

Putting a Label on Clinical Trial Success

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Summary:

Using automated label verification technology in clinical trial supplies is a consequence of the drive to shorten lead times and get drugs to market more quickly against an increasingly challenging regulatory background, contends Derek McKay at Clinical Trial Services

Licensing authorities are demanding additional data to demonstrate drug safety and efficacy prior to issuing the marketing authorisation (MA). As a result, clinical trials are becoming ever more complex in terms of design, patient populations, geographical coverage and labelling requirements. Some blockbuster drugs able to achieve annual sales in excess of \$1 billion therefore any delays in getting drugs to market can mean lost revenue of millions of dollars on a daily basis.

Compared with marketed products, packing and labelling of investigational medicinal products are more complex and liable to errors. This complexity stems from the need to provide blinded supplies with unique kit or patient identifiers on each pack (see fig 1). In addition these supplies may be packed over several smaller runs compared with larger commercial scale batches. One potential bottleneck in the manufacture of clinical supplies is the printing and checking of labels. Large phase III trials often require millions of unique labels to be printed over 30 – 40 languages, this presents a stern challenge to those responsible for the manufacture, packing and labelling of the clinical supplies. Fortunately technology now exists which enables some of the most labour intensive aspects (i.e. label checking) to be automated. This article assesses the challenges and potential benefits of implementing such a system.

Regulatory requirements

While various machine-readable formats such as barcodes and RFID can be used to identify the pack number or kit type throughout the supply chain, the key focus from a regulatory perspective is that of the

Figure 1: In Clinical Trials, Every Patient is Unique, so are the Labels



end user i.e. the patient. In the case of an investigational medicinal product, labelling must ensure protection of the subject and traceability, to enable identification of the product and the trial and facilitate proper use of the investigational product¹. It is therefore imperative that the human readable format of any pack is

accurate and fully legible.

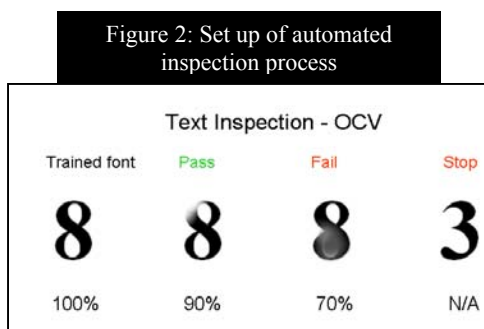
Barcodes may be used to electronically verify that the correct pack number was

scanned, packed and shipped by the distribution depot. The electronic verification of the pack removes the possibility of the operator misreading the pack number to be shipped to the investigator site. In addition, RFID can provide additional electronic back up that the correct material has been issued at various stages of the packaging and distribution process. While the above technologies may reduce errors and increase efficiencies in delivering the correct pack to the correct site, it is the investigator and patient who must be able to read the label to ensure they are using the correct medication. Unfortunately sites are unlikely to have electronic verification technology available to them, the printed text on the labels therefore should be clearly visible to the patient. By ensuring the correct text is on the label, the sponsor is facilitating the protection of the patient, traceability of the pack and adherence to the regulatory guidance.

- Comparison against fixed
- Variable text including batch number, expiry date
- Colour and shade of text and labels
- Correct formation and shape of letters or numbers (variances may arise due to printer settings)
- Relative positioning of text and objects
- Letter spacing, line spacing and margins (can be caused by crooked paper feeds into the printer).

For blinded, randomised studies, comparative checks also need to be performed against label sets from other treatment groups (assuming they are printed in separate runs). The checking of one label set against another is performed to ensure there are no differences such as boldness of text or label shade which may be caused by the issue of a new batch of labels to the printing operation. Individual patient numbers or Med Id numbers, week numbers and visit numbers also have to be checked field by field. Once the above checks have been performed another person, typically a QC function, must repeat all the checks again!

