Speeding Time to Market with a Preclinical Stage Gate

John Avellanet at Cerulean Associates LLC promotes the use of a series of structured, cross-functional reviews aimed at highlighting the best products in a portfolio

Improving R&D productivity is the holy grail of today's biopharmaceutical landscape. Yet strengthening biopharmaceutical creative productivity requires a delicate balancing act between structural rigour, flexibility and adaptability. Firms need to react rapidly and adopt new technologies, new scientific discoveries and new methodologies as they emerge. Flexibility is necessary to allow creativity to blossom. And yet the regulatory requirements of good laboratory, clinical and manufacturing practices necessitate a structured new medicinal product development process.

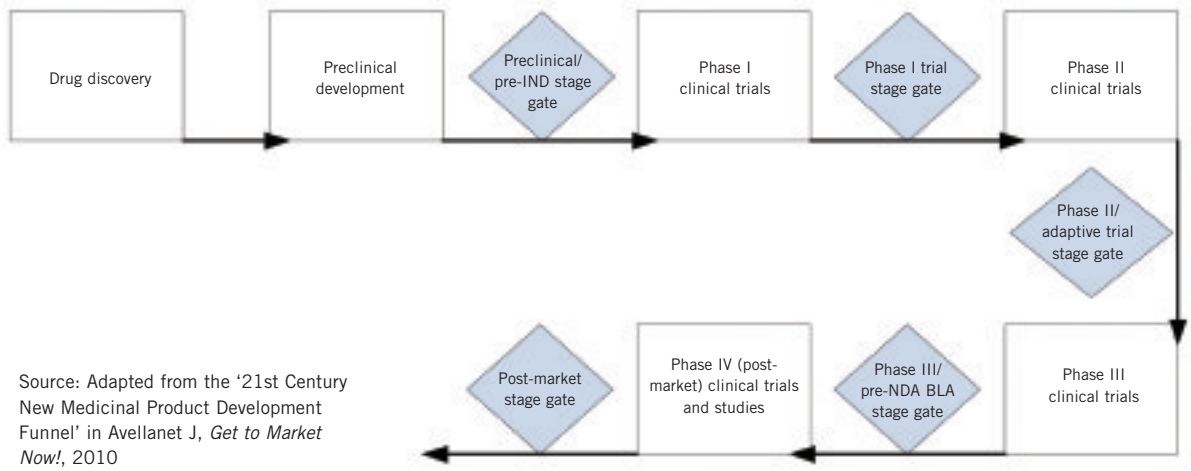
For decades, we have tried to squeeze flexibility and adaptability into the 'follow the science' new medicinal methodology, leaving regulatory rigour as an afterthought. When executives try to force compliance structures onto R&D, creative productivity plummets as scientists and engineers struggle to handle rapidly evolving science and technology complexities with regulations largely written in the last century. Increasing global pricing pressures and generic competition have only exacerbated the situation. All of this continues to exert a greater and greater drag on a company's ability to innovate and compete.

Today's biopharmaceutical executive has a unique opportunity to turn the old drug R&D model on its head: to employ constant adaptability and flexibility and lay down a series of cross-functional, systematic reviews over the new medicinal process, a series of reviews that slowly transition and channel creativity into regulatory rigour without jeopardising either innovation or compliance (1). The result of this has been, for many clients, an average 12 to 15 per cent increase in R&D productivity, a decrease in costs and an improvement in time to market. To improve R&D productivity, the adoption of a series of structured, cross-functional reviews – stage gates – is emblematic of a new medicinal development structure that begins with a light touch in the preclinical stage, adding increasingly stringent reviews as the clinical development stage proceeds. This article focuses on how to incorporate a light-touch review at the preclinical stage, the point at which biopharmaceutical executives have the greatest opportunity, at the least cost and least risk, to spot the 'winners' in their new medicinal product portfolio (1).

WHAT IS A STAGE GATE?

A stage gate is simply a structured review session that provides a 'go/no-go'

Figure 1: An example of a new medicinal product development stage gate framework



Source: Adapted from the '21st Century New Medicinal Product Development Funnel' in Avellanet J, *Get to Market Now!*, 2010

decision and a blueprint for what needs to be done as a result of the go/no-go decision.

