Process validation:
Manufacturing peptide APIs

Trishul Shah of the **Polypeptide Group** overviews the steps involved in the life-cycle approach encouraged by the US FDA in API manufacture

Quality cannot be tested into products; it has to be built and designed. So say the FDA Guidelines & General Principles of Process Validation from May 1987. This was a concept first outlined by the well-known quality expert Joseph M. Juran, who believed that quality could be planned and that most quality crises and problems relate to the way in which this was done in the first place.

In 2002 the US FDA launched a two year initiative 'Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach' to enhance and modernise its regulation of pharmaceutical quality for veterinary and human drugs. As part of this, pharmaceutical and CMC regulatory programmes were evaluated to encourage the early adoption of new technological advances, promote the use of modern quality management techniques, encourage the implementation of a risk-based approach and ensure that regulatory review and compliance are based on pharmaceutical science.

After the initiative was completed, further steps were identified as part of the next phase of modernisation of the agency. Critical to this phase was an overhaul of the 1987 guideline to include concepts of risk management and a life-cycle approach.

On 27 January 2011, the FDA released the 'Guidance for Industry: Process Validation: General Principles & Practices'. This aligns process validation activities with a product lifecycle concept, existing FDA guidance, and the ICH guidance for industry, which includes Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality System.

As defined by the FDA, process validation is the collection and evaluation of data, from process design stage through to production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation is one of the steps towards process excellence and, if prepared, executed and evaluated properly, establishes a robust manufacturing process capable of consistently yielding a high quality product. It is expected that any variation in any given parameter of the process will decrease over time.

The new FDA guidance for process validation places prominence on a life-cycle approach. This promotes the use of risk assessment with an emphasis on process knowledge and process understanding. The life-cycle approach can be divided into three stages of development:

RPN	Class and action
≥ 200	High risk Specific actions required to reduce any of the three ratings (S, O or D) thus lowering the RPN
80-199	Medium risk RPN ratings between 80 and 199 indicate an intermediate level of control where improvement should be considered
11-79	Low risk The process component is considered under control at a level of 'as low as reasonably practical'
≤ 10	No risk The process component is considered well under control with no, or negligible, contribution to the process variability

Figure 1 - RPN v. class & action

process design, process qualification and continued process verification (CPV). The PolyPeptide Group, the world's largest independent contract manufacturer of therapeutic peptides, has implemented this in all of its operations.

Stage 1: Process Design

During this stage, a manufacturing process is designed that is fit for purpose, scalable, economical and robust. A feasibility study may be undertaken to evaluate different manufacturing routes. A Quality by Design (QbD) approach is used in order to enhance process understanding and process knowledge and a strategy for process control is established.

Once a manufacturing route has been recognised, several scale-up batches may be manufactured to gain experience and determine the level of variability in the manufacturing process. The critical quality attributes (CQAs) of the scale-up batches are defined by product characteristics like specifications, yields, and overall projected process economy.

To formalise the current process understanding and thereby prioritise R&D efforts a risk assessment is performed. A standard failure modes effects analysis (FMEA) methodology is used to perform the risk assessment on the manufacturing process. The FMEA procedure for the manufacturing process will involve:

1. Formation of a cross-functional team from development, production, validation and QA. Evaluation of the risk is subjective, depending on a person's experience, so it is important to have a broad risk assessment team.
2. Review of the process and identification of potential or known failure modes
3. Determination of the potential or known effect of the failure mode
4. Assignment of estimated severity (S, the estimated effect on the CQA), occurrence (O, estimated or determined number of failures per operation), and detection (D, the ability of the current control scheme to detect then prevent a given cause) ratings for each failure mode.
5. Calculation of a risk priority number (RPN) for each failure mode. The RPN is the product of SxOxD. An evaluation of the RPN numbers for all the unit operations in the process shows the overall process state of control and is the basis for deciding the number of PPQ batches required to provide evidence of a robust process yielding high quality material (Figure 1)
6. Development of an action plan to mitigate highest risk events and reduce the overall RPN scores to acceptable levels.
7. Compilation of the risk assessment report, which is a living document that only reflects current process knowledge, but which can be updated as more knowledge of the manufacturing process is gained

During the risk assessment, every unit operation is carefully evaluated, starting with the raw materials. A risk analysis performed on the raw materials will involve the evaluation of the analytical methods to release them, their cost of goods, availability for commercial manufacture and impact on the CQAs.

Current in-process controls are also assessed at this stage and areas where further in-process controls required are identified. An evaluation

of the manufacturing process is performed to identify the critical and key process steps. The critical process steps impact the CQAs, whereas the key process steps influence process economy parameters, such as yield and throughput.

The manufacturing process can be analysed for cause and effect to determine the criticality of individual process steps and the parameters that control these steps. The process step and process parameters can be classified as critical, key, not critical and not concluded.

