Quality by Design: Defining your Preclinical Package

John Avellanet at Cerulean Associates LLC demonstrates the advantages of using quality by design to define preclinical package

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Shareholders and large investors alike are increasingly scrutinising a company's biopharmaceutical pipeline through the critical lens of today's reality; to bring a new biopharmaceutical product to market requires 10-15 years, costs an average of $1.2 billion and has a paltry success rate of one out of 250 (1). For investors, shareholders and executives alike, the crucial question – how to speed time-to-market, lower costs and improve the success rate – remains unanswered. And yet, over the past few years, regulators have steadily put forth one answer: 'quality by design.' Given my experiences over the past 15 years in product development, commercialisation and regulatory compliance programmes, quality by design can cut development time by at least one to three years, save at least $102-290 million, and ease regulatory approval with one caveat: if tackled in an overzealous, process-validation manner, similar to the early misinterpretations and costly attempts at 21 CFR Part 11 compliance, adoption of quality by design will stumble, proving more promise than fact.

In light of that risk, this article presents a real-world quality by design strategy for biopharmaceuticals looking to develop a faster, less expensive and more user-friendly preclinical package for a new product. The article is based on published FDA insights, discussions with FDA officials and other scientific experts, plus recent client experiences.

QUALITY BY DESIGN

Quality by design is part of the FDA's good manufacturing practices for the 21st century. However, before the FDA's adoption, quality by design had been in widespread use throughout the consumer product and software development marketplaces for the past 25 years. Toyota is famous for its use of quality by design techniques to incorporate predefined product aspects (such as consumer preferences) as early as possible in the product design phase. Such predefined product aspects establish a product vision which serves as a reference to arbitrate conflicting constraints, limit late stage changes, increase product quality and lower overall development and manufacturing costs.

The FDA has defined quality by design as "designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process" (2). In other words, quality by design incorporates predefined product characteristics (such as safety and efficacy) during the preclinical product development stage to ensure the new drug, biologic or medical device meets these critical thresholds.

At an FDA conference in May 2007, Dr Barry Cherney, the FDA Deputy Director of Therapeutic Proteins, stated that the goal of quality by design in biopharmaceuticals is to use

scientific judgements and risk-assessments to ascertain "a reasonable level of expectation" regarding important product characteristics, while eliminating non-value added work and bringing innovative products to market (3). The fact that Dr Cherney and other senior FDA officials have consistently and actively discouraged misinterpretations of quality by design as any kind of process and validation methodology should give life science engineers, scientists and executives all the more incentive to take a closer look.

IDENTIFY ATTRIBUTES AND LINKAGES

The first step in adopting quality by design at the product development stage is to link product attributes to patient safety and product efficacy. Developing a matrix that first defines patient requirements, then matches these to product requirements (that quantify those patient requirements), and correlating them with a therapeutic function is recommended. Depending on the specifics of the product in question, there are other columns as well, but in classical design control terms these are the design inputs. The end result looks something similar to Table 1.

Once this is complete, the product components that achieve the therapeutic function can then be added to the matrix. For pharmaceuticals, these would be the active pharmaceutical ingredients (APIs), for medical devices it might be the aerosolising action such as in a nebuliser, and so on.

The results of this exercise can be examined, and other information gathered, in order to undertake two tasks – assessing risk and impact to safety and efficacy, and segregating the critical product attributes from key (but not critical to patient safety and product efficacy) product attributes. In the case of a simple pharmaceutical drug, the inert ingredients would be key product attributes, but the API and its purity would be critical. The risk and impact assessment will then provide the parameters fundamental to achieving the product requirement (20 per cent less pain is achieved by an API purity level between four to eight per cent). In manufacturing, these are the parameters critical to control, and the risk assessments will identify any control points and thresholds. Identifying and laying this out at a preclinical stage is incredibly helpful to increase the flexibility of a company while simplifying controls, and thus lowering costs and speeding up development.

Table 1: Attribute matrix

Patient requirement	Product requirement	Therapeutic function(s)
Noticeably less pain	20 per cent or greater reduction in pain when applied	Promote faster healing, consistent use of product
No (or little) scarring	50-100 per cent level of constant hydration to burn minimise scarring	Promote faster healing, consistent use of product,
etc	etc	etc

Source: sample information from Hydrogel Burn Products (4)

In order to accurately assess the risk and impacts, the company needs to obtain a broad range of information. As Dr Cherney from the FDA pointed out: "This information in and of itself does not need to be perfect, but taken together it can provide a good, reasonable level of information that then goes into proving the range of safety and efficacy for the intended final product" (5).

Taking a multi-spectrum approach to gathering this information is most effective, both to minimise disruption and avoid conducting non-value activities (such as validating a process to control a key product aspect with no impact on safety and efficacy). Depending on the product, company and personnel involved, the best formula is:

- Mine previous preclinical and clinical work
- Review any databases and previous work of development partners
- Conduct scientific literature surveys
- Ask universities and hospitals for any relevant data (stripping any confidential information, of course)
- Summarise the previous experiences of personnel with this type of molecule
- Draw upon other platform experience

The goal is to build an information portfolio that provides parameters supported by scientific judgements and independent data.