Stage gates were originally developed based on new product development research that modelled what successful project teams did at an intuitive level (2). Robert Cooper, one of the original researchers and creators of the stage gate concept likens stage gates to how people decide to invest: "Initially one purchases an option [investment] for a small amount of money, then does some due diligence, and finally decides whether or not to continue to invest" (3). A series of these reviews and decisions comprises the stage gate framework.

The overall framework begins with a cross-functional review of the new product discovery and business case. Company management then make the decision to proceed or not with future development and commercialisation based on the structured review. Part of any decision includes a defined action plan. In the event of project closure, this blueprint describes the steps involved. In the event of a move to the next stage of development, the stage review generates not only the specific action steps, but also outlines the deliverables of each plus the tentative date of the next stage gate review. Stage gates are designed to be cross-functional in order to give company management a full picture of the costs, benefits and risks involved in investing further in the development of the new product.

In the biopharmaceutical context, a stage gate review goes significantly beyond a compound development team to include regulatory affairs, quality, manufacturing, supply chain management, reimbursement, medical affairs, finance, legal, marketing and so forth. To be effective, and to successfully channel R&D productivity while encouraging flexibility, stage gate reviews must be as inclusive and cross-functional as possible.

Stage gates are also designed for speed. They are a specific business process designed to come to an agreement on whether a new product (that is, a new medicine) is worth investing in further, and then to come to agreement on which next step activities should occur sequentially and in parallel. Thus, to employ stage gates effectively, a biopharmaceutical firm must have a certain level of knowledge and analysis brought to the review so that the session can be one of productive decision-making. The most natural place for executives to first adopt a stage gate review is toward the end of the preclinical phase of development when a decision must be made as to whether or not to proceed into early clinical trials.

PLANNING A PRECLINICAL REVIEW

Few of us want to be in a meeting for any more time than is necessary. In order for a stage gate review to be successful, it must be focused around decision-making, not project updating. Thus, a lack of planning will ruin any attempt to implement stage gate reviews as a means to increase time to market and improve R&D productivity. Planning is also crucial to ensure that speculation and opinion are replaced by facts and analyses. And ideally, proper planning will ensure that go/no-go criteria are objective and appropriately prioritised to align with a company's overall business strategy. This is why the cross-functional nature of a stage gate review is critical; it is virtually impossible to try to align decision-making criteria with business strategy using only a compound development team or other functionally-aligned group.

When planning a preclinical stage gate review, all attendees must be crystal clear on the meeting's objectives. A preclinical stage gate review must answer three questions:

- Should development lead into clinical trials or not?
- What resources are required as a result of the go/no-go decision?
- What actions and deliverables will be completed by the next stage gate review (presumably at the end of Phase I clinical trials)?

Thus, as part of the planning for a preclinical stage gate review, regulatory affairs and clinical management teams will want to develop a draft integrated strategy (a clinical regulatory integrated strategic plan (CRISP)) (4). Regulatory affairs, quality and the compound development teams will want to have preliminary critical quality attributes (CQAs) defined, along with the supporting data and analyses, and the specific trial components and nonclinical studies necessary to confirm these CQAs as part of Phase I clinical development (5). Marketing and business development will want to have customer data and analyses along with any proposed studies intended to confirm and refine this data. Reimbursement and finance groups should have analyses of competitor products and preliminary reimbursement options, along with the next steps needed to verify (6).

Other items to plan and gather include:

- The proposed manufacturing site(s) and their compliance status
- The proposed clinical site(s) or contract research organisations and their compliance status
- Suppliers of raw materials and other relevant services and their compliance status

Ideally, specific functional teams will try to determine and assemble the information necessary to help the first clinical trial phase and the transition from preclinical into Phase I clinical trials. For instance, the compound development and manufacturing teams might want to answer questions such as:

- Have upper and lower limit boundaries been defined for preliminary manufacturing processes?
- Have samples (including photographs) of passing grade components, formulations and so on been created?
- Do such samples note specific characteristics for easier identification?

Being well prepared for a preclinical stage gate review will allow faster, easier decision-making on the part of the company, which can in turn invest further in development and commercialisation.

