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Defining quality attributes to enable measurement assurance for cell therapy products

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Cell therapy products (CTPs) represent a broad class of therapeutics poised to move toward commercialization due to recent discoveries, technological advances and increased investment. The industry is racing to develop, manufacture and translate promising therapeutics for treating a range of diseases and injuries but must address significant manufacturing and regulatory challenges, including the development of robust analytical methods and assays. Measurements for producing high-confidence data underpin the decision-making process from research and development (R&D) to regulatory submissions, including understanding and establishing critical quality attributes (CQA) for candidate CTPs. In the United States, the Food and Drug Administration defines CQA as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" [1]. Each CTP will likely have its own set of CQAs based on the products' intended use and/or mechanism of action (MOA). CQAs are generally considered to be *quality attributes* tied to the intended clinical response or MOA. Here, we focus on the process for defining quality attributes and designing appropriate measurements for a given cell preparation (during manufacturing or as a product), regardless of its association with clinical response or MOA.

It is well recognized that measurements for quality attributes are influenced by variability in the analytical method and variability in the cell preparation. CTPs are composed of dynamic living entities whose properties can fluctuate with time. CTPs also contain a complex mixture of biological and non-biological materials that support the living cells, and variability may come from changes in these components. Changes in a processing parameter, sample handling procedure and reagent can also affect the quality attributes of the CTP. Inability to separate actual changes in the sample from variability in the analytical method hinders the subsequent decision making in R&D and translation. As such, many are eager to develop industry standards to reduce variability in analytical methods as well as in manufacturing processes. Some have called for the development of standard methods or reference materials, including reference cells, to enable comparability. Efforts are underway to address technology challenges associated with developing a stable and homogenous (sample-to-sample consistency) reference cell that is fit-for-purpose. Discussions for documentary standards have focused on those that address common, industry-wide (horizontal) challenges for analytical methods and manufacturing and have avoided highly restrictive standards that may unintentionally hamper the development of this rapidly evolving industry.

We propose that a generalized framework for designing and conducting cell measurements is needed to improve the overall measurement confidence. Components of this framework include (i) clearly defined quality attributes, (ii) well-designed measurements that are fit-for-purpose, (iii) robust measurement processes with built-in measurement assurance, and (iv) appropriate documentation, reporting and communication. This commentary focuses on the necessary first two steps of this framework. The measurement process may include sample collection, sample preparation, sampling, measurement or data collection and data analysis. Strategies for improving the measurement assurance, such as through process controls, reference materials and design of experiments, were examined at a 2015 National Institute of Standards and Technology Workshop [2,3]. Documentation,

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reporting, and communication of measurement results and key meta-data are critical for interoperability, but are beyond the scope here.

Establishing well-defined quality attributes through clearly defined components

For a given cell preparation, one might ask, "What is in the vial or container at this moment in time?" to identify it or compare it with another cell preparation. Ideally, the full list of ingredients should be known to properly answer this question. If the identity and quantity of each ingredient is known and the function of each ingredient is well understood, it may be possible to predict the performance of the product with a high confidence. For a complex cell preparation, it is generally not possible to list all ingredients. Instead, CTPs are commonly described with a set of quality attributes (e.g., identity, quantity, viability, purity, sterility, stability, biological activity). Strict definitions for quality attributes are impractical due to the uniqueness of each CTP.

One strategy to define quality attributes for a specific CTP is establishing clearly defined and quantifiable components. In this process, we bin the contents of a cell preparation into the following broad categories: cells, potential impurities and suspension medium (Figure 1), where each category can be further divided into sub-categories. For example, potential impurities can be divided into adventitious agents (e.g., bacterial and viral contaminants), biological impurities (e.g., cellular components), and non-biological impurities (e.g., extractables, leachables and other non-biological contaminants). Suspension medium is a complex mixture that includes biologically and chemically