTERFACING

ERP systems are required to conduct and manage the business processes. In essence, to ensure the product is available for dispatch at the right place and at the right time and that the complete inventory and supply chain is automated and controlled.

The clinical trials world is varied in its use of ERP, MRP, inventory management, packaging management and logistics systems because of the nature of the business. Consequently, there is the need for 'best of breed' point solutions for labeling, printing and packaging to interface seamlessly to a range of systems. Whatever system has been adopted there will be the need for global trials labeling to link to the data within an organization.

The type of data required from say an ERP system may include use by date or batch codes and other manufacture specific information.

This product batch information needs to be accessed and recorded for traceability purposes.

Particularly in the case of pharmaceutical discovery companies, there is the need for integration with various internal systems.

The way this can be integrated includes:

- Database – staging and production tables
- API's – commercial and custom
- File import

Data for the creation of labels and overprinting of booklets can come from a range of systems. It is a preferred process that the data be managed centrally for a particular trial.

There tends to be three main types of data:

- Randomization data
- Trial Data - subjects, stratifications, treatments, study center, visits
- Production data from ERP systems

The creation and management of this data needs to be based on all the key principles as mentioned previously and the solution needs to be flexible in the input and export of data in readily available and readable formats.

ROBUST END-TO-END PROCESS

The clinical trials supplies process requires that the design of labels, booklets and IFUs be populated by information and data from a range of data repositories or systems, including trial data and production data. There are a number of fundamental capabilities that should be regarded as the building blocks for an approach and/or solution for efficient clinical trials label printing. If these building blocks are not in place, the stack of cards will be fragile to say the least. Therefore, it is vital they are in place to provide a robust validated approach.

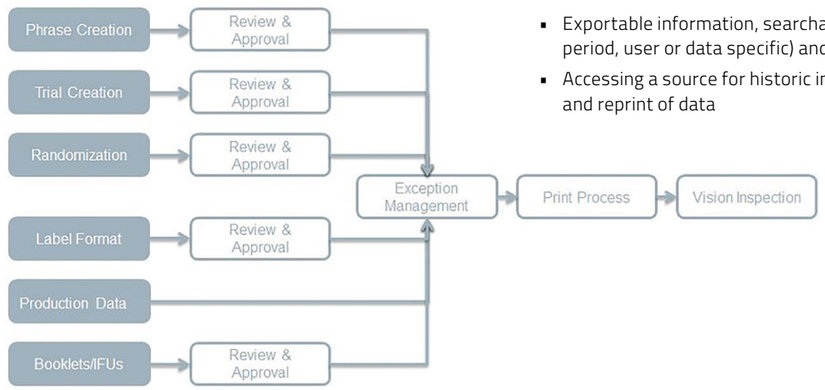
A simple process map illustrates the areas of data creation and management plus design of booklets and labels:

There are a number of base capabilities that are common throughout any fully compliant system that meets current Good Manufacturing Processes (GMP) and clearly one that meets country specific requirements such as the FDA in the US.

It makes sense to consider these elements briefly and to understand in principle what they offer, as disparate systems that use different approaches will not only cause complications but can increase the operational overhead and risk.

In essence the processes need to be proven, reliable and robust and if the pieces of technology that provide this functionality are able to be reused and are common throughout the system, the user's experience will be enhanced by a standard approach throughout all the processes that take place in the field of data and language management plus label and booklet design.

Common belief is that a robust system with a solid foundation will have a common and reusable approach to:



- Security
- Version and revision control
- Searching plus
- Audit and reporting

When some of the diverse users requiring access to a system are considered, including multiple departments, regulatory specialists, label designers and third party organizations, it is clear that all parties needing access to the system must be able to do so unhindered and in a controlled and well managed way. The level of security, flexibility and ease of administering such a capability is fundamental. Specific tasks must be controlled by 'user permissions' – in essence, if a user does not have the rights to undertake a certain function they will be restricted from using that function.

The granular approach to user permissions for setting up a 'label designer' includes:

- Create change request
- Create image
- Create label format

If third party access to a system is considered, the solution will need to provide a range of user rights to be able to record and report all actions. For instance, when language management and translation is looked at there may be a need to set up third party access for an external translator to be able to submit translations. A highly secure audit trail is required to be maintained, as would be expected from a solution meeting the requirements of the FDA.

All stakeholders will want a common approach to:

- Secure historical transaction logging
- Maintaining a complete history of all actions
- Recording the format design, source phrases, trial phrases and all variable data
- Actions logged against user, workstation and date and time
- Exportable information, searchable (e.g. by time period, user or data specific) and printable
- Accessing a source for historic information and reprint of data

There are three main elements to reporting:

- Reporting on the audit log (i.e. by time period, transaction type, user, machine and data)
- Access to and reporting on the data held within the system (i.e. product data, translation and trial information)
- Version and revision control should be common throughout a system

The process will need to follow something like the 'three stage approvals' process which is a common approach that should be used wherever possible to provide a standard reusable approach. Assets that need to be version controlled will include dictionaries and phrases, template designs, with country specific content, and data. The approach to approvals is important as it can be based on either 'single item' approvals or 'job based approvals,' but the principles are the same.

The approvals of assets can and should be an automated process where assets are routed to specialists for approval or rejection. A standard approach to automated, rules based routing of assets is fundamental to a rounded solution. In addition, the ability to add additional supporting information, such as documents, and the ability to provide approval and rejection comments during the process can be very useful.

In more advanced systems several things are starting to appear proactively managed approvals and e-mails being sent to required approvers and more sophisticated management of rejected approvals.

Plus advanced rules that can be configured and enforced may include "group approvals" type rule and/or "must be approved by" type rules.

A BRIEF SUMMARY

A solution and process is required that manages users throughout every step of data creation, design, management and printing with the underlying system based on GMP compliance and in terms of technology a web-based solution makes sense.

The solution should use a standard approval and version control process throughout maintaining separate versions of each asset with an approval management system that allows the users to highlight and comment on any areas for corrections that are relevant to the assets being reviewed.

The process used must provide a coherent identification approach to maintain the integrity of each version of each asset and incorporate collaborative approval management. An approvals management system that allows multiple items to be grouped together into logical containers and when multiple items are grouped into a single review process, the system should allow users to make decisions on individual items without having to compromise the decision on the entire job.

The overall goal should be a complete end-to-end controlled and approvals based process - from label and booklet design, data integration to print and finally label inspection - eliminating any possible room for error.

PRISYM ID

World Class Label Management Software

PRISYM ID designs and delivers label lifecycle management solutions for organizations that need complete product auto-identification and lifecycle traceability. With the continual tightening of labeling regulations and audits, PRISYM ID empowers its clients to safeguard their reputation by ensuring compliance, and significantly reduce costs by eliminating recalls through labeling errors. PRISYM ID is the market leader in world-class label lifecycle management, and is trusted for delivering personalized service excellence to clients in varied sectors including medical device, life sciences, healthcare, automotive, chemical and manufacturing.

For further information, please go to:

+44 (0) 1189364400 | +1 508-948-6100
www.prisymid.com | info@prisymid.com | @prisymid

Speak to our Team of Experts

UK TEL +44 (0) 118 936 4400 | **US TEL** +1 508-948-6100
www.prisymid.com | info@prisymid.com