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QbD: A New Horizon in Pharmaceutical Product Development

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ABSTRACT

Quality by Design (QbD) is the recent trend for maintaining quality in the product during its manufacture. This paper discusses QbD as a measure to produce high-quality pharmaceutical preparations. It involves the identification of unique quality attributes. Pharmaceutical products can profit from Quality by Design and the way that can be taken to apply it. The core of pharmaceutical R&D involves high-quality pharmaceuticals and their manufacturing processes. This document includes a breakdown of the product's quality profile and the most important aspects of QbD which makes it impossible to verify the quality of the product. Quality by Design and end-product testing helps to compare the quality of various products. This technique is based on the ICH guidelines. ICH guidelines govern the development of drugs and the perpetration of quality assurance systems. QbD provides benefits to pharmaceutical development and production.

INTRODUCTION

The goal of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design [1]. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support the establishment of the design space [2].

In all cases, the product should be designed to meet the patient's needs and the intended product performance but, in a few scenarios, root causes for failure are usually not well understood due to the poor process understanding and uncertainty about how characteristics of substances impact the target product profile. As a result, the manufacturers must restart the procedure until the root causes of failure are understood and addressed or FDA approves supplements to revise. This causes poor cost-efficiency and product variation, which may lead to poor drug safety [3].

Fortunately, with the development of the concept of "Quality by Design (QbD)", there will be a significant transformation in pharmaceutical quality regulation, from an empirical process to a more scientific and risk-based approach [4].

HISTORY

Quality by design (QbD) is a concept first invented by the quality scientist Dr. Joseph M. Juran. Dr. Juran believed that quality should be designed into a product and that most quality crises and problems relate to how a product was designed in the first place. Woodcock defined a high-quality drug product as a product that should be free from contamination and reliably deliver the therapeutic response promised on the label to the consumer [5].

In 2002, the Food and Drug Administration (FDA) announced amendments to 'current good manufacturing practices and the pharmaceutical industries started creating a more systematic science and risk-based method [6,7] (Table 1).

Table No 1: List of regulatory guidance or other QbD-related activities

Agency	Guidelines/Activities	Month Year
USFDA	Pharmaceutical cGMP for the 21stCentury - A Risk Based Approach: Second Progress Report and Implementation Plan [6].	Sep 2003
USFDA	Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance [7].	Sep 2004
USFDA	Pharmaceutical cGMP for the 21stCentury - A Risk-Based Approach:Final Report [8].	Sep 2004
EMA	The European Medicines AgencyRoad Map to 2010: Preparing theGround for the Future [9].	March 2005
ICH	Pharmaceutical Development (Q8) [10]	Nov 2005
ICH	Quality Risk Management (Q9) [11]	Nov 2005
ICH	Pharmaceutical Quality System(Q10) [12]	June 2008
ICH	Pharmaceutical Development(Q8(R2)) [6]	Aug 2009
WHO	Quality Risk Management [13]	Aug 2010
EMA	Road map to 2015 [14]	Dec 2010
USFDA	Guidance for Industry: Process Validation: General Principles and Practices [15]	Jan 2011
EMAUSFDA	EMA-FDA pilot program for parallelassessment of Quality by Designapplications [16]	March 2011
ICH	ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation [17]	Dec 2011
EMA	ICH Quality IWG Points to consider for ICH Q8/Q9/Q10 guidelines [18]	Feb 2012
EMA	Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) [19]	March 2012
EMA	Guideline on Process Validation(draft) [20]	March 2012
USFDA	Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms [21]	April 2012
ICH	Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological entities) (Q11) [22]	May 2012
EMA-USFDA	EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel Assessment [23]	Aug 2013
EMA	Guideline on process validation for finished products - information and data to be provided in regulatory submissions [24]	Feb 2014

What is Quality by Design (QbD)

The concept of "Quality by Design" (QbD) was defined as an approach that covers a better scientific understanding of the critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment [8].

QbD is a systematic approach that helps in the development of pharmaceutical products by improving their quality. It begins with the predefined objectives and processes understanding and process control, based on sound science and quality risk management [9, 10, 11] (Fig 1).

