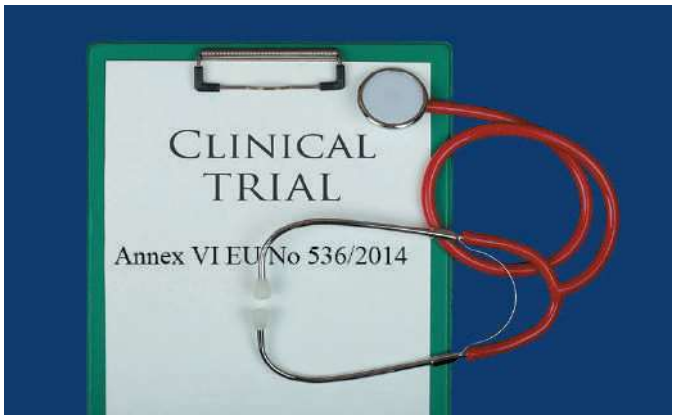
Adjust in Time: Beware of the Challenges Annex VI Brings for Labelling

The pharmaceutical industry is on the brink of new regulations that will bring added complexity to the labelling of clinical trial supplies. Five years after Clinical Trial Regulation (EU) 536/2014 first came into force, development of the clinical trials portal and database that will trigger its official application is about to begin. Six months after it's completed, the regulation will take full effect and the rules governing clinical trials will transform quickly although you will have a one-year transition period after that where you can continue to register a trial under the existing EU Clinical Trial Directive. The EMAs management board say that the regulation will come into effect in 2020. Their impact on labelling is profound.



Annex VI of the new regulation mandates the inclusion of 'period of use' dates on both immediate and outer packaging, removing the option for companies to reference the information centrally via IRT or RTSM systems. Under the previous directive, the inner packaging needed an expiry date and if changed, did not need to be updated on the inner pack and could be updated on an IRT system. Whereas, Annex VI requirements state that if subject to change, the expiry date must be physically replaced on both the inner and outer packaging, which cannot be done by an IRT system.

Although adding dates to labels is itself quite straightforward, *changing* those dates as IMP stability becomes clearer is much more problematic. For example, with biologics where stability is often difficult to determine up front, expiry date changes during clinical trials are becoming increasingly frequent. However, with repackaging needing to be carried out in a GMP-controlled environment and overseen by a qualified person (QP), the requirement to update period of use dates on primary and secondary packaging presents major challenges for products that have already been shipped in bulk. If the packaging is then sent to a site with no DMP environment, then repackaging can be difficult or even impossible.

Many trial or distribution sites don't have the facilities or infrastructure to relabel products in-country, increasing the risk of costly delays as supplies are reshipped to GMP-controlled environments for repackaging. In some instances, companies may be forced to scrap and remake expensive compounds. Conversely, failure to comply puts them in breach of clinical trial regulations and could invalidate a study.

The potential implications are severe. Therefore, as the industry counts down to the official application of the new regulation, companies need to rethink their clinical trial supply processes and adopt agile technologies that unlock more efficient and responsive ways of working. Leading organisations are exploring a range of measures to ensure operations are fit for purpose.

1. Smart Packaging
One option is to use 'smart' packaging, which allows labels to be updated without opening an outer pack. This reduces the risk of breaking tamper-proof packs and can be an elegant solution. However, there are costs associated with the adoption and validation of new packaging while the options available are dependent on the IMP being trialled. Smart packaging is not always suitable.

2. Weather the Storm
The uncertainty surrounding when the new regulations will become applicable has led some companies to take a pragmatic view, keeping a weather eye on emergent best practice rather than committing to a solution in advance. This approach is not without risk; once the portal and database finally go live, companies have six months (plus the option of an additional one-year transition period) to implement a workable solution. That's still cutting it fine.

3. Leverage Partner Network
A third option is to leverage existing CRO and CSO partnerships. Many industry partners have good in-country GMP facilities and are well-placed to help pharma meet the new labelling requirements. However, success is not just about a partner's capabilities, it depends on the availability of their QPs to release products. Moreover, leveraging partner networks still requires pharma companies to change their labelling strategies and inevitably adds time and cost to clinical trial supplies.

4. Small Batch Production
Some organisations are exploring new production models. One example is to produce smaller but more frequent batches of primary packaging. This approach requires no changes to existing processes and, since production volumes are smaller, minimises the likelihood that packs will carry incorrect expiry dates. The model, often incorrectly referred to as Just in Time, is well suited to early-phase trials involving lower volumes of patients and studies. However, at scale the approach can be inefficient. As volume increases, the number of batches required increases too, intensifying the QP effort to release products, particularly in later phases.

