Redundancy Based Development (RBD) for a dry powder inhaler (DPI)

Inspired by Toyota's methods, a new approach to inhalation product development helps avoid costly, time-consuming delays.

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Introduction

In the inhalation industry, the challenges of developing inhalation products are well known. The development process can be extremely difficult, costly and time-consuming. Project delays and budget overages are very common. This is often a deterrent to entering new development projects. Even though pharmaceutical companies developing new inhalation products are often very experienced in the inhalation field, projects can drag out for years due to technical flaws and loop-backs. Typical development time for new inhaler is at least five years. A typical budget for the development of a new inhaler reaching phase III clinical trials is in the range of tens of millions in US dollars. The cost for clinical trials and drug development must be added to this.

The reason for the high cost and long timeframe is the complexity of an inhalation product. A typical dry powder inhaler (DPI) can be split into several fundamental parts: drug, formulation, manufacturing process and device. These parts interact and, together, give the performance of the product. In a typical inhaler, the interaction between the formulation and device is very complex and its contribution to performance is inextricable. Pharmaceutical products are highly regulated and the inhaler must deliver the same performance independently of the user's inhalation effort and the operating environment. Due to the high cost of development, the same inhaler and manufacturing equipment are often intended for many different drug products. All of these factors put multiple layers of complexity on the development process.

In an effort to address and mitigate development challenges, a new product development methodology has been created. The new methodology has been inspired by the Toyota product development methods that have been successfully used in many industries to avoid costly and time-consuming back-loops.[1-7] The core of the new methodology is to build redundancy into the development. The new development process, called Redundancy Based Development (RBD), is based on a massive parallel development scheme to provide multiple back-ups should a preferred technical solution fail. RBD is a comprehensive framework that handles the complete development process, including specifications, prototyping, user studies, performance testing, data management, QbD, industrialization, etc. In addition, RBD covers the development of both the product and the manufacturing processes. RBD was originally developed by the author of this article, Orest Lastow, as a part of the AstraZeneca new dry powder inhalation platform development program. AstraZeneca has no claims to RBD and has granted Zenit Design Group unlimited access to the methodology.

Traditional methodology

A traditional development approach uses an initial brainstorming session and identifies a number of technical solutions or concepts (see Figure 1). The best concept is selected and all of the inferior concepts are dis-

carded. Then, in a serial way, the single concept is developed and optimized. The design is adjusted to resolve technical issues and the concept is developed until it meets the requirement specification. Resolving a technical issue often imposes restraints on the design. These restraints can lead to a loss of flexibility and control of direction. In many cases, development comes to a halt when the original concept cannot be redesigned any further and the requirement specification cannot be met. In these cases, the project needs to take several steps back and a major redesign is necessary. This back looping is associated with severe cost increases and major delays. The project development risk is significant and makes any predictions of cost and delivery time very uncertain. In many cases, a drug project is dependent on a new device and the plans for the clinical trials are based on the predicted delivery time of the device. To delay a clinical study as a consequence of a delayed device is extremely costly and can jeopardize the launch date of a new product. This can, in worst case, mean a missed opportunity to be "first on market" with a new drug.

The RBD methodology

In RBD, a more extended brainstorming is carried out and all concepts, that are not obviously flawed, are developed further, (see Figure 1). Only when a concept is proven faulty, is it discarded. The traditional approach is to "keep the best and discard the rest." However, as the RBD approach is based on parallel development for an extended period of time, the criteria is instead "discard the flawed and keep the rest." The multiple concepts provide a valuable redundancy and fall backs.

Redundancy in product development can be achieved in two ways. One way is to develop a large number of independent parallel solutions or components. This is a linear redundancy and is costly and resource consuming.

The approach used in RBD is, instead, a modular development of interchangeable building blocks (modules). The basis of RBD is the split of the product into modules. For each module, a number of independent concepts are developed and assessed separately. The concepts can then be pieced together to form a product candidate. The number of possible combinations grows exponentially with the number of modules and concepts. Should a concept for any reason fail, it can be readily replaced by another concept from the same module. The concepts can be combined in many different ways, providing a family of products. A module is an abstract entity and is used to bring structure to the problem solving process. Modules should be independent and have a clearly specified function. Modules can be defined by their function, a unit operation or a process.

