

Though much has been achieved in the security of labeling and packaging of operations both FDA and MCA still report a substantial number of product recalls resulting from errors in packaging process. Further progress to resolve this issue cost effectively is dependent on the ability to objectively reconcile label, pack and product on-line.

Improved Product Security Using on-line Near Infra Red Spectroscopy

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Currently product identity is implied and one of the main factors limiting effective quality control in the packaging process has been the inability to chemically qualify and quantify product at line speed.

Spectroscopy, particularly the NIR region is now playing an increasingly important role in quality control across the industry from raw materials acceptance testing to product release testing nondestructively. Using fiber optics NIR can also be used to interface directly with packing lines to carry out qualification and quantification measurements non-invasively at line speed.

Zeneca is using NIR to carry out such measurements to chemically quantify vials of emulsified product on-line with the long-term objective of on-line product, pack and label reconciliation. This article will describe such an application, and the underlying philosophy and business benefits that can accrue from applying NIR in this way.

Introduction

It is very interesting how some apparently inherently simple processing operations seem to be fraught with difficulty. Packaging is one such operation where a substantial number of incidents leading to recalls continue to occur in spite of the effort taken to resolve these issues.

As a leading company within an industry where the ethos is to get it right first and every time this continues to be an issue that we still spend considerable time and effort to address.

However experience shows that history has a habit of repeating itself. So, when this problem area was revisited recently it was decided that to arrive at an effective solution we had to be sure that the underlying causes of these problems were fully understood - i.e. to clearly differentiate between symptom and cause.

Clearly lot numbers differentiate batches of the same product and of course there are extensive procedures in place and documentation generated to ensure that the required GMP's have been adhered to. So everything must be in order!

This of course may be prior to attaching product labels to each container, as often filling, labeling and packaging cannot be carried out on an integrated line.

It is in these gaps that a very high potential for mix-ups exists where the logistics are such that unit operations have to be carried out at geographically separate locations. However in keeping with best industry practice labels are read and verified downstream on the packing line using automated electronic systems, which of course gives assurance that mix-ups cannot occur! But does it?

It certainly gives high levels of assurance that the labeling and packing operation has been carried out correctly but we can still have errors stemming from assumptions that the product in the primary container is the correct formulation and batch and that is invariably where such

problems begin.

So in spite of rigorous GMP control practices and advanced labeling and packaging code reading, product recalls stemming from logistic errors still occur across the industry.

Fortunately, with appropriate systems, technology, and a belt and braces approach few of these occurrences result in compromising patient safety. But they could!

The underlying problem is not new. The thought that actions are to be checked by others at a later stage in any process invariably translates to - (once the initial error is made) increased chances that it will not be picked up until it is too late. So unless we can be 100% sure that the product in the primary container/dosage form is indeed what it purports to be, The integrity loop through the labeling packaging operation cannot be closed irrespective of the control systems in place because of dependence on inferred information.



Illustration of the Filling Operation: The Measurement Systems are Located in the Laminar Flow Area on the Right.

So that became the problem solving issue. At the front end of the process how can one measure chemical composition of a product non-intrusively at line speed and link it with a secure identification system? More importantly if this could be achieved how might the measurements be used most cost effectively in quality control to resolve these potential problems once and for all?

The Problem

The product we were investigating was a white fatty emulsion, emulsified in 3 homogenizer rooms. Each of the rooms is equipped with the same equipment and the processes are operated in the same way to ensure consistency of the product. The product is terminally sterilized after filling and sealing and available in two formulations of different strengths. The difference between formulations is chemical in nature. A schematic of the initial filling and packing process is shown in Figure 1 overleaf. with an illustration of the filling line below which shows the space constraints that one is faced with in such projects.

The initial production line is in reality the vial filling line. It is operated at a speed of 85 vials per minute to fill either of 2 sizes of vials for each formulation and strength. Like every other liquid filling line, the vials are filled, stoppered and crimped prior to terminal sterilization. The crimp has

identifying marks distinguishing the concentration by color and the formulation by pull as shown diagrammatically in Figure 2 overleaf.

In addition to rigorous GMP control practices this system was seen as being capable of providing the necessary security to allow the labeling and packaging of the sterilized vials on the secondary packaging line separated physically from the sterile filling operation.

