LABELS IN LESS: Streamlining Label Creation for Investigational Medicine 6/17/09

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When a drug candidate enters phase III, it is the drug development equivalent of "the Major Leagues in baseball or the Premier League in soccer/football". Clinical trials in Phase III have grown from studies at a limited number of sites to major operations involving thousands of patients often across multiple countries and regions. Clinical trial protocols are now increasingly complicated and there is more to track -- multiple doses and different time durations, for example. The logistical concerns are similarly more involved, requiring shipping, packaging and distributing larger quantities to multiple sites. And there are the chemical challenges that go along with making the drug from small batches to scale-up levels in regulated conditions. In a sense, running a correct phase III trial is practice for the kinds of attention to details and quality needed if the drug is approved -- though some might even argue that many aspects of phase III trials are even more complicated than the approved scenario.

Today's clinical teams often spend a disproportionate amount of time on the single biggest challenge confronting initiation of phase III trials – patient recruitment. However, in the background, multiple work streams must also diligently progress in order for phase III trials to quickly and smoothly commence. One important, but often overlooked step in the multi-faceted planning for phase III clinical trials, is creating the text for the label that goes onto the bottle or blister pack of any clinical trial material that is being tested. This is complicated by the ever-increasing use of clinical trial sites that span the globe, necessitating the labels to be created in many languages.

Label creation can be trickier than expected; there are often overlooked challenges in this endeavor that can cause delays at the end if the process is not managed well. In the worst-case scenario, a mistake in a label can cause a new drug application (NDA) to be rejected. The phase III clinical trial results could be successful, but if the label on the package of the investigational drug that the patients were taking was inaccurate, it can call the results into question.

Formally known as labels for investigational medicinal products (IMPs) but also referred to as 'clinical labels', IMP labels have been required by the FDA since the 1960s. Labels ensure that all patients receive the same set of instructions; harmonized labels reduce the potential for variability. The FDA also has some specific requirements as to what needs to be included on the label, such as the warning "*Caution: New Drug - Limited by Federal (or United States) law to investigational use.*"

The label on an IMP is similar in only some respects to the label one would find on a drug once it is marketed. As an example, the label details how much of the IMP the patient should take and how often. However, there can be several versions depending on how many different dosing 'arms' or possibilities there are in the clinical trial. The process of making the label for an IMP is, from the outset, more complicated and by extension more complex than it is for a marketed drug that simply requires a single label.

Creating a label for an IMP is not a simple matter of just having an approved PDF file or word document being printed onto the appropriate stickers/pamphlets. Each IMP needs its own unique number so that its distribution can be tracked and correlated with which patient took which IMP. The tracking and number of different labels required becomes more complex for phase III trials which are usually placebo-controlled, blinded and have different treatment arms, so there is a larger set of different types of labels needed.

To add to the complexity of label production, more clinical trials than before are being conducted in other countries, requiring the label to be translated into multiple languages and to satisfy the regulations of the country in which the trial is being run. A recent article in the New England Journal of Medicine reported that the number of FDA-regulated clinical trials being conducted by investigators outside the US has grown annually by 15% since 2002. This is another indication of the rapid growth within emerging regions. As of November 2007, more than 50% of study sites are outside of the U.S. for phase III clinical trials sponsored by the largest US pharmaceutical companies. Some industry projections have this number as high as 65% by 2010.

Timelines for making labels for phase III IMPs

Text for clinical labels is usually written by the clinical team after the clinical trial protocol is approved and while the team is also recruiting patients for the trial. Around the time the label text is created, the countries in which the study will take place are being finalized. Once the countries are selected and the clinical team has finalized the label text, they need to have the text translated into the correct language and make sure it conforms to regulatory standards of the relevant country.

The final label is needed at the start of phase III clinical trials, when the clinical trial material is being packaged. If the label isn't ready but the investigational medicine is ready to be shipped to the clinical trial sites, there is valuable time lost. It typically takes at least 3 weeks, but many times it takes months to have the final labels (including translated ones). Ideally the process should take a few weeks or less, so that the investigator sites can have the IMP as soon as the trial is ready to start.