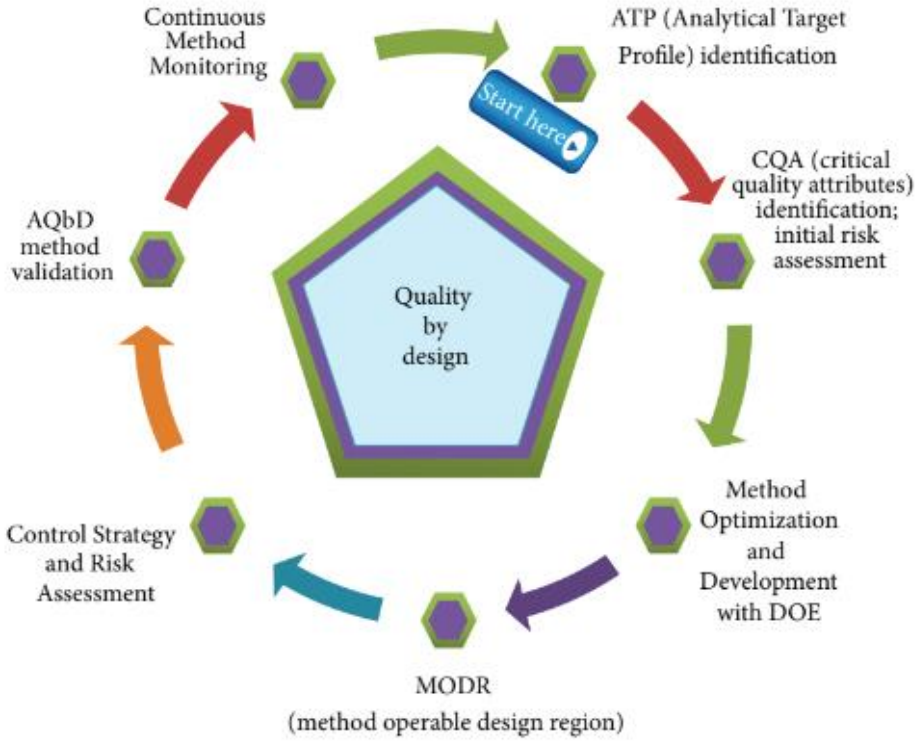


Figure no 1: Approach of QbD

Comparison between QbT and QbD

Quality by Test (QbT) [fig:2] was the only way to guarantee the quality of drug products before the FDA launched the current Good Manufacturing Practice [12, 13]. To clearly understand the manufacturing processes, FDA generalized Quality by Design (QbD) [fig:1] in the field of pharmacy.