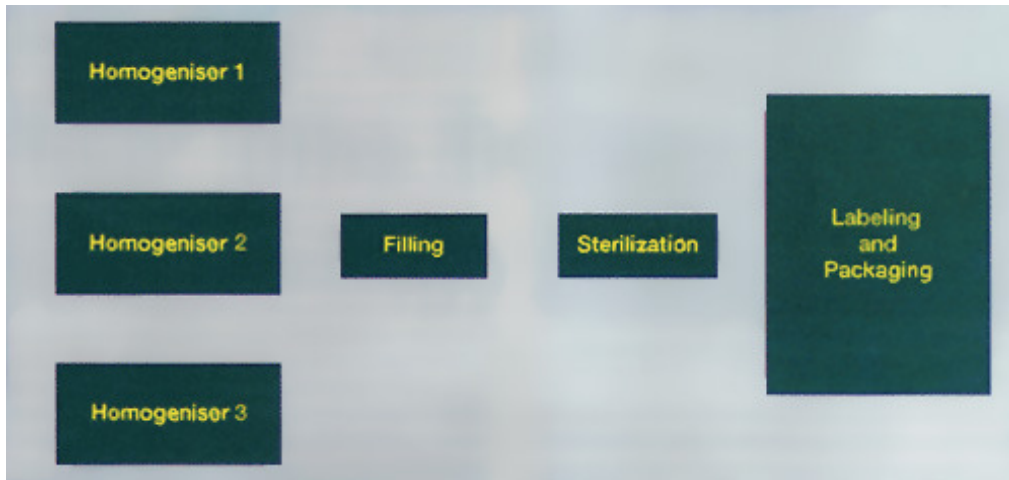


Figure 1: Schematic of Homogenizing Filling Sterilization and Packaging Operations.

In spite of the security offered by the identifying marks on the crimp and control of transfer to the secondary line, operators and inspectors over the years have identified potential mix-ups due to filling line operation error, as well as crimp manufacturing errors. Overall control is therefore still heavily dependent on rigorous standard operating procedures and operator vigilance.

As part of the continuous improvement strategy the benefits of providing an objective chemical assessment of the contents of every vial immediately before checking and confirming the correctness of the crimp was seen as a way of resolving these problems for once and for all.

The challenge was obvious.

To provide the holistic level of security required we had to develop a means of reconciling the vial content and crimped seal in the filling process with the label in the packaging operation. Label reading technology is well proven and will not be discussed here. The technologies not in place were vial identification reading and more importantly the ability to carry out chemical confirmatory testing capable of identifying the contents of every vial with high level of statistical confidence non-invasively and nondestructively.

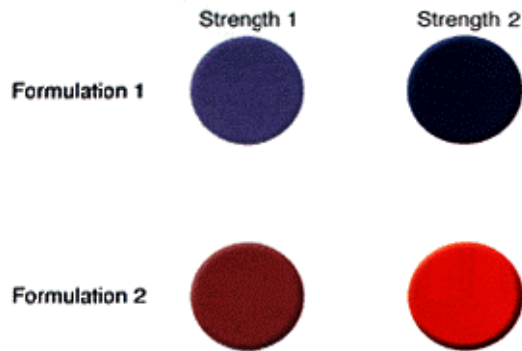


Figure 2: Formulations and Strengths

Crimp Identification

At the outset this seemed to be a simple task - two different colors of crimp seal for concentration, and 2 different pull-rings for formulation were selected which would uniquely identify each of the product strengths and formulations. However as in many companies we had lost sight of simplicity - the key to consistent quality. The decisions on crimp color and seal pulls were made on aesthetic grounds not those that were most amenable to reliable detection by current vision technology. Not surprisingly the task proved just too difficult for most established vision technologies. Novel methods of lighting had to be investigated and devised to enable the vision system to differentiate the colors. Though a burden for the measurement engineers, it was far simpler and preferable to the alternative - product re-registration.

After the vision system makes its decision on the vial crimp status, rejected vials are displaced from the line using a handling mechanism and the finding reported to the master PC as shown in figure 3.

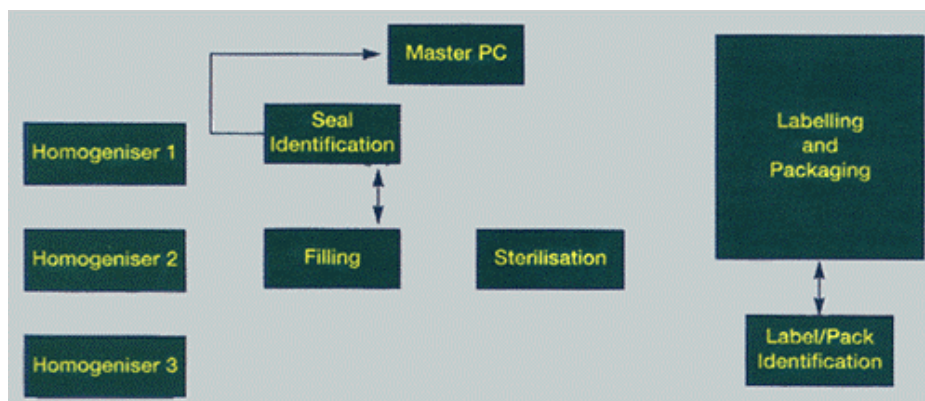


Figure 3: Schematic with Security Checks

On-line chemical analysis

This was by far the more difficult issue to resolve from a variety of perspectives the main issues being:

1. The methodology had to be non-invasive, as the seal could not be tampered with since that would defeat the whole process of secure filling.
2. The emulsion is an opaque fatty formulation, not the most tractable matrix to work with.
3. It was contained in molded glass vials of a few mm thick walls with the inherent thickness variability one finds in such containers.
4. The technique selected had to reliably discriminate between formulations and strengths at the line filling speed of 85 vials per minute.
5. The filling line was designed with minimum space and tie travel between filling and crimping.
6. The inspection, similarly, had to be carried out as close to the crimping station as possible.
7. Space on the line was limited as this was a retrofit
8. Management would not accept anything less than 100% inspection.

To achieve these objectives we clearly had to devise and implement a non-invasive, non-destructive, high speed, on-line analysis.

After an initial technology assessment NIR was considered to be the most promising on the basis that it is a "finger printing" technique which allows the normal variability of:

- glass vials wall thickness
- excipients
- homogenizers

to be accounted for in the calibration models.

The technique also supports fiber optic technology allowing remote location of the analyzer and non-invasive acquisition of a spectrum of the emulsion at line speed without any major change to the filling line.

Furthermore, after establishing NIR as a viable tool with the plant personnel, it could if necessary be used to monitor the homogenizers, even though it was not placed in the process.

The equipment was to be configured to allow spectra to be acquired from the contents of each vial as it passed down the filling line, analyzed using a calibration model capable of coping with the variability described above to determine the compliance of its contents with appropriate specification. The findings were then to be reported to the master control PC which would compare these results with those transferred from the vision system. If either result from the same vial is out of compliance then the vial is diverted into the reject track to provide fail safe operation.

NIR Instrumentation

Extensive feasibility studies were undertaken to determine whether NIR could easily and reliably discriminate between the formulations and strengths using spectra acquired through the vial walls. These studies were successful. The remaining challenges to be addressed were speed of operation, and equipment reliability in a relatively hostile production environment, particularly with respect to vibration.

After detailed consideration of the environment and possible installation with no moving parts would be the preferred technology if it met the spectral performance criteria for the application.

The next task was to identify a well engineered, solid state process instrument capable of achieving the following performance characteristics: - inherent noise had to be low, and the S:N ratio high per scan to keep the number of scans to a minimum.

The above requirements directed our attention toward Acousto Optical Tunable Filter (AOTF) technology.

An AOTF spectrophotometer is a solid-state electro-Optical device with no moving parts. It consists of a TeO₂ crystal, which is capable of monochromating an incident broadband light source into its constituent wavelengths using radio frequencies (RF), which modify the crystal's transmission characteristics. The wavelength of light transmitted by the crystal is a function of the frequency applied to the crystal, therefore by varying frequency the wavelength of the transmitted beam can be specified and varied independent of device geometry. AOTF instruments are distinguishable from the NIR instruments by their basic design and performance is dependent on crystal performance.