Often the personnel performing the manual inspection of the labels will only be familiar with 1 or 2 languages, the range of languages used in a large trial may exceed 30. The checking personnel are therefore faced with a situation where they have to check letters, accents and symbols that have no intrinsic meaning to them. The check is a literal comparison of the printed 'shape' against the master label text. Chinese, Japanese and Hebrew fonts for example present some of the toughest challenges to label checkers who are not native speakers. Personnel who are checking label text for languages with which they are familiar face a slightly different set of problems. Even when looking at text character-by-character, letter-by-letter, humans will inadvertently try to assign meaning to the text – it is part of the natural reading process. Any inadvertent interpretation of the text to 'make sense' can result in the human brain



Traditional approach to label printing and checking

Printed labels are normally subjected to at least a 200% manual inspection within a production process. This approach is very slow, labour intensive, potentially prone to error, difficult to validate and ultimately subjective depending on the personnel performing the work. In addition, due to the human element involved, regular breaks need to be factored in to any anticipated checking rates. The label checks will be performed against an approved master, checks will typically include:

seeing what it wants to see as opposed to what is actually printed on the label. For a machine, there is no conflict of interest, it will not add or remove letters intuitively in order to make a sense of a sentence or statement.

Challenges

When designing and implementing an automated checking system the total scope of the challenge faced by the human checker must be addressed in a machine friendly format. Due to the nature of clinical supplies labels will vary greatly in their overall dimensions, while individual vial labels may only cover a few square mm, patient pack labels may cover 1,000's of square mm in area. Some aspects of the checking process present no great difficulty to the human checker e.g. size of label. Whereas the 'field of vision' is theoretically unlimited for a human, there has to be a finite value associated with an automated checking system. Fortunately with some lateral thinking and advanced software solutions, the maximum label dimension need not be restricted to the capacity of a single camera or detection unit. However, an automated system should be designed with other issues in mind:

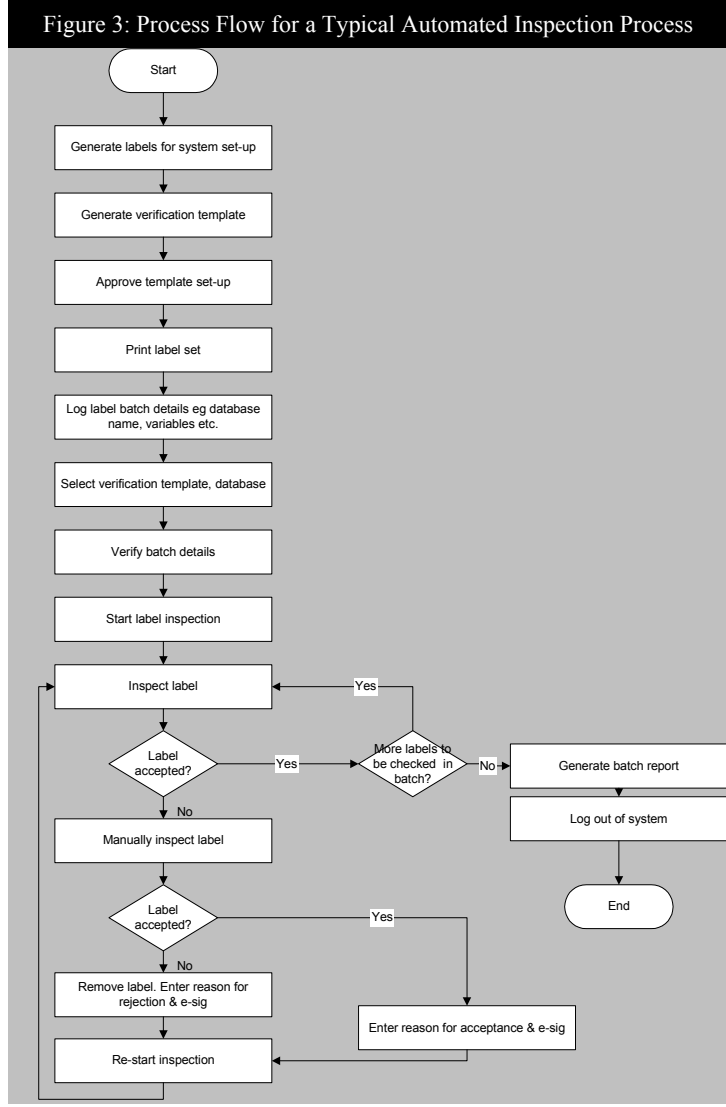
As a product-critical process, an automated label verification system must be subject to validation in accordance with standard policies and procedures to provide operational confidence and to demonstrate compliance with regulatory requirements (e.g. EMEA and FDA – 21 CFR Part 11). It is also worth clarifying the difference between Optical Character Recognition (OCR) and Optical Character Verification (OCV), as both are employed in the automated inspection process. OCR refers to

