Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

Role of raw materials in biopharmaceutical manufacturing: risk analysis and fingerprinting

Anurag S Rathore, Deepak Kumar and Nikhil Kateja

Accurate fingerprinting of critical raw materials that have significant impact on process performance and product quality is a necessary precursor for implementation of QbD in process and product development. This article presents a review of major developments in this space in the last 10 years, with a special emphasis on those in last 5 years. A step by step approach for managing raw materials in the QbD paradigm has been proposed. We think that it is necessary for the biotech industry to better manage variability originating from raw materials if holistic implementation of QbD is to be achieved.

Address
Department of Chemical Engineering, Indian Institute of Technology, Delhi, India

Corresponding author: Rathore, Anurag S (asrathore@biotechcmz.com)

Current Opinion in Biotechnology 2018, **53**:99–105

This review comes from a themed issue on **Pharmaceutical biotechnology**

Edited by **Amanda Lewis** and **Nripen Singh**

https://doi.org/10.1016/j.copbio.2017.12.022

Introduction

Biopharmaceutical manufacturing, because of its complex nonlinear nature, is fraught with a myriad of process variations that can impact safety and efficacy of the drug. Since the introduction of concepts such as process characterization and design of experiments (DoE) over two decades ago, the biopharmaceutical industry has created and demonstrated considerable expertise in unravelling how the process affects the product. However, the role of raw materials (RM) has been somewhat overlooked and as a result has become the primary source of variability in process performance and product quality. The growing significance of the role of raw materials in the process control strategy is evident from the ICH Q8 guideline, which suggests that in the Quality by Design (QbD) framework the manufacturer must understand all sources of variability including the raw materials [1•,2].

Raw materials used in biopharmaceutical manufacturing are a diverse source of materials and include media components for cell culture and fermentation, fine chemicals for purification and chemical modification processes, and excipients used in a formulation of a final drug product [3]. They also include product contact materials like the plastic used in disposable bags. Variability in raw material can come from a change in a chemical or physical characteristic of the material [4]. This variability can affect characteristics and quality of drug product and potentially impact the product's safety, stability, and efficacy [5]. At times, this has resulted in major adverse events and even resulted in drug recalls [6]. For instance, presence of glass particulates in drug product have led to more than 20 product recalls in the last few years, including the recall of Procrit and Epogen injections [7].

Types of raw material variability

Variability in raw materials can be subdivided into three broad categories. The first category includes trace impurities that alter the quality of the biotherapeutic, either by directly modifying it or by catalysing its modification such as peroxides, aldehydes, reducing sugars, and catalytically active metal ions. The second category consists of trace impurities that are themselves toxic to humans, such as lead and aluminium. The third group comprises of microorganism contaminants (and their associated endotoxins) that lead to variabilities in the bioburden of raw materials and can cause severe immunological responses in patients [5]. Each of these require their own approach for monitoring and control.

Sources of variability

Cell culture processes used to make recombinant proteins use complex growth media. Although some cells can be maintained in a basal medium with no supplementation, majority of cells require addition of up to 100 components such as hormones, growth factors, vitamins, peptides, amino acids and hydrolysates to grow [8•]. Naturally derived media can contain a large number of compounds [9,10]. They also have micronutrients in trace amounts.

Variability may creep in the media because of several reasons. Degradation of raw materials, impurities, and contaminants present in the media; non-uniformity in milling and blending during manufacturing of large batches of media due to loss of micronutrients; and inconsistency of content levels and changes in raw material sourcing due to constraints in availability can result in raw material variability. Though there has been a shift