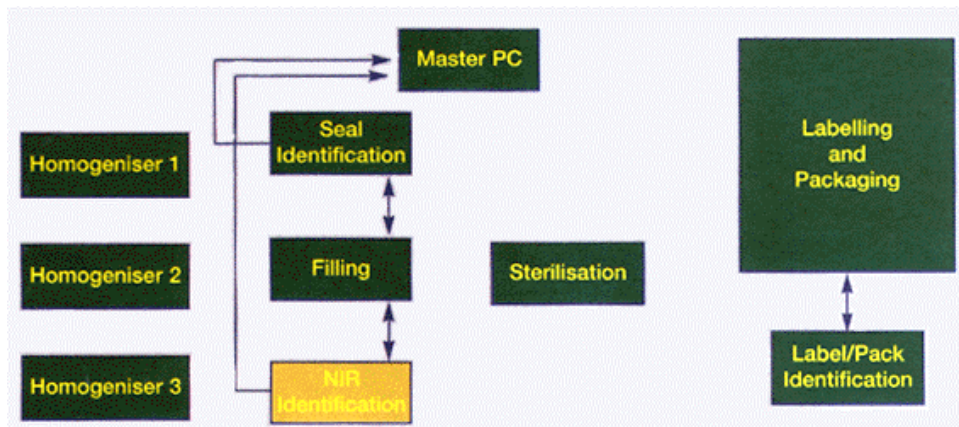


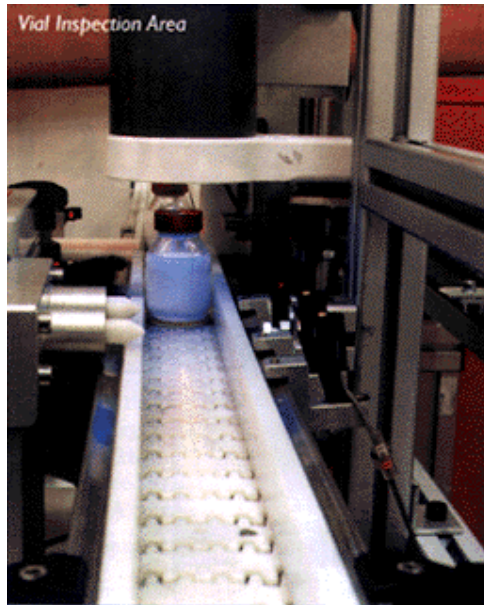
Figure 4: Schematic with Security Checks

The AOTF spectrophotometer chosen for the application was a Free Space Luminar 3030 available from Brimrose Corporation of America as it fulfilled all the spectroscopic applications requirements:

- spectral performance required to discriminate between different formulations and strengths
- non-invasive acquisition of spectra
- a scan rate capable of acquiring multiple scans per sample as it traveled in front of the Free Space window
- robust engineering

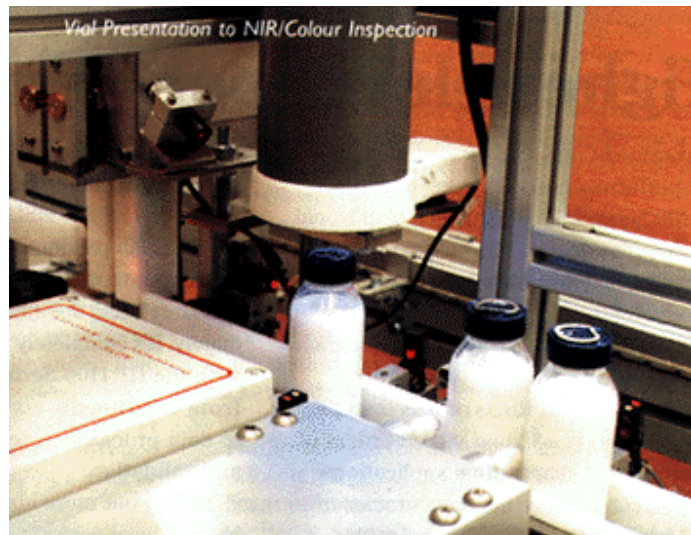
To convert the project into a reality as outlined in Figure 4 Mecelec Developments Ltd. was commissioned to design, manufacture and install the complete inspection system consisting of vision system, NIR, handling mechanisms and the software necessary to operate the system as an on-line tool integrated with our filling line.

The complete system comprising of NIR analyzer, crimp checking system and vial handling systems as an installed on-line system is shown in the photographs on this page.



Calibration Procedure

The main problem that the project team now faced analytically was calibrating and validating the NIR system. The models had to be built up over a period of time, to take account of the normal variability of the process, active materials, excipients and vials, which was not a trivial exercise. The algorithm employed for discrimination was the binary PLS model identified in the feasibility study.



Summary

At the outset we were reasonably confident that on-line identification of these formulations non-intrusively was feasible though by no means with certainty.

This project has clearly demonstrated that on-line chemical verification of matrices, which are difficult to handle conventionally, can become quite tractable using NIR spectroscopy remotely.

In addition we are already seeing that the progress made with this project is changing the way that we think of the value of measurement. It is not just the measurement that you make that are important but how you can use them.

In this application NIR provides an objective 100% assessment of compliance that cannot be achieved by conventional testing methodology, but the greatest cost benefit it provides in stand-alone operation is the means of managing risk, allowing a process to be closed down at the first sign of non-compliance. However returning to compliance, linking NIR identification with crimp seal identification gives an immediate increase in process compliance confidence that is probably significantly greater than an additive relationship. The challenge to be faced now is how the value of this philosophy can be further maximized across a process.

Could integration with objective measurements gathered from other unit operation in the manufacturing process provide a cost effective alternative to conventional quality control replacing documentary evidence of process compliance by objective assessment?

On-line measurement has been one of if not the major hurdle to overcome to make progress toward parametric release. Perhaps today this is not as big a hurdle as one might think?