This type of undertaking usually requires two to three months of work, but can often proactively highlight potential trouble-spots that the company can resolve prior to clinical testing or floating their new product out to prospective investors. Several years ago, Monarch Systems (6) discovered during scientific literature surveys that the non-API delivery chemical (propylene glycol) that their new combination device depended upon turned toxic when heated. Under more traditional biopharmaceutical product development methodologies, such a discovery might have ended development, or at least set the product on the back-burner. However, under a quality by design approach, this literature finding was only one piece of the puzzle. A more detailed investigation of the literature revealed that the research conducted in the field had only used one method of heating, and once the toxicity had become apparent, no further research (that was publicly available) had been conducted. Monarch Systems then undertook its own laboratory tests utilising different methods of heating and targeting multiple thresholds of chemical purity, temperature and time. Within three weeks, a number of critical control points were identified that demonstrated, in the lab, that toxicity could be completely avoided by controlling heating method, temperature and time. Further feasibility testing in humans bore these lab results out. This is the type of proactive critical product attribute and control point identification that quality by design

exemplifies. Even if Monarch Systems itself had not discovered the scientific literature indications, one can easily imagine the reaction of a potential pharmaceutical partner when Monarch revealed it used heated propylene glycol to deliver the API.

VALIDATE WITH PRECLINICAL STUDIES

Once the critical product attributes, their parameters and control points have been identified and agreed upon, the company should look to what Dr Janet Woodcock, Chief Medical Officer of the FDA, has termed 'intermediate measures' to verify and validate (7).

Analytical testing, toxicology testing, bioassays, *in vitro* and *ex vivo* tests are all part and parcel of such 'intermediate measures'. In addition, given the rapid technological progress in computer modelling, bioinformatics analyses and models can also be added to the list. In the case of Monarch Systems, a feasibility test with *in serum* analysis proved the complete absence of any level of toxicity given the critical product attributes and control points identified in the preclinical stage.

Dr Peter Byron, Chair of Virginia Commonwealth University's School of Pharmaceutics, has also noted the applicable potential to use pharmacokinetic studies and *in serum* testing with feasibility tests to clarify, verify and validate biopharmaceutical products, particularly at the molecular and nanotechnology level. Smaller companies and startups who cannot afford to fund a feasibility or pharmacokinetic study may simply be able to pay for access to university databases. Either way, this scientific information further minimises costs of development for a company, while allowing an independent eye (such as a School of Pharmaceutics board) to verify and validate the critical product attributes, their impact upon safety and efficacy, and the effectiveness of the identified control points.

ESTABLISH CLINICAL GOALS

Finally, in developing the preclinical package, a company needs to tie these preclinical specifications to its goals for clinical data and experiences. Assuming the company has used sound scientific and risk assessments, a key goal for clinical trial planning should be how to get the most value out of the clinical trials. There are two aspects to this: prioritising where more information is needed to finalise safety and efficacy product attributes, and determining how data integrity from both the clinical and preclinical stages will be maintained.

Given that most Phase I clinical trials are small, the preclinical package should identify how some level of variability will be introduced to test minor levels of change to the product quality parameters and to provide trending baselines that can then be carried forward into Phases II and III. Appropriate levels of variability can be difficult to ascertain, and thus the preclinical work to identify ranges is absolutely crucial. For instance, if a firm determines through preclinical testing, literature surveys and previous public clinical trials, that their new product's API purity can be between two and 10 per cent and still hit the expected targets of efficacy and patient safety, then the company might consider conducting three different Phase I trials at two, six and 10 per cent API purity repectively to see if there is a statistically significant difference in safety and efficacy. Over Phases II and III, trend analyses can be conducted to look for other unintentional variables that impact safety and efficacy.

In order to gain the most value from clinical trials (and from their preclinical work), a company's information integrity is of paramount importance in quality by design. Drawing upon a wide array of information to justify critical product parameters introduces the temptation to fudge the numbers.

Such a temptation exists because, in essence, the greater the range of the critical product attribute, the greater the flexibility of controls and the less narrow the specifications and thresholds that will need to be consistently maintained. This results in lower costs and faster product development. In today's reality of costly, time-intensive biopharmaceutical product development, the temptation to push the limits of the data beyond statistically relevant levels can be too much for some executives. Or, if ideal results are obtained from a randomised statistical analysis of the data, the temptation may be to hardcode the randomised formula that created those ideal results before the data are archived.

It is therefore crucial to determine ahead of time how to capture, transmit, analyse and store the preclinical and clinical data. Just like a manufacturing flow, this information flow – whether electronic, paper or both – can then be assessed for risk to consistency and integrity, and controls put in place to verify and monitor. It is worth considering bringing in various subject matter experts such as regulatory affairs, quality assurance, information technology, legal and records management to help assess the integrity risks and determine potential controls.

In its preclinical package, a company should identify both the steps it has taken to ensure information integrity and the variables it intends to test in the Phase I clinical stage; include the logic behind the variable selections and the methodology for ensuring data integrity. Quality by design is proactive when it relies upon multiple levels of tests and investigations. By highlighting the critical product quality aspects, control parameters and critical thresholds identified during the preclinical stage, the company can then provide strong data that support its intent to test particular variables in clinical trials to get the best information possible to finalise and verify its new product's critical attributes and their impact on safety and efficacy.

CONCLUSION

Ideally, by the end of Phase I clinical trials, a company using quality by design for product development will be solely focused on making micro-refinements of their critical product attribute ranges, optimising controls and honing their production processes to ensure consistency; the remaining trials would simply be used as verification and validation of those improvements. The end result: faster time-to-market, more revenue, better success rates and easier regulatory approval.

For a company still in the development stage of its new biopharmaceutical product, quality by design provides a streamlined approach to building a preclinical package designed to appeal to investors, pharmaceutical suitors and regulators alike.

And for pharmaceutical executives scanning the globe for potential pipeline acquisitions, keying in on the adoption of quality by design elements will lower risk, improve success rate, and speed time-to-market, something that shareholders and market analysts will greatly appreciate. ◆

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