systems scan a character or string of characters and try to interpret the character(s) by comparing against a pre-trained library of characters. On the other hand OCV systems scan a character or string of characters and compares these to a predefined character or string of characters. This can be a more robust system than OCR as each scanned character is compared to a single character as opposed to all pre-trained characters – see fig. 2.

Many of the rules associated with the manufacture and packaging of clinical supplies hold true when specifying the requirements of an automated checking system. Key considerations including flexibility, traceability, ease of set up and batch turnaround times must be factored in to the system design. In the author's experience, comparative evaluations of human versus machine checking rates show that automation can improve on human rates by 10 times or more on like for like labels. However, checking efficiencies over multiple batches can be diminished if the time taken to 'train' the machine per label type is extensive. In addition the time required to reset the machine for a different set of labels, but the same label type (e.g. different treatment group) must also be minimised. The flexibility in the system therefore must ensure that it can be set up as quickly to check a label with 3 specified fields of text as one with 10 fields. Each set of labels that are checked must also have an associated identifier preferably with version number for the checking run, an operator ID including user name and password in order to provide an easy GMP trace as to who did what, when and where. The overall process flow for a typical automated inspection process can be seen in fig. 3.

While the system needs to be able to handle a range of fonts, texts and characters associated with many different languages, provision also needs to be made for confirmation of graphics, barcodes and any electronic markers e.g. RFID where applicable. In addition it should also be possible for the system to measure and confirm the overall label quality i.e. check for marks on

labels. In order to assess and verify the criteria above a number of software solutions need to be employed to analyse and interpret the digital image obtained by the system's viewing mechanism. The speed at which the software processes the images also needs to dovetail with the transport system that displays the labels in front of the viewer. If the software cannot process one label before the next arrives, the checking process will grind to a halt. Alternatively, if the conveyor is moving slower than the system can check then the process is not maximising its output potential. The wide variation in the size of clinical trial labels means that a variable conveyor speed will be required. A conveyor running at constant



velocity but with variable label dimensions (in the line of transfer) will result in variable hourly throughput, the conveyor speed therefore must be capable of adjustment in order to temper the throughput rate.

Overprinted booklet labels and the associated materials used in their construction present another challenge to the automated checking process. In comparison to booklet labels, single panel labels are relatively easily analysed by the system's viewing unit. Protective

plastic covers, tear off sections, perforations and a range thermal transfer print resolutions add to the complexity of the checking process for booklet labels. The automated system therefore should be able to handle all of the above variables so that it can be used with the full range of clinical trial labels that it is likely to encounter.

Conclusion

The use of automated label verification technology for clinical trial supplies has significant benefits. By specifying, designing and implementing the right system contract packagers and sponsors can realise substantial savings in time and

money for clinical trial supplies. Automation of the label printing and checking process during the manufacture of supplies can take this step off the critical path. Meeting the ever more ambitious study start dates can also be achieved more easily using this approach. Ultimately, large, late phase trials can be started with reduced lead times and the blockbuster drugs of tomorrow are brought a little closer to today.

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References:

1. Commission Directive 2003/94/EC, Article 15.