5. Just in Time Labelling
Perhaps the best response is to take a Just in Time (JIT) approach. JIT is a procedure for printing, packing and shipping packs as and when supply plans state they're required. A similar, nuanced option is 'on demand labelling', where printing is done in response to confirmed patient attendance at study sites. JIT is different in that printing, packing and shipping is done in line with a pre-existing plan so that levels of stock can be kept to a bare minimum, an approach which can

improve inventory turnover. In both models, labels are printed using the latest data – dosage and period of use dates – close to the time products are actually required. This also reduces the need to update inner or outer packaging, providing further flexibility to respond to future trial design changes or regulatory fluctuation. JIT and On Demand offer real potential for cost savings and efficiency gains.

JIT requires a labelling solution that can pull in data in real time and configure it into an approved format to be printed, validated and applied at speed. The best label management solutions leverage integration and automation, ensuring clinical supply teams aren't required to calculate expiry dates or re-enter data that's already in the system. Automation and integration are crucial for JIT; since expiry dates will change with greater frequency, teams cannot afford to rely on manual processes to change and validate data.

Making the move to JIT may naturally increase a company's QP requirements. With QPs potentially required to manage and sign off multiple runs – rather than large single batches – organisations will need to redesign and automate their QP processes accordingly. Once again, good labelling software can make a huge difference but it is not all you need. The smartest solutions include 'vision inspection', which automates the inspection of labels and provides reports (and audit trails) to help QPs validate the process.

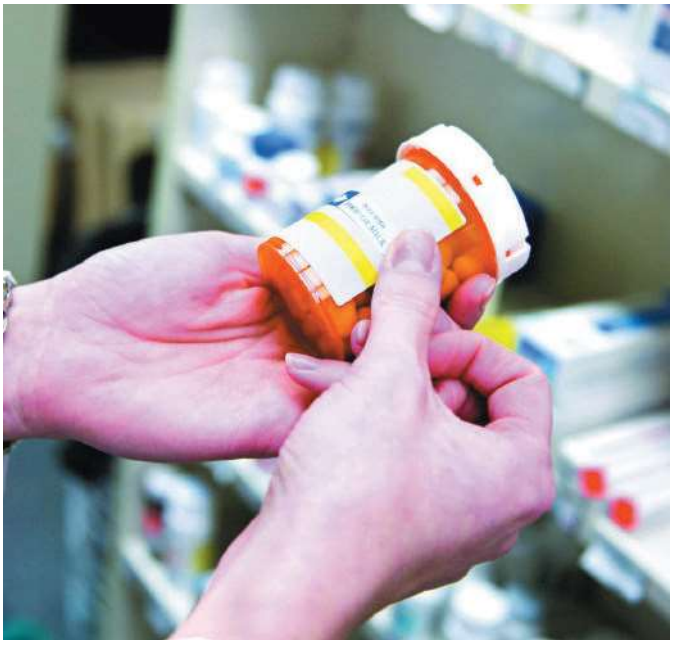
Next Steps

Change is coming. As pharma awaits the dawn of new regulations, organisations must evaluate their existing processes to identify the best solution. The considerations will vary according to individual company needs; how often do you anticipate the period of use changing throughout your trial? Using your current processes, how much will it cost to make those changes and what's the associated wastage? What impact will the new regulations have on your QP requirements? Does your planned solution support that QP effort and do enough to mitigate risk?

In most cases, JIT is likely to be a good option – but it's not without its challenges. To overcome them, organisations need a labelling solution that uses automation and integration to remove manual effort and reduce risk. Crucially, they need to apply the same level of automation around QP processes.

Although the precise timing of the application of Regulation 536/2014 remains uncertain, a new era for clinical trials supply compliance in the EU is almost here. The smartest organisations are those that have recognised it takes time to roll out a new system and are partnering early with labelling solution experts to prepare for the change.

It is important to be prepared during times of uncertainty. The strategy of waiting to analyse what competitors or partners do is risky as it takes time to integrate a new system. To adjust in time, it might just pay to think Just in Time.



Gordon Alexander

Gordon Alexander, Enterprise Pre-sales Engineering, PRISYM ID is involved in understanding customer needs and industry challenges to drive solutions to improve efficiency, minimise risk, address regulatory requirements and provide new approaches to business systems and processes. Gordon has 20 years of technical software experience with roles as industry consultant, business analyst, and pre-sales engineering.

Simon Jones

Simon Jones, VP Global Products, PRISYM ID has 20 years of experience in delivering product strategies and product positioning which address market opportunities effectively. He is a subject expert in clinical trials labelling, researching this market, discussing the industry challenges with the PRISYM ID customers and remaining up to date on market trends, regulatory changes and technology alternatives.