Any number of delays can hold up the creation of clinical labels including:

- Varied preferences on translated phrases
- Revisions to proofs by several people
- Changes to clinical trial protocol
- Workload of the 'approvers' or project manager
- Errors in translation
- No accountability for missing timelines

Another conundrum within the label process itself is that while you need a correct label when you start phase III trials, you're not told if it is 'correct' until the trials are finished. In other words, approval for the label is submitted as part of the NDA (new drug application). So it is imperative that clinical management teams ensure correct translations and verify that all the regulatory language is included.

Who writes the label

Usually the clinical trial team does not have the expertise for the regulatory requirements of each country, nor the ability to translate into all the needed languages. Typically they send out the English text to companies or country affiliates who can translate into each language and provide regulatory guidance. The most challenging projects, such as some multi-national clinical trials, have the clinical project manager sending the label text to and receiving edited versions back from as many as 40 different country affiliates.

Upon receipt of all the final label text, approved by consultants in the relevant languages, multiple PDFs of the approved text are sent to the labeling/packaging company for them to make the labels, package and ship the drug. Today however, unlike the marketed drug sector, there are only a handful companies in the world that specialize in labels for clinical trials.

What can go wrong

For a phase III trial that is occurring in many different countries, requiring text in multiple languages, it is easy to see how the clinical project manager working with a large number of files could get mixed up. The most common mistakes we see are usually the most mundane – the project manager losing track of which is the latest version or even which version was approved. The current process today is most often managed manually, through individual emails and homegrown excel spread sheets to track the translations and version approvals for as many as forty countries or more.

Also slowing the current practice is the fact that there is a high level of individual company-specific preference regarding translated phrases; as a result, sponsor companies often create their own database of common phrases in different languages. Like their tracking spreadsheets, these text libraries are often maintained on an Excel spreadsheet and manually pulled to populate multiple trial labels. Figure 1 outlines the typical workflow and inefficiencies for creating clinical labels.

Improving the process

Clintrak is pioneering ways to reduce errors in label creation and speed up the process. With institutional history and internal expertise, efficiencies have been gained to developthe process of managing the 'label writing'.

The result is that we have created a clinical translation management system that enables the clinical project manager to electronically track the approvals from the multiple translation contacts/consultants to whom they have sent their label text. The system involves an easily accessible web browser that is secure and contains the following features:

1. A **dashboard** that on one screen allows the project manager to quickly view all jobs and tasks and view due dates immediately.
2. Ability to track **job information** which shows current job status of each label/text sent out, tracks due dates, contacts in the study and label text documents.
3. **Email notifications** enable one standard e-mail to all affiliates, automatic e-mail reminders and the ability to configure emails on a job-by job basis.
4. A **Task Information** section enables one to keep track of all approvals on a task basis. One can view different versions of all document, store approved documents for easy access. Having the documents in one central place cuts down on the possibilities of errors since there are fewer versions of PDF files floating around.
5. A proprietary, certified phrase library
6. Regulatory text approval services
7. The system can also customize a clinical trial company's database of common label translations so that is has a quick and easy phrase library function.

The service offering has cut down the time it takes for label text to be translated and approved by the various consultants from months down to days. For example, in a recent partnership with a large pharmaceutical company the label translation process was turned over to this clinical labeling management system. For the pilot project, the pharma company selected a large Phase III study involving 18 countries. As a result of the standardized processes, automatic reminders and streamlined quality checks ingrained in the service, the label creation process was reduced by more than 50% - from an original 52 days to 24 days total. This process included the translation of the text, regulatory approval and proof creation and approval. Manufacturing and printing of variable data took only 7 more days. The entire process, from the day the client provided the basic English text to the day the final printed booklets were completed in 31 days. The previous process from start to finish averaged 72 days.