Typical examples of major inputs into the preclinical stage gate process are shown in Table 1 (note that these are meant to be representative only and will vary by size, functional responsibilities, and capabilities of any company). Each of

these cross-functional items is an element of a new medicine's overall business plan. The information feeding into the preclinical stage gate session is the information usually needed before major investments are made, be it from corporate headquarters or venture capitalists.

PRECLINICAL STAGE GATE AGENDA

Scheduling the review session is another task that needs adequate planning. Leave enough time for attendees and their staff to conduct their information analyses and derive preliminary action plans and meeting inputs (see Table 1). It is best practice to draft a project closure action plan in the event that further new medicinal development is cancelled, put on hold, or otherwise given a no-go decision. A common no-go decision is a determination to out license the new compound. In general, try to provide approximately four weeks' notice. This is enough time to gather and analyse the necessary information, while minimising the potential for 'analysis paralysis' to develop. Keep in mind that this is a preclinical stage gate review; by default, thoroughly comprehensive information simply will not be available, no matter how much time is allotted for assembling data and conducting analyses. Therefore, as necessary, consider using the Pareto Principle (the 80-20 rule) as a guide to how much information gathering and analysis is enough.

As part of the scheduling notice, it is important to include the agenda. Make sure the decision-making objectives of the session are clearly delineated. Stage gate meetings that do not result in go/no-go decisions will not aid new medicinal product development productivity or speed time to market. It may be helpful to conceptualise this agenda in order to let each cross-functional group determine which decision-maker should attend and represent that department.

I suggest that clients try to keep attendance limited to decision-makers and less than 15 to 20 people – anything more will become unwieldy. Apply caution when trying to define attendance by job titles. If asked what level of individual should attend a stage gate review, I typically respond that anyone who has to ask for approval to spend $50,000 to $100,000 or above is not a good choice. Remember that attendees at the session are the same individuals who will be funding and allocating personnel to any next steps as a result of the decisions in the meeting. Conveniently, this also provides these individuals with a vested interest in making a fact-driven, risk-based business decision. They will not be afraid to decide whether or not they should continue to spend their budgets on further product development.

Table 1: Example of preclinical stage gate review inputs by business function

Business function	Potential input items
Marketing	Market analyses, customer analyses
Finance	Revenue projections, opportunity cost estimates, other costs
Legal	Intellectual property landscape review
Regulatory affairs	Regulatory pathway and risks, preliminary labelling and physician inserts, potential CE requirements, draft CRISP (with clinical)
Reimbursement	Preliminary reimbursement rates, proposed confirmatory studies/trial components, critical quality attributes (CQAs) from an efficacy to cost-effectiveness perspective
Manufacturing	Preliminary critical process parameters (CPPs), overview of manufacturing process, distribution plan
Clinical	Phase 0 and/or Phase I investigation plans, adaptive trial recommendations, draft CRISP (with regulatory affairs), draft investigator's brochure
Quality	Qualification and verification plans associated with relevant CGMP production and clinical sites
Supply chain	Preliminary list of suppliers, due diligence and qualification process (with at least quality and regulatory affairs input)
Medical affairs	Safety assessment, CQAs from safety and efficacy perspective, preliminary product risk assessment and control plan
Formulation	Raw material specifications, formulation testing plans, relevant voice of the customer inputs and confirmatory testing plans, efficacy assessment and preliminary efficacy CQAs
Compound development	Nonclinical studies, toxicology testing and so on
Project management	Draft project plan incorporating all of the above, tentative date of next stage gate review, draft abbreviated project closure plan

CONDUCTING THE PRECLINICAL STAGE GATE REVIEW

Try to conduct the stage gate session as an open discussion. Set up a handful of slides to review the core risks, benefits and costs, but otherwise do not let this meeting devolve into one PowerPoint show after another (two to four slides in total is ideal). The goal is for discussions to be fast paced and wide reaching in order to provide management with the best opportunity to make an informed decision and come to an overall consensus on the next steps to take.