Another important aspect is the risk mitigation the RBD approach provides. If there is a functionality that carries a higher risk than others, it is favorable to make it into a separate module. The module definition should always be preceded by a comprehensive risk analysis of the product. Examples of DPI modules are formulation, filling, drug dispersion feature, dose compartment opening, air flow path, etc. The modules are defined and described in the Module Requirement Specification, MRS (see Figure 2). The list of all modules and the ways they work together on a system level are described in the System Requirement Specification (SRS).

Requirement specifications

The development is governed by a set of requirement specifications (see Figure 2). The User Requirement Specification (URS) describes customers' needs and requirements. This is a very qualitative set of requirements, expressed in terms that the customers would use. The System Requirement Specification (SRS) describes,

Figure 1

Redundancy based development compared to traditional development

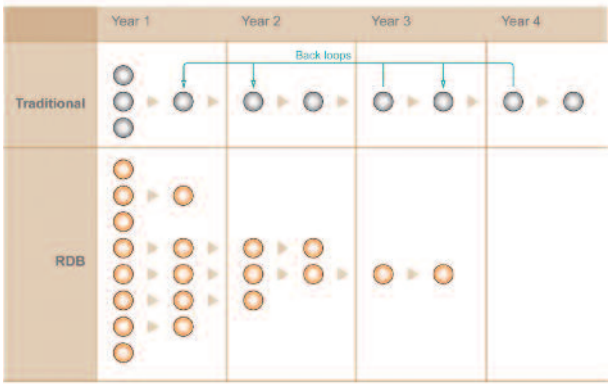


Figure 2

Requirement specifications hierarchy

in very technical and quantitative terms, a product that meets the URS. The SRS also includes tests and acceptance criteria. The Module Requirement Specification (MRS) describes the requirements on the modules and the interfaces between the modules. The concepts are developed to meet the MRS. When they are combined into a product candidate, it is tested against the SRS. The requirements play a key role in RBD. Since the possibility of replacing one concept by another is a key feature of RBD, it is paramount that the concepts fit together. The MRS and SRS are developed to guarantee compatibility.

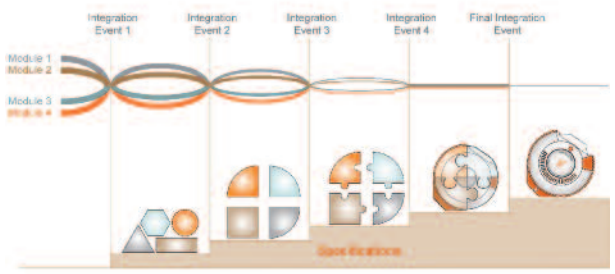
Integration events

The pace of RBD process is set by integration events (IE) (see Figure 3). The integration events are recurring review meetings that take place a few times per year. The key integration event objectives to assess the concepts' ability to integrate, update specifications, identify and assess risks and define development actions. The integration events are key milestones in the RBD process. At the integration events, all available concepts are evaluated and assessed against the MRS and SRS and the latest risk analysis results are presented. For the evaluation, the concepts are presented in forms of tangible prototypes, CAD drawings, animations of functions and concept reports. The assessment is made on a very detailed level. It is of great importance that the integration events are well prepared both by the project manager and the persons responsible for the modules. During the process, the concepts not likely to meet the MRS and SRS are discarded.

In Figure 4, it can be seen how the concepts can develop over time and between the different integration events. One of the benefits of RBD is that the process allows very late introduction of new concepts. In traditional development, such late introduction would be impossible.

Figure 3

Module and specification development



In many cases, the concepts chosen in the end have not been available during the initial concept generation phase. This is a testament to the flexibility of the RDB methodology. It is rare that the best solution is generated during the first brain storming session. Often the best solutions come when the development has matured and all the details are well understood. RBD can make use of this more informed design solution and incorporate the best ideas even if they come very late.

