Validation of Pharmaceutical Packaging Lines

Afshin Hosseiny, Ph.D.
Tabriz Consulting Limited

A validated process is one which enables consistent manufacturing and packaging of products in accordance with the product and market requirements in a cost effective and secure manner. Since consistency and cost effectiveness are, without doubt, key business considerations, a validation activity should be seen not as a regulatory requirement but as a business necessity. To achieve the ultimate goal of packaging product perfectly every time, equipment engineers, packaging technologists and quality teams must plan and work through a validation program together in order to create a robust operation. As with any other multi-disciplinary project they will need to plan their work (objectives, timescales, deliverables, roles & responsibilities and key milestones) and report their findings. As you read through the notes that follow, you should view the primary objective not as regulatory compliance but as the establishment of an efficient process with minimum down time, rejects and errors.

Packaging has been defined as
"the art, science and technology of preparing goods for sale in a cost effective manner."

In considering what is meant by "preparing goods for sale" in the context of pharmaceuticals we should remember that the packaging must:

- preserve the product - from degradation or contamination
- contain the product - to avoid leakage
- identify the product - providing traceability and information regarding expiry date, etc.

and will also be required to provide:

- security - against tampering and counterfeiting
- information on use - an "aide memoir" for compliance.
- convenience in use - for medical staff or patient;
- a marketing tool - supporting features and/or graphics appropriate to the sales medium (OTC vs. ethical).

All this must be ensured for the life of the product and achieved within a complex regulatory environment. The latter extends beyond the pharmaceutical company packaging lines to the warehousing and distribution of packaged goods and to the manufacture of packaging components and the supply of raw materials.

There are several key areas that impact the robustness of a packaging process and should be considered in validation including:

- Packaging materials
- Packaging equipment
- Line layout
- Operator training
- Standard operating procedures.

Packaging Materials

In 2000/2001, 42% of the defects reported by MHRA in the UK related to printed packaging components; either because they were incorrectly printed or because the wrong components were used within the pack. In order to minimize the risk of defective product reaching the patient, it is therefore vital that there is strict procedural control of artwork development, review and approval and of the handling of printed components from printer to packaging line.

A good relationship with suppliers is essential, together with rigorous packaging material specifications. Pack design needs to be carried out by personnel who know how the materials are manufactured and understand what is required for production lines to operate effectively and efficiently. It must be recognized that with most packaging materials, pharmaceuticals represent a very small market segment (for example only 4% of the LDPE (low density polyethylene) produced is destined for pharmaceutical use). With their long production runs (polymers for example are manufactured in 20 ton batches or as continuous production), packaging materials suppliers may be under significant commercial pressure from larger customers with regard to specification. In a good relationship, the supplier will have been made aware of the implications of such changes for the packaging line and technical personnel from both companies should be able to work together to address the problem.

An efficient production line needs consistent materials and the storage and handling of components is as vital in this respect as their specification. Fiber-based materials such as leaflets (inserts), cartons and labels for example, can be adversely affected by changes in temperature and relative humidity.

Packaging Equipment

The design and layout of equipment has major impact on the efficiency of the packaging line. Well designed equipment will lend itself to efficient production of a consistent standard, whereas older equipment can often be inflexible and may have elements of poor design such as areas where packaging components or product may be trapped. These "traps" can result in products being incorrectly packed, e.g. a carton containing the wrong leaflet or product from a different batch. This represents a significant risk to the patient and is one of the major reasons for product recall in the industry. The greater the number of stages there are in a packaging line, the lower its efficiency will be. With modern order patterns of short runs it may for example be better to have two slow speed fillers feeding a single cartonner rather than a single high-speed filler. Appropriate validation of the packaging lines will challenge the robustness of the packaging operation establishing the conditions under which efficiency is maximized.

Line Layout

Design considerations for a line layout should include the ability to manage quick change-over, perform line clearance between batches of product and clean the line in an easy and controlled manner. The majority of problems on packaging lines are related in some way to poor line clearance; it is therefore important to design these problems out.

A typical packing line will consist of several feeders for packaging components and product. Devices will normally be located in critical positions on the line to detect presence or otherwise of the materials. For example, a device installed on the carton feeder will ensure that a carton is supplied for each product or tray of product and a barcode reader will verify that it is the correct one. A checkweigher will make certain that underfilled or overfilled bottles are identified and ensures via the reject device that they are excluded from the batch. The layout of the equipment should guarantee that easy access is provided for operators and the engineers to access this equipment when adjustments and or maintenance are required.

