EARLY VALIDATION

the difference between success and failure?

Validation is typically associated with drug production and manufacturing, and often considered not to impact drug discovery and development. In fact, this assumption is not true and despite the fact that early-stage research may not require the same level of validation effort as large-scale manufacturing, thinking about validation from the outset and having a long-term compliance strategy delivers significant business benefits.

By Mike Benevento and Victor Bornsztejn

Some scientists in early-stage discovery and development have the misconception that validation is not applicable to them and that, because it is resource-intensive, is best left to those working further downstream who need to ensure that their facilities, processes and equipment are compliant with regulations. While companies do not need to be intimately involved in validation, we believe that there is often not enough thought and consideration given to validation and compliance activities in the early R&D stages. Yet it is at this stage that companies have a great opportunity to start thinking about some aspects of validation and begin to plan for the longer-term. This is particularly true if you have aspirations to progress your molecules to preclinical and clinical trial stages, because the earlier you start planning for validation, the more efficient and cost-effective it becomes.

For the company, it is a question of how far you want to take your compounds. Once a suitable entity has been discovered, the natural step is to quickly move into process development and further testing (eg, screening tests, toxicity testing, etc). When those initial tests are completed, you need to be in a position to produce the drug in a reasonable quantity for early clinical trials. However, as soon as the company starts to go down the route of developing materials for clinical trials, then its facilities, processes and equipment will have to be validated.

Effective and appropriate validation comes from leveraging as much information about the drug as is possible – its critical quality attributes and process parameters that will be used to manufacture it. It is the drug discovery and process development operations that can provide much of this information from their early-stage work. It also involves thinking about what is going to be needed from a validation perspective later and, therefore, leveraging those concepts in the planning of their development activities. The regulators are encouraging companies to perform risk-based validation, based on what will truly impact the quality of the product. The only way we can

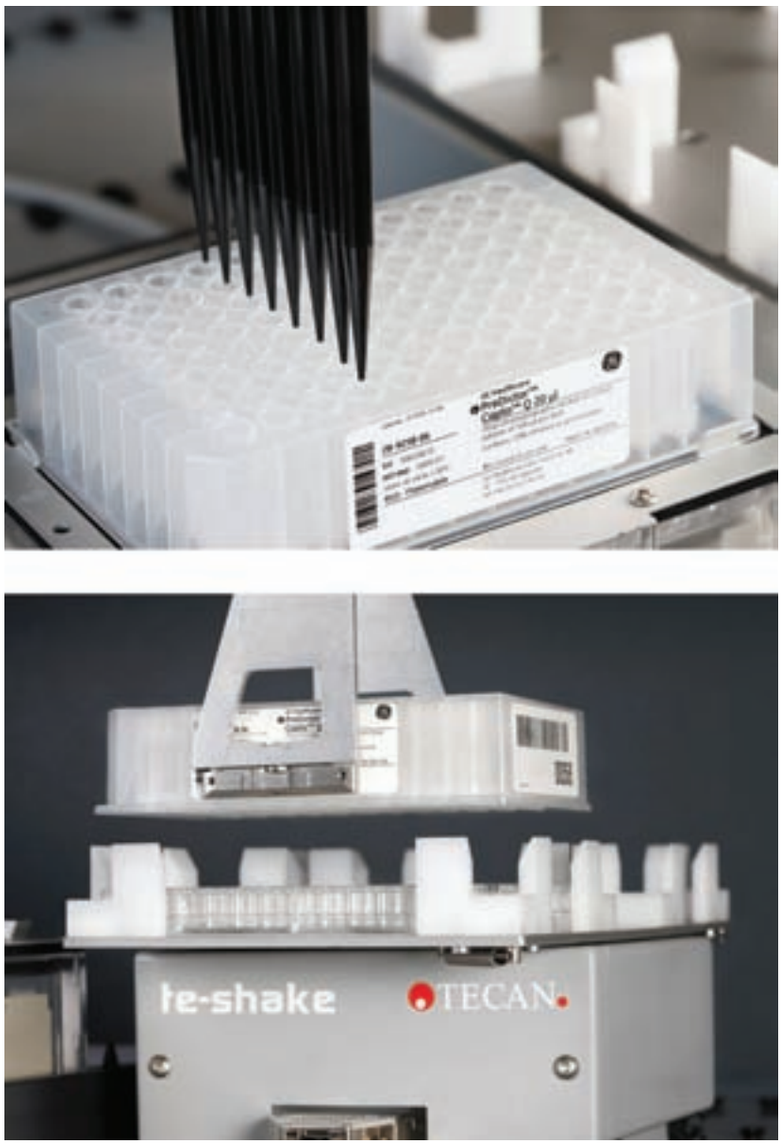

Figure 1
High throughput process development tools provide a wealth of information, enabling the development of not only a more robust manufacturing process, but also a more appropriate validation effort

make the most intelligent decisions about what really affects the quality of the product is if we identify and understand the critical quality attributes of the drug product, and the critical parameters of the manufacturing process. Understanding this data will enable the most effective and appropriate validation to be planned.

Changing mindsets

The onus is on companies that provide validation services to come up with new ideas, approaches and solutions that progress drug discovery and development, part of which involves knowledge-sharing and education. From our discussions, pharma companies throughout all stages of the product lifecycle deeply appreciate what needs to be done from a validation perspective and the way regulators are directing the industry to follow a risk-based approach. Where possible, we need to develop and provide the appropriate tools to enable pharma companies to do that.