Templates – so long as they are not rigid or overly long – can help consolidate disparate information and bring useful summaries to the stage gate review session. This allows stage gate attendees to focus valuable meeting time discussing and coming to an agreement on core costs, risks and benefits, and thus formulate future investment priorities.

It may also be helpful to structure the review and discussion around six major areas in order to ensure the new medicine is ready to proceed into early clinical trials:

- Opportunity costs – reimbursement, revenue, trial and study costs, licensing options and more
- Regulatory and clinical strategies – including major regional requirements

- Manufacturing, packaging and distribution – the critical process parameters need to be identified
- Critical quality attributes – safety, efficacy and verifications, especially related to active pharmaceutical ingredients (APIs) and formulations
- Supplier management and raw materials
- Risk management plans and controls

Each of these points should be mutually supporting. For example, specific clinical trial components and nonclinical studies should support specific reimbursement considerations. Likewise, to verify critical quality attributes and risk controls, customer studies may need to be conducted in parallel with early clinical trials.

MAKING THE PRECLINICAL STAGE GATE WORK

Many companies inside and outside of the biopharmaceutical industry – Procter & Gamble, 3M, Ethicon, Kimberly Clark, Biosense Webster and others – have successfully adapted the stage gate framework to their new product development pipelines. The key is to balance the idealised version of the structure with the realities of the company. A preclinical stage gate session at a global conglomerate will, by necessity, involve significant preparation time (including the possibility of numerous pre-stage gate meetings to assemble all the necessary information, analyses and gain consensus across the organisation). Conversely, a small- to mid-sized biopharmaceutical firm will have fewer layers of input- and consensus-building to wade through in exchange for significantly greater bottom-line implications if a potential new medicine with only marginal regulatory approval prospects is given the go-ahead to enter clinical trials.

There are a number of pitfalls that exist for any biopharmaceutical firm looking to implement effective stage gates. First is the inevitable need to determine how and where stage gates fit into the firm's quality system. For instance, should there be a standard operating procedure for stage gates? Will stage gate effectiveness be assessed in a firm's regular quality systems management review or its periodic product-specific reviews? Another challenge facing firms in adopting the stage gate framework is finding the right mix of structure and flexibility in adopting stage gates. Questions that arise include whether or not gates should be set up at the end of each clinical trial phase or only at the end of Phase II and III trials to coincide with regulatory agency meetings? Should a postmarket stage gate review take place and what are its objectives? Answers to these questions tend to be specific to the company involved, often requiring the executives to seek outside advice in order to ensure effective implementation.

The third most common challenge arises when a stage gate review is seen as an extension of project management. This mistake can be easily recognised with 90-slide decks that seek to educate attendees on the project. As I alluded earlier, proper preparation for the stage gate review should result in attendees who know the project and are now meeting to review the risks, benefits and costs in further pursuing the new medicine in light of other business initiatives and strategies.

CONCLUSION

The amount of work that goes into preparing for and holding any stage gate review session, especially a preclinical stage gate, should vary based on the risk of the product to patients, to a company's compliance posture, and to a firm's bottom line. In simple terms, a wholly new compound tends to have more associated risks than a product extension or generic version, and as such, the new medicine's preclinical stage gate review will require more information to be reviewed, analysed, synthesised and summarised. Conversely, focusing only on risk to the patient or compliance is a recipe for financial loss. Thus, the stage gate must be cross-functional in order to be a true business process that is designed to speed time to market, allow for a wide latitude of flexibility, and encourage development productivity and creativity.

By ensuring the preclinical stage gate is a light, yet comprehensive, review, biopharmaceutical executives can take advantage of this tried-and-tested product development method to get their new medicine to market faster, easier, for less cost and less risk.

About the author

John Avellanet is an FDA lean compliance consultant and founder of the monthly regulatory compliance intelligence executive newsletter, *SmarterCompliance*™. He is the author of the book, *Get to Market Now! Turn FDA Compliance into a Competitive Edge* (2010) and a contributing author to the book *Best Practices in Biotechnology Business Development* (2008). John has gained wide recognition for his speeches, workshops and teleconferences for corporate clients and conference venues around the world. He earned his Bachelors at the College of William & Mary in Virginia and his Masters degree at the University of Kansas.

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