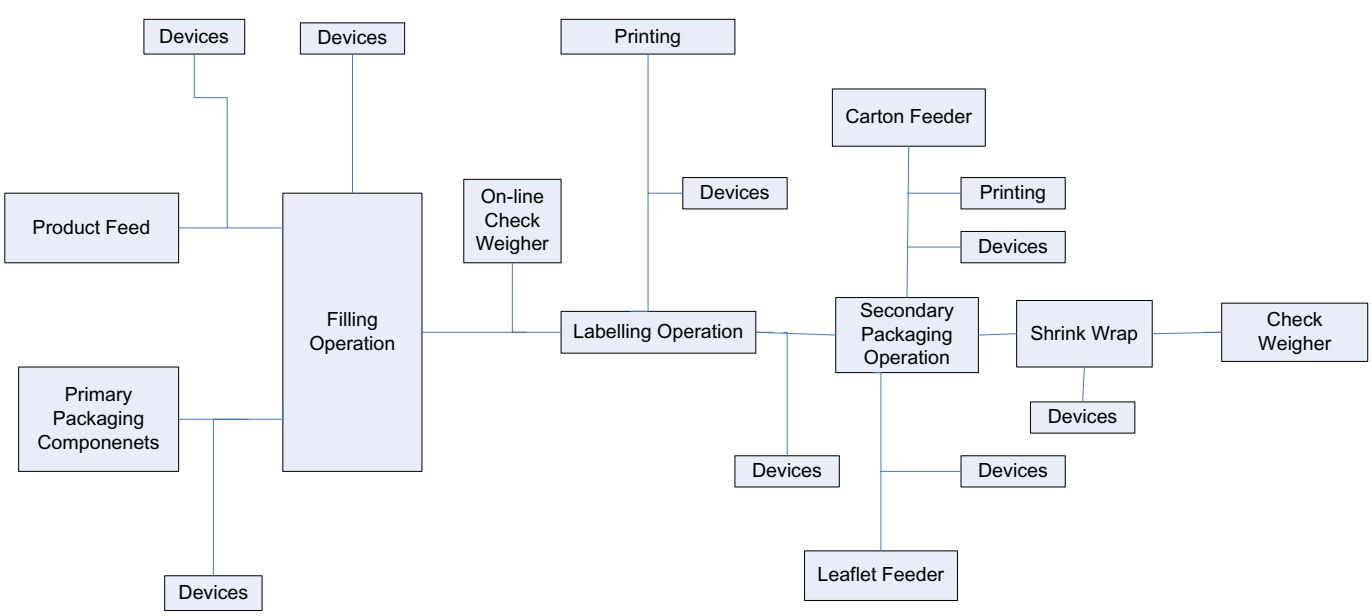
Operating Procedures and Training

To manage a packaging line, adequate standard operating procedures (SOPs) will be required. It is vital that there are clear and unambiguous instructions on how to operate, adjust, and maintain each piece of equipment. In addition, there will be procedures to detail how a batch is packaged, SOP usually explains how each material is received on the line and checked for correctness, quantity, etc. by the operators. Details of In Process Control (IPC) tests will be given in these SOPs. Involving the line operators in developing the SOPs will result in documents that more accurately reflect what is actually happening on a day to day basis. Operators will also take ownership of the SOPs ensuring better compliance and hence less problems on the line.

Planning a Validation Exercise

Any validation exercise must start with a detailed Validation Master Plan (VMP). A VMP will normally include the company validation policy, explaining how the company will manage the validation exercise and details of the organizational structure relevant to the validation activities. The VMP should also include a summary of the facilities, systems, equipment and processes which are to be validated and indicate the format which is to be used for documentation. All critical equipment and systems must be identified and listed

Figure 1. A typical packaging line layout



in the VMP, including a list of critical devices and/or details of the operating system and the software used. A high level plan of activities should be developed and broken down into stages within a schedule. Any validation activity is only as good as the change control process used; the VMP should include details of how any changes will be managed. Finally, a list of references to any other relevant documentation should be included.

Documentation

Any validation activity will generate a mountain of documentation. These will include validation protocols, test results, calibration records, change control documents and the validation report.

Validation protocols should be designed to test all the critical steps in the process. They provide a list of tests which are to be performed and the acceptance limits for each test. The tests must demonstrate that the system is able to do what is expected within the operating range required for the process. It is also important however, to test the system beyond the normal operating range to provide information on the system behavior, which can be used to finalize operational limits.

A classical approach to validation is to prepare test protocols for Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). Information gathered from each of these stages must be fed into the next to ensure that the system is adequately tested. Protocols should test each piece of equipment or step in the process, however, it is important to have one overall protocol to test the interaction between different pieces of equipment and/or systems.