Supporting data and scientific knowledge and rationale are used to determine the classification of the parameter and steps. If there is no data or rationale available for classification, then the step or parameter is considered critical until more experience and data is collected. For any step classified as not concluded, further investigation is necessary.

A better process understanding and a better defined process can be achieved, by challenging the critical process parameters (CPP) and there by decrease the risk of failure. This is accomplished by applying statistical software, Design of Experiments (DoE) and process analytical technology.

After the risk assessment report has been generated, DoEs are performed to identify the design space by challenging the ranges of the CPPs. Pilot batches are then manufactured to verify the validity of the design space. The risk assessment report is revised to include the new data.

The revised risk assessment report will form the basis of creating a validation master plan (VMP). This serves as the validation roadmap by justifying the strategy, outlining the preliminary test and acceptance criteria, and documenting the necessary programmes that will ensure a continued state of validation.

The VMP should be product-specific and can serve as a resource and task planning tool. It aids in identifying timing and the level of anticipated resource needs. It addresses a number of issues, including:

- Equipment, utility & facility qualification
- Analytical equipment qualification
- Validation of QC release methods
- Validation of in-process control methods
- References to any cleaning validation work
- Number of PPQ batches, based on overall risk level (RPN numbers) in the risk assessment

Stage 2: Process Qualification

The purpose of this stage is to confirm the process design established in Stage 1 and demonstrate that commercial manufacturing process performs as expected. The RPN numbers determined in the risk assessment are used to determine the number of process performance qualification (PPQ) batches that need to be manufactured: the higher the RPN, the more PPQ batches that need to be manufactured. The process used to translate the RPN numbers to number of PPQ batches for the product and the process will have to be justified.

During the manufacture of the PPQ batches, all critical parameters will be monitored and the data collected (Figure 2). A selection of key and non-critical parameters will also be examined to demonstrate consistency of the process. Any sources of variability in the manufacturing process are challenged and hold time data collected.

The collected data from the manufactured batches is summarised and evaluated in a dedicated report, including any deviations and their follow-up. In the report, a conclusion is made on whether or not the process can be considered validated. If the process cannot be validated, recommendations to further improve the manufacturing process are made.

Any changes to critical process parameters based on the PPQ data will be introduced via a change control system. Depending on the importance of the change to the manufacturing process, further activities in stage 1 or 2 may be required to establish a commercially validated process.

Based on the data and conclusions in the PPQ report, the risk assessment document will be revised to reflect the newly obtained process knowledge. If the process can be validated, the product can be commercialised and the life-cycle approach enters the continuous process verification stage.

Stage 3: Continued process verification

The goal of the third validation stage is to provide continued assurance that the process remains in a state of control (the validated state) during commercial manufacture.

Continued data collection and data trending from the commercial batches is performed during this stage.

Process understanding is continually increased by establishing a CPV monitoring plan to evaluate the on-going impact of variability in the process, raw materials, facility, equipment and other key inputs. Through the CPV monitoring plan, variability estimates are generated, which are then used to form statistical process controls and determine the frequency of routine sampling and monitoring.

The CPV plan is developed by subject matter experts, such as technical personnel, statisticians, and is approved by the appropriate functional groups, i.e. QA, QC, validation and manufacturing. The input and output parameters and attributes that will be monitored for each product, the manner in which the data will be collected, the statistical methodology that will be used to evaluate the data and the frequency of evaluation are all identified in the CPV plan.

The CPV plan is product-specific and ought to include the roles and responsibilities of various functions, management reviews and mechanisms to prompt changes that require redesign and re-qualification. Periodic review processes, data collection and evaluation are leveraged by incorporating the CPV plan into the quality system at the manufacturing site.

Initial Stage 3 monitoring plans involve the monitoring of a high number of parameters. As more knowledge and experience is gained, the extent of testing and monitoring is adjusted, based on specific residual risks decreasing or being identified. Any rationale for changing or