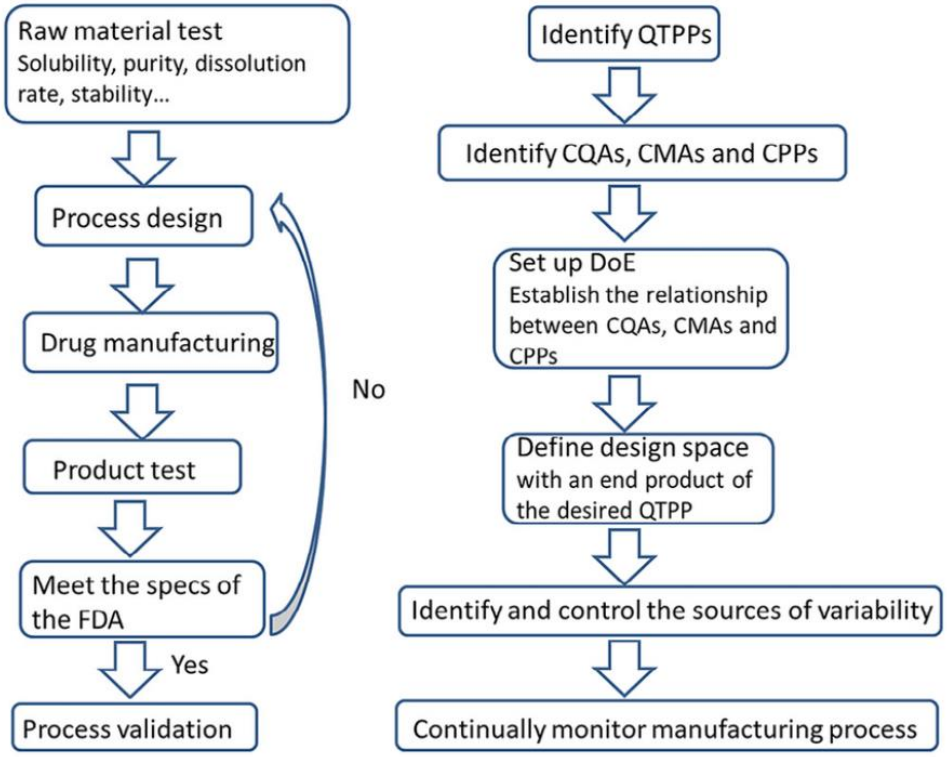


Figure no 2: Comparison of QbD and QbT

Characteristics

- It is a tool for focused and efficient drug development.
- Dynamic and systematic process.
- Relies on the concept that Quality can be built in as a continuum.
- It applies to Drug Product and Drug Substance development (chemical/biologics).
- It applies to analytical methods.
- Can be implemented partially or totally.
- Can be used at any time in the Life Cycle of the Drug.
- Always encouraged by Regulators [14, 15, 16].

Objective of QbD

- To achieve meaningful product quality specifications that are based on clinical performance.

- To increase process capability and reduce product variability and defects by enhancing product and process design, understanding, and control [17].
- To increase pharmaceutical product development and manufacturing efficiencies [18].

Elements of Qbd

As ICH guidelines define the QbD for pharmaceutical development. ICH Q8 defines the various elements of quality by design. These in combination with the enablers form the fundamental basis for the QbD approach to development. It involves the following key elements during pharmaceutical development.

- Define the Quality Target Product Profile
- Identify the Quality Attributes
- Perform a Risk (Assessment) Analysis
- Determine the Critical Quality Attributes and Critical Process Parameters
- Determine the Design of Space
- Identify a Control Strategy [19, 20]

Advantages

- A better understanding of the process.
- Less batch failure.
- More effective and efficient control of changes.
- It includes both product design as well as process development.
- A science-based risk assessment can be carried out by this approach.
- It is a robust process.
- Prevention of the rejection of batches [21, 22].

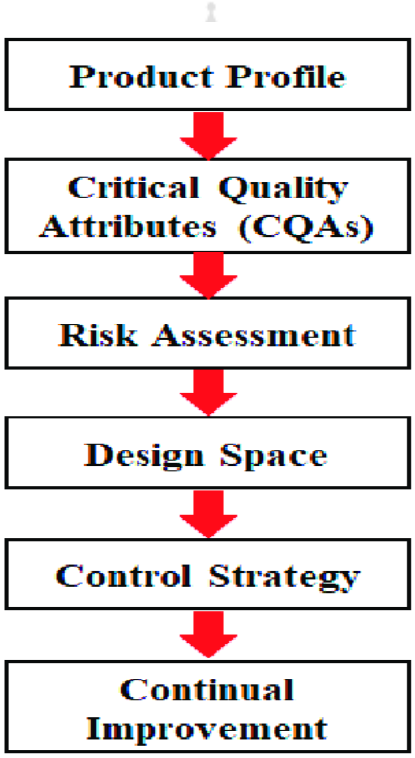
Disadvantages

- Internal unwillingness in the company.
- Lack of technology to implement.

- Alignment with third parties.
- Lack of belief in a business case. It is assumed that QbD would require more time to file generic products or that the number of clinical trials necessary to implement QbD for drug substance production [23].
- Lack of concrete guidance for industry [24].

Workflow of QbD

Process development and formulation design cannot become a product without a prescribed process. Process design is the initial stage of process development, in which an outline of the commercial manufacturing processes is documented, including the intended scales of manufacturing. The outline should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during process development are the QTPP and CQAs [25, 26].



A. Quality Target Product Profile (QTPP):

It is a prospective summary of quality characteristics of a drug product to be achieved, considering dosage strength(s) and container closure system of the drug product, together with the attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic

performance) and drug product quality criteria (e.g., sterility, purity, stability and drug release).

It facilitates the identification of what's needed/critical for the patient/consumer in the Quality Target Product Profile (such as Critical Quality Attributes, CQAs).

- Identifies risks and best approaches to manage.
- Uses tools/enablers in an optimized fashion (such as integration of QbD and biopharmaceutics)
- Generates and enables knowledge sharing.
- An iterative, learning, life-cycle process for optimizing decision-making and the therapeutic outcomes for the patient benefit [27].

B. Critical Quality Attributes (CQA):

It is necessary to identify the critical quality attributes, i.e., those defining purity, potency, and surrogate for Bioavailability Criticality, etc (Fig. 3). It is based on the impact of quality attribute/ parameter on the safety, efficacy & quality (manufacturability) of the product. The CQA element is very important, and it is associated with raw materials, intermediates as well as drug products [28].

Figure no 3: **Quality attributes of QbD**

C. Risk Assessment:

Risk assessment is a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. It is the first step of the quality risk management process; the other two steps are risk control and risk review. Risk control includes decision-making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. At the final stage, the output/results of the risk management process should be reviewed to consider new knowledge and experience.

Several tools are involved in the risk assessment:

- Failure mode effects analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault tree analysis (FTA)
- Hazard analysis and critical control points (HACCP) [29]

D. Design Space:

Design space is defined as the multidimensional combination of input variables (e.g., material attributes) and process parameters that have been demonstrated to assure quality. Movement out of the design space is a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval [30].

E. Control Strategy:

A Control strategy normally includes input material controls, process controls and monitoring, design space around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive process tests, such as blend uniformity or tablet hardness [31].

ICH Q10 characterizes a control technique as "an arranged arrangement of controls got from current item and procedure understanding that guarantees procedure execution and item quality. The controls can incorporate parameters and ascribe identified with medication

substance and medication item materials and segments, office and hardware working conditions, in procedure controls, completed item determinations and the related techniques and recurrence of observing and control." [32]

A QbD-based control strategy for the blending process is shown below (Fig 4):

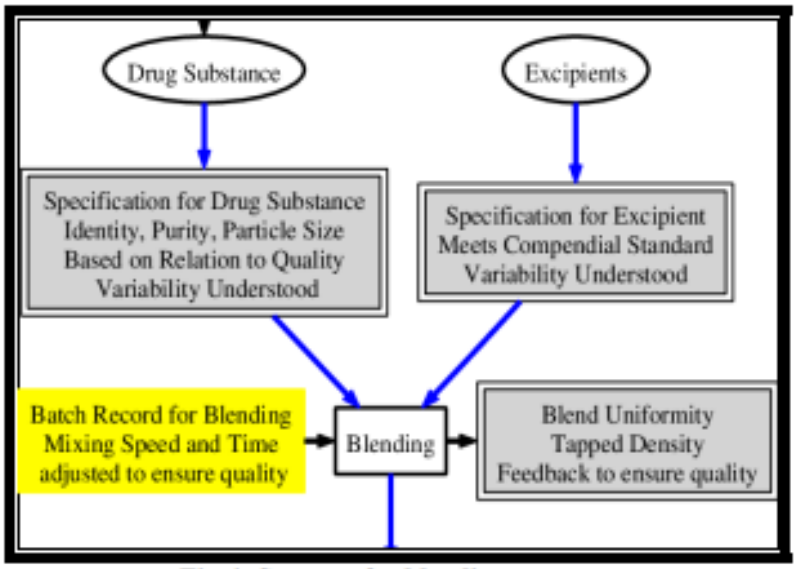


Figure no 4: Strategy for blending process

Tools of QbD

QbD has two components- the science underlying design and the science of manufacturing. Upon understanding the elements of QbD and the steps for QbD implementation, it is important to be familiar with the commonly used tools in QbD, including risk assessment, design of experiment (DoE), and process analytical technology (PAT) [33].

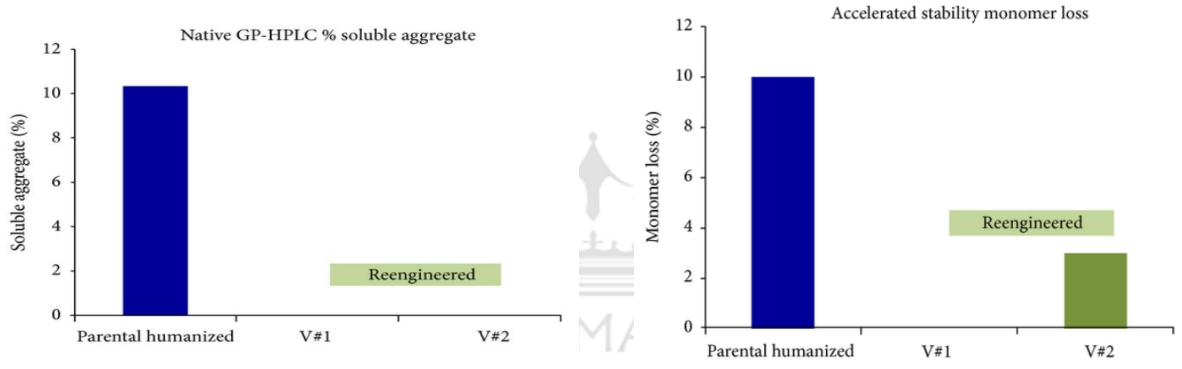
Regulatory Perspectives

Quality suggests client satisfaction in terms of service, product, and method. The client demands perfection in quality, reliability, low value, and timely performance. Client satisfaction is achieved in two ways in which, that is, options and free from deficiencies within the product. There are recent regulative developments that will cause a better desire for the integrated use of QbD and quality. Regulative agencies today emphasize not just “Quality by Testing” or “Quality by Chance” but solely on QbD [34].

Recent Developments in QbD

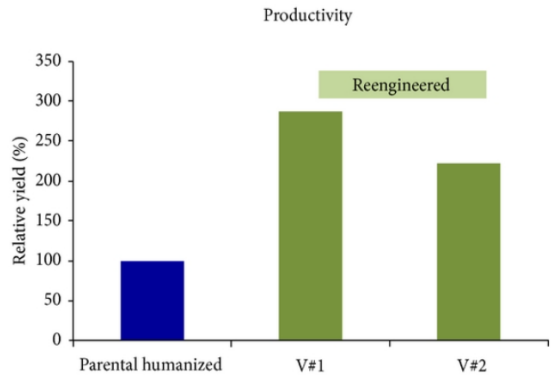
Engineering Antibodies with Improved Manufacturing Properties That Retain Biological Activity:

Reengineered antibodies display improved developability properties. Panel (a) shows the virtual absence of aggregation for both re-engineered variants under native conditions when assessed by GP-HPLC. Panel (b) shows that the percentage of monomer loss after incubation 2h at 60°C is significantly reduced in both re-engineered variants, and virtually eliminated in V#1, indicating improved stability upon reengineering. Panel (c) shows that productivity increases more than 2-fold in re-engineered variants. Panel (d) shows that biological activity is not negatively impacted upon reengineering, with one of the variants V#1 showing an increased affinity for the ligand.

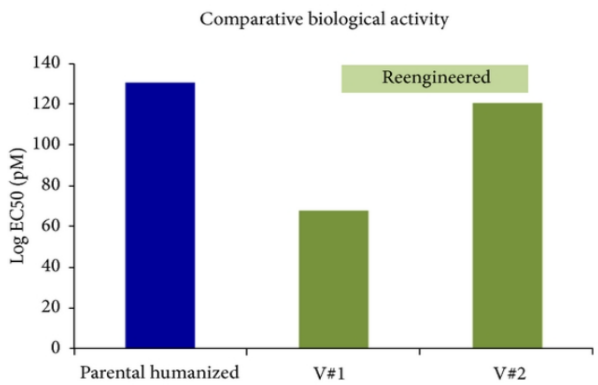


(a)

(b)



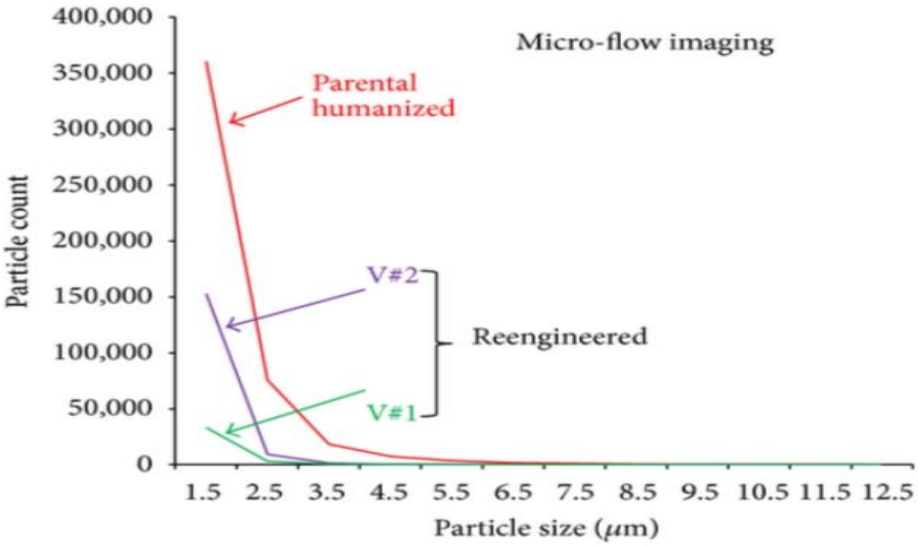
(c)



(d)

The number of subvisible particles, including protein aggregates, in the humanized anti-IFNɤ and both re-engineered variants, were characterized using Micro-Flow Imaging (MFI). V#1 and V#2 variants display a 5- to 10-fold reduction in the number of particles below 3.5µm

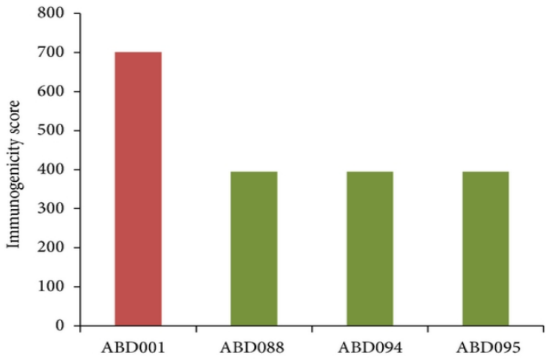
compared to the humanized anti-IFNɤ. Both reengineered variants contain no detectable particles over 3.5µm.



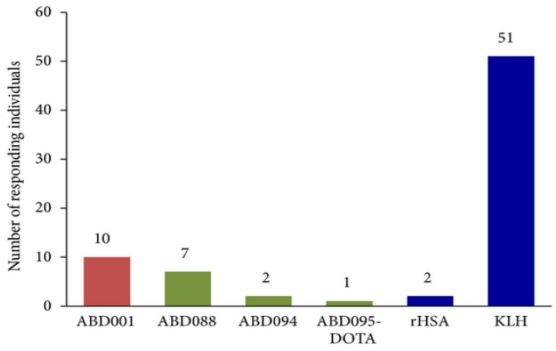
This project highlights how the application of computational and adequate analytical tools during the initial stages of drug development can lead to a significant improvement in the development of a drug candidate. It also exemplifies the implementation of reengineering to control or improve essential design criteria that can have a significant impact on product quality attributes, thus decreasing the likelihood of quality and safety issues that could creep in during later stages of preclinical and clinical development [35].

Selecting Half-Life Extension Products with Reduced Risk of Immunogenicity Risk:

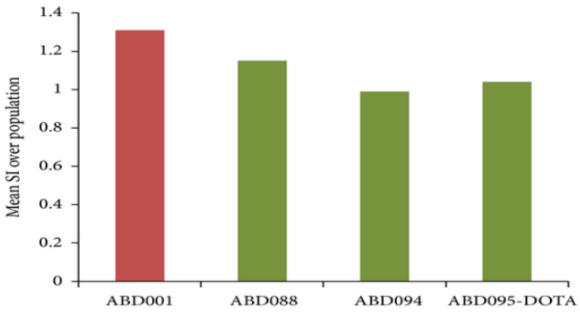
Immunogenicity assessment of ABD variants. (a) Predicted immunogenicity scores for three ABD variants and parental sequence ABD001. (b) Relative CD4+ T cell proliferation responses to ABD variants in a cohort of 52 donors, expressed as number of donors with proliferative responses to each of the ABD variants compared to negative (rHSA) and positive (KLH) controls. (c) CD4+ T cell proliferation responses to ABD variants in a cohort of 52 donors expressed as mean stimulation indices (SI) over the population. rHSA is used as a reference (SI = 1).



(a)



(b)



(c)

This project demonstrates the successful use of a combination of in silico predictions and in vitro immunogenicity assessment tools as suitable platforms to guide protein reengineering to remove T cell epitopes and to enable lead selection based on the relative immunogenicity risk of different candidates [35].

CONCLUSION

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data

meeting predefined criteria when operated within defined boundaries. QbD can be applied to the development and evaluation of analytical methods.

It is progressively turning into a significant and broadly utilized method in pharmaceutical item improvement. It is also a cost and time-efficient approach in design and manufacturing.

This paper explains the utilization of QbD including:

- Accentuation on the significance of the Target Product Quality Profile in articulating a quantitative execution focuses for QbD.
- Distinguishing proof of basic material properties gives a robotic connection of the item's quality to the assembling procedure.
- The job of the control technique as the component for steady usage of QbD components in training.
- An effective way to plan space is through the recognizable proof of non-interfacing process factors and their avoidance of formal test plans.

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