The process improvements are highlighted in **Figure 2.**

Side Bars and Figures

Side Bar 1: SUMMARY OF INFORMATION REQUIRED ON CLINICAL LABELS[1]

1. name, address and telephone number of the sponsor, contract research organisation orinvestigator
2. pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency
3. the batch and/or code number to identify the contents and packaging operation
4. a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere
5. the trial subject identification number/treatment number and where relevant, the visit number
6. directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product
7. "for clinical trial use only" or similar wording;
8. the storage conditions
9. period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity
10. "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

[1.] Guidelines followed by the European Union to which most US clinical labels also conform. FDA clinical label requirements can be found in the instructions for a new drug application (NDA): 21 CFR, part 210 and 211 but are not as explicit.

Figure 1: TYPICAL WORKFLOW For Managing Translations

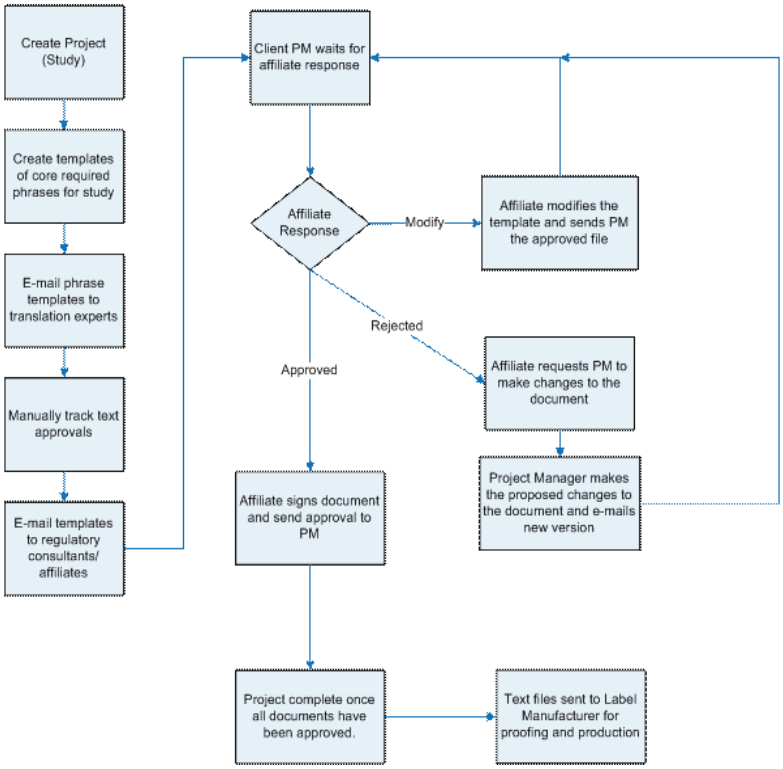
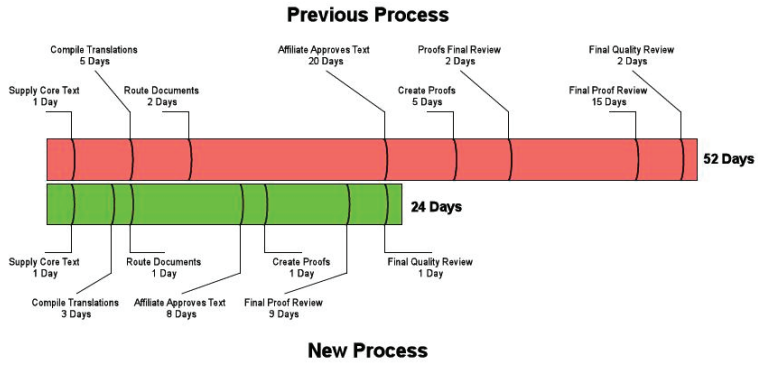


Figure 2: LABEL TRANSLATION AND PROOFING TIMELINE



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About the Author

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