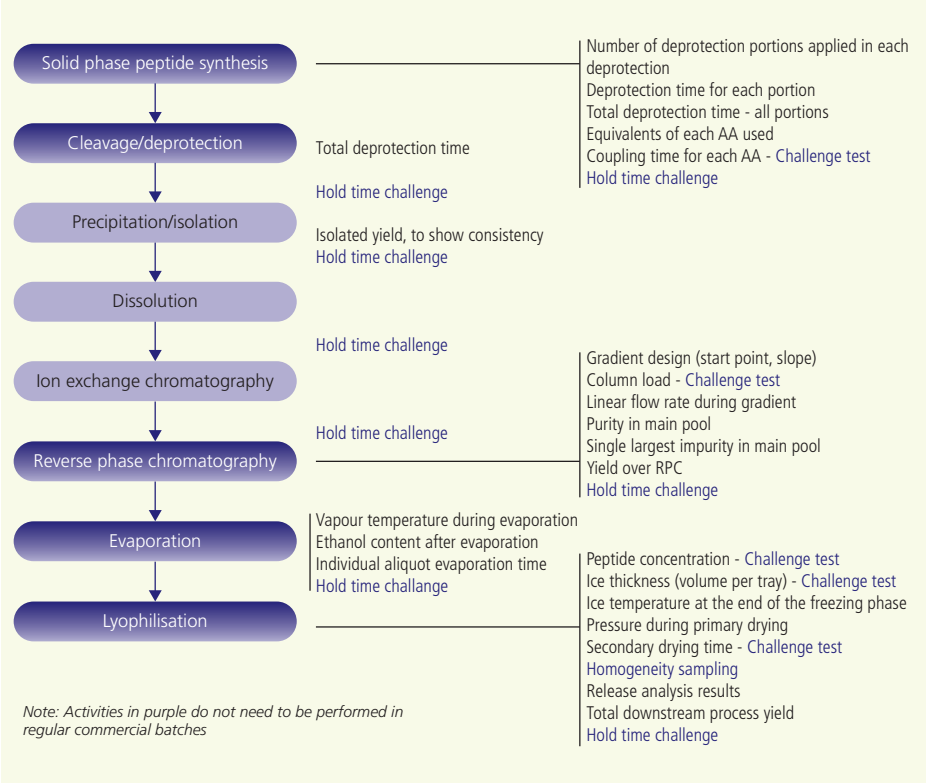

Figure 2 - Non-exhaustive list of parameters monitored during the manufacture of a peptide process performance qualification batch

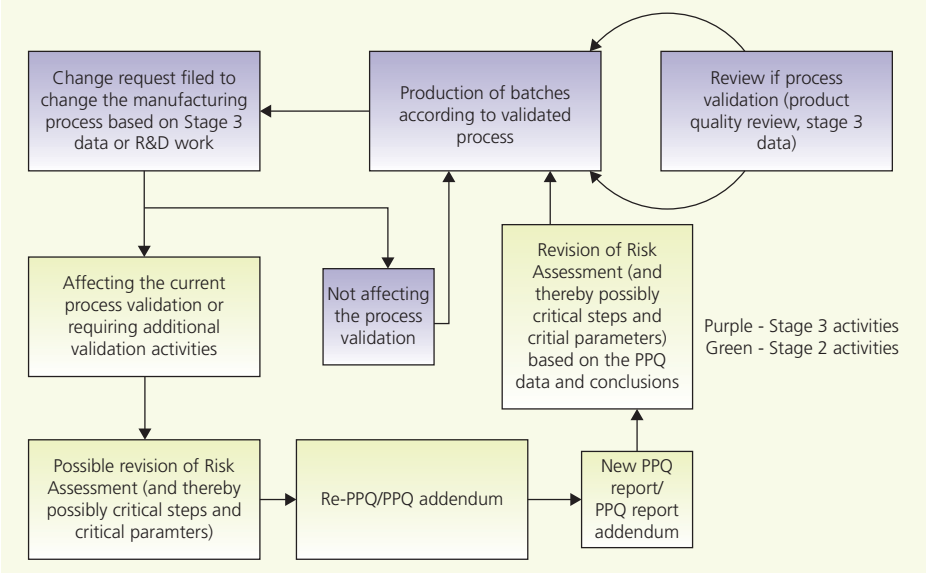

Figure 3 - Decision tree for process improvement

discontinuing the monitoring of a parameter is documented.

To assess whether the CPV plan remains appropriate, it is reviewed periodically, after a set of number batches or after a change to the process that could affect product quality or process performance. Various statistical tools of varying complexity are used to analyse data on an ongoing basis and the selection of the statistical tools used depends on the distribution of the data. These tools are used in both real-time and off-line and are very useful in identifying process trends and signal-to-input-output correlations.

Any statistically out-of-control or out-of-trend data identified during continued process monitoring may trigger opportunities for changes in the control strategy, the elimination or addition of monitoring parameters, or process improvements. If the process change does not affect the current validation, a change request may be submitted to improve the process. If the current validation is affected by the process change, then the risk assessment will have to be revised and process qualification repeated (Figure 3).

Conclusion

The new FDA process validation guidelines establish a regulatory pathway to approval that promotes good science and continued improvement of the manufacturing process. The guidelines favour the use of modern risk and quality management tools and concepts. The ultimate goal is the discovery, development, manufacture and approval of safer, affordable and more effective treatments for the growing population.

* - The author would like to thank Jens Finnman, process validation specialist, and Jon Holbech Rasmussen, director of global development, both of PolyPeptide, who provided ideas and comments during the preparation of this paper

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