Quality by design

The RBD process, with its modular approach, is readily compatible with the Quality by Design (QbD) initiative outlined by the FDA and ICH. The development of the MRS and SRS will provide a foundation for the definition of the three QbD spaces (explored space, design and control space) of the product. After the final integration event, the finalized MRS and SRS will define the design space and the control space of the modules and of the complete product. The careful analysis of the interfaces between the modules provides a valuable contribution to the interaction analysis, which is a key part of QbD. Developing and testing different concepts and the various combinations of the concepts will provide a thorough exploration around the design space. The critical performance characteristics are defined in the SRS and the critical quality attributes are obtained from the risk assessments.

A summary of RBD

To provide an overview, the RBD process can be summarized as in the flow chart shown in Figure 5. The workflow summary provides a high level, step-by-step description of the RBD process from first product requirement definition to the delivery of the developed product.

Figure 4

Concept development history. Bold type depicts the preferred concept. In this example, A11 was the chosen concept, although it was first introduced at IE#3.

PreIE	IE#1	IE#2	IE#3	IE#4	IE#5	IE#6
A1	A1	A1	A1	A2	A2	A10
A2	A2	A2	A2	A10	A10	**A11**
A3	**A8**	A8	A8	**A11**	**A11**	
A4		**A10**	A10			
A5			**A11**			
A6						
A7						
A8						
A9						

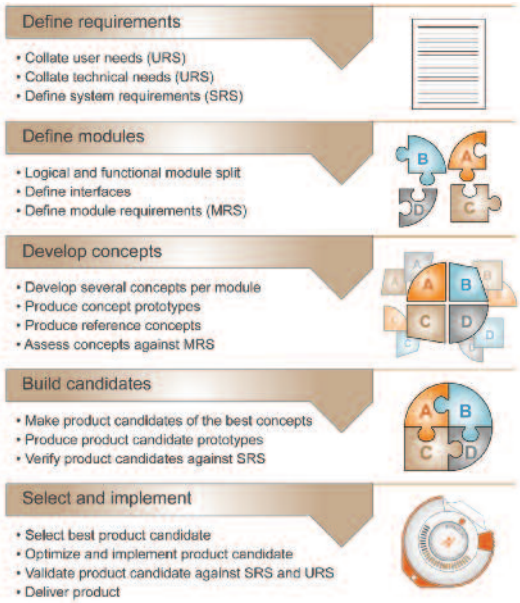
Conclusion

The use of RBD has proven to be very successful and was used by AstraZeneca in the development of a new dry powder inhaler. The project delivered on time and on budget. The manner in which RDB is structured provides a focused development process, minimizing waste of resources and funds. RBD gives a logical structure to the development process and a standardized working model. The evolutionary development of the specifications provides a good rationale for the requirements. Traditionally, specifications are used as targets and documentation of the product. In RBD, specifications are used as tools to aid development. The specifications and integration events drive the development with clear objectives, tasks and timings. One valuable benefit of RBD is that it stimulates innovation and creativity by allowing late design changes without adding delays. The increased knowledge and number of available concepts will make the developed product more flexible and predictable. RBD is particularly suitable when developing a product platform. The redundant concepts will simplify the adaptation to new product and formulation requirements. Developing a second product based on the platform can be done with reduced development time and cost. The principal benefit of RBD is to deliver on time even when the project hits pitfalls. The benefits can be summarized as:

- Deliver on time and on budget
- No long loop-backs due to design flaws
- Minimize risk of development delays
- Clear project tasks and timings
- Lower total development cost
- Comprehensive and relevant specifications
- Increased knowledge and quality of the product
- Robust product with predictable quality
- Increased versatility of the platform
- Stronger IP protection
- Compatible with quality by design, QbD
- Better understanding of design space

Figure 5

Schematic description of the RBD workflow. The DPI product shown is only an illustration.



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