Our opinion is that there are alternative, and more efficient and effective, ways of performing validation than are currently being practised, and we, as an industry, need to start working closer together and should not be afraid to consider new strategies. There is no risk to using new approaches as long as they have a really solid basis in good science – they are just going to be a little different. Of course, it is completely understandable that people may become nervous about using novel validation methods, particularly when they are familiar and comfortable with tried and tested approaches.

Validation must be considered as early as possible to maximise its effectiveness and resultant corresponding efficiencies. We appreciate that there are usually limited resources at the early stage, and the focus is on identifying molecules, but that also means that opportunities to generate information and knowledge that can be used in future validation can be missed. This leads to a disconnect that we often see between drug discovery and development, process development and validation in general. There may be people who work on early stages of drug development and process development who think it is just too early to think about validation at that stage. We think it is necessary and can be done without having to spend much time or money. Remember that there is a lot that can be done in the early stages to properly structure the development of data and understanding of your product and process, which can then make a positive impact on validation later on.

It is important for people working in early-stage discovery and development to be aware they need to make sure that the information (knowledge and understanding) they are generating is geared towards future validation. To achieve this you can consider employing readily-available techniques; for example, take a scientist working in a development laboratory who is trying to develop a process for the purification of a particular biopharmaceutical. You can take the tried and tested approach of taking each unit operation and then doing repeated experiments where you test a lot of different chromatography media and conditions, which can take a long time. Or, as a result of modern techniques and solutions, you can work much faster by employing High Throughput Process Development,

testing many different conditions at the same time. With this approach, you achieve two things:

- Screen a greater number of different chromatography conditions for a particular step in the process more quickly, thereby optimising processes much faster.
- Generate a large amount of data around the process, enabling greater understanding of the process and design step.

A similar example is the use of High Content Analysis Imaging instead of traditional microscopy or flow cytometry, whereby more data are generated in a much shorter time. Such high throughput tools provide a wealth of information, which then enables a focus on critical quality attributes of the product, the critical process parameters which can influence those quality attributes, and ultimately enable the development of not only a more robust manufacturing process, but also a more appropriate validation effort. Put simply, you can do things faster and more efficiently, and at the same time develop much more data to help you understand more about the drug and the process. It is that data (eg, critical quality attributes and critical process parameters) that can be leveraged later on into the validation.

Building confidence and trust

There is no doubt that effective validation builds trust and confidence between the drug developing company and its stakeholders such as regulators, customers and employees. The absolute last thing that any pharma or biopharma company wants is a warning letter, citation, or worse from the regulatory authorities. The ramifications can be huge and, simply put, compliance is your licence to do business.

For patients, safety is key and there is always an expectation from consumers (physicians included) that the product is safe. Breaches of that confidence can have vast implications. Effective validation minimises exposure to such adverse events, and from a regulatory standpoint helps build confidence with auditors as they see a risk-based and consistent approach across multiple platforms and sites. Furthermore, rapid access to safe and efficacious therapeutics is high on everyone's agenda, and incorrect or poor validation can reduce or prevent the availability of urgently required drugs.

Early-stage biotechs often develop and use innovative new technology platforms to discover and develop new compounds, but not much thought is given to validation. What tends to happen is that such companies often rapidly move into a mode where they are starting to scale-up some of their activities, particularly when they are thinking of stepping up process development and production capabilities for clinical trials. As soon as that happens, they have to be thinking of validation. Even if they outsource to a contract manufacturing organisation (CMO), the CMO will need as much product and process information as possible for its validation procedures.

Drug developers should therefore not put validation on the backburner. It may simply require initially engaging an experienced validation expert for one or two days to provide direction about what they need to do. At that stage, it only costs a small amount of money, but it could make a huge amount of difference later on. Getting it done right the first time will save lots of resources in the future. Get good advice, be prepared and get your house in order. The later you leave validation the harder it gets, which can lead to the 'sticking plaster solution' of short-term fixes to long-term issues – over time this approach can become very unstable. You also open yourself up to deeper regulatory scrutiny, you miss many opportunities for increased efficiency and perform a lot of work that possibly does not need to be done.

Quick, safe and effective

The industry's approach to validation will definitely develop in the coming years as a result of the economic climate – every business is under considerable pressure to become more productive with fewer resources and reduce costs, thereby increasing the focus on effective validation, LEAN processes and operational excellence in general.

Pharma/biotechs know that discovering, developing and manufacturing novel drugs is becoming more difficult. Therefore, proper execution becomes even more important to ensure that all commercially viable products maximise their market potential.

There is an emphasis from regulators to move toward a truly risk-based approach and a continuous verification model as opposed to validation/requalification carried out at discrete points in time (ie, a true lifecycle verification process).

Our advice to pharma and biotech companies is to consider validation as an enabling function rather than a regulatory requirement. Understand how it can help play a role in the development of your company's product and processes and do not be afraid to explore new approaches. If the methodology is justified and based on good science there is limited risk. It is important to appreciate

that your drug development status can change very quickly from when validation is a low priority to when it becomes crucial, so it is essential to be prepared. In the end, an effective validation programme can reduce the costs associated with designing, operating and maintaining a facility, and manufacturing drugs; it verifies that you have a safe and effective product on the market. This will ultimately help to position your company more favourably for potential partnerships, investment and acquisition. DDW

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