Design

DQ protocols should be designed to test the conformance of the system to the original design (user requirements) and the GMP requirements. For older equipment it is worthwhile to conduct this exercise even if detailed information on the original design is not available; any potential shortfall of the system with respect to the current GMP (CGMP) requirements should be assessed. It is important to test the equipment adequately, for example it is critical to run printed components down the line, as plain components display different characteristics. It is therefore recommended that such tests are included in the factory acceptance tests.

Installation

IQ protocols should consist of checklists to ensure that the system or equipment is properly installed. At this stage engineering drawings should be checked and updated as appropriate.

Operation

OQ protocols will challenge the system to demonstrate that it can operate within the specified parameters. Tests should be developed based on the knowledge of the process and the systems, ensuring that the upper and lower operating limits are challenged. Equipment calibration should be performed at this stage and the frequency of in-process control (IPC) checks should be established. The line operating procedures (including those covering calibration, cleaning and preventative maintenance) should be finalized and operator training should be completed. The issue of procedures and assessment of operator competency with respect to the SOPs should be listed as key deliverables on the OQ protocol.

Performance

PQ protocols will be the last stage in any validation activity and should reflect the 'real' production environment, using production materials in a normal daily operation. The PQ exercise should extend over a time period sufficient to ensure that shift working patterns and normal lunch breaks etc. are included and to certify that the systems are challenged for stop/start, batch changes etc. This approach may create problems for the QA groups if they are required to release batches prior to issue of the final validation report. The need for the PQ and its extent should therefore be evaluated when developing the VMP and the rationale for the acceptance of the validation must be documented in the VMP prior to start up of the validation activity. It is worthwhile to look for opportunities within the early production schedules to organize a matrix of PQ tests so as to speed up the collection of data while ensuring that all aspects of the system have been challenged and tested. It is important to document the rationale for a matrix approach in the VMP so that it is clear what and why it will be done.

The Report

The final validation report should include all the test results together with details of any changes made to the system. If there are test failures, these must all be reported and the resulting actions detailed. Any learning points from the activity should be logged and recommendations for future improvements documented. It is important to include a recommendation on the timescale for review of the system validation. The validation report must be reviewed and approved by QA.

Some Hints & Tips

1. Spend as much time as is necessary to understand the system and its critical steps. Never underestimate the amount of time needed to develop plans, the more time you spend in design of the protocols, the less you will waste in resolving issues and investigating failures.
2. Ensure that you develop a good sound sampling plan so that your IPC tests are meaningful and provide you with useful data on the line performance (samples should reflect the normal operating conditions). The frequency of IPC tests can be reduced after review of data, so have a procedure in place to ensure that all the IPC data is routinely reviewed and assessed by knowledgeable people.
3. Device challenges will provide more information if performed before and after stoppages.
4. Finally, any validated system is as good as the associated change control process. Therefore, make sure all changes

are fully assessed and documented. The impact of the change on the validation status of the system must be fully assessed before any changes are made.

In the pharmaceutical industry we are constantly challenged to reduce costs while new markets and new packs add complexity to the operation and while an ever changing regulatory environment demands our compliance.

To ensure pack integrity, manage complexity, maximize efficiency and minimize costs; appropriately designed packs, running in validated packaging lines, are a business necessity rather than a regulatory requirement. Regulators simply require that validation be documented properly to demonstrate that it has been done in accordance with the GMP expectation.

In my experience, if the business needs are correctly addressed and validation is well planned and documented, then GMP compliance will naturally follow.

Formerly Director of Quality Assurance for the Global Supply Network of GlaxoSmithKline, Dr. Afshin Hosseiny is now Managing Director of Tabriz Consulting Ltd. With a wealth of research and development experience gained over 10 years of post-doctoral research appointments, Afshin joined Glaxo in 1985 and over the course of subsequent years enjoyed a wide variety of roles with increasing responsibilities in manufacturing and later in the corporate Quality Assurance. He has many years of first-hand validation experience and was actively involved in the design and subsequent validation of a multi-million dollar facility for the manufacture and packaging of Cephalosporin Oral products destined for the USA supply. Afshin set up a quality system for the new product introduction group in GlaxoWellcome and was instrumental in the development of GSK's validation policy. He has over 15 years of experience of both preparations for, and fronting of, European and US FDA regulatory inspections. Afshin is a regular speaker at Pharmaceutical industry conferences in Europe and the USA. He continues to provide advice to pharmaceutical manufacturers on quality and regulatory issues.

Correspondence should be addressed to:
info@tabrizconsulting.co.uk