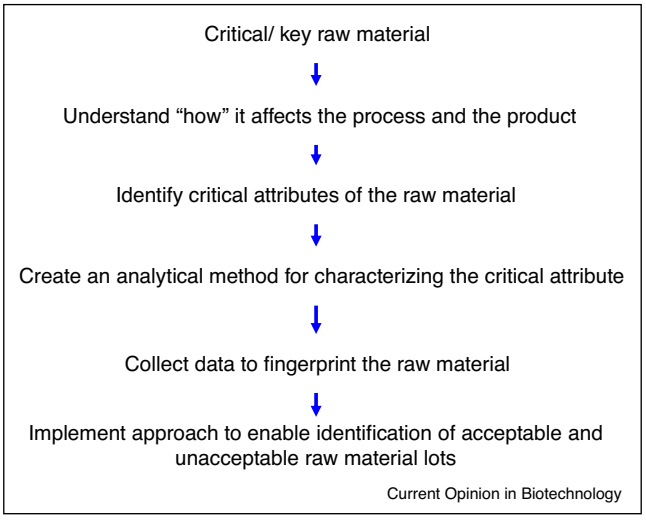
towards use of chemically defined media in the last decade, natural media continues to be used by the industry and continues to offer a challenge in maintaining a consistent product quality. Even chemically defined media have a complex composition which necessitates its characterization to achieve consistent process performance.

Inconsistency in excipient quality can have an adverse impact on drug product quality. Excipient-derived contaminants can be listed in the following categories — trace metals, peroxides, aldehydes, reducing sugars/polyols, and organic acids. The purity levels of these excipients may vary significantly and affect the product quality/stability to different degrees. Even with pure excipients, contaminants may be generated during storage through various degradation pathways [11]. Polysorbates, for instance, undergo autooxidation which can influence the stability of a biopharmaceutical product [12]. Leachates from the container/closure system have been shown to have significant impact on product quality as evidenced by recent issues associated with glass lamellae in glass vials [13], tungsten with prefilled syringes [14], silicon from vial stoppers or prefilled syringe barrels [15], leachates from filters [16], and shedding of nanoparticles from a filling pump's solution-contact surfaces [17,18]. Lot-to-lot variability in chromatography resins can also result in unanticipated changes in yield or product quality [19].

QbD based approach for managing raw materials

International Conference on Harmonization (ICH) in its Q7 good manufacturing practice [20], Q8 pharmaceutical development [2], Q9 quality risk assessment [21] and Q10 pharmaceutical quality system [22] guidelines have stipulated stringent requirements regarding product quality. Current practice for raw material analysis has been described in ICH Q7 Guideline [20]. The document states that materials used to prepare active pharmaceutical ingredients (both small molecules and biologics) need to have the identity of each batch confirmed on receipt and a Certificate of Analysis (C of A) provided from the supplier. Pharmacopeial and formulary monographs such as the *USP/NF*, *EuP*, *JP*, and *BP* provide standardized test methods for the most common and widely used materials. Manufacturers take various approaches towards testing compliance of raw materials. Some qualify a raw materials supplier by performing an initial detailed vendor audit followed by an annual qualification consisting of testing as per the pharmacopeial monograph on three lots of raw material. If the qualification lots test successfully, then subsequent material shipments will require only monograph identification testing. However, companies that take a more conservative approach to raw materials release require full monograph testing for each lot of supplied material [16]. In addition, the supplier must be qualified as suitable based on audits of their facility, their analytical results must be confirmed to be reliable, and a sampling plan is needed for each incoming material [19].

Figure 1



Managing raw materials in the QbD paradigm.

A key challenge is the relatively large number of raw materials that are used in biopharmaceutical manufacturing (typically > 100). To effectively deal with such a large number of raw materials, a multistep Quality by Design (QbD) based approach has been proposed [23•,24•] (Figure 1). It is recommended that this evaluation be performed at every major milestone of product development (First in Animal, Phase I, Phase II, Phase III, Validation). Although an arduous task when performed the first time, the effort significantly reduces in the following times as most of the raw materials are the same amongst products of similar kind (e.g. monoclonal antibodies):

- A risk assessment is performed encompassing all raw materials used in the process. There are a number of different risk assessment tools available in a range of detail and complexity, and it is important to use a methodology suited to the purpose of the assessment [24•]. Appropriate stakeholders including process development, manufacturing, quality assurance, and quality control are included in this assessment. The team discusses if the raw material is likely to impact the process performance and if it is likely to impact product quality. Those who are likely to impact both are termed as critical raw materials, those who just impact the process and not the product are termed as key raw materials, and those who are not expected to impact either are called as non-key raw materials [23•].
- Critical raw materials are therefore thoroughly characterized and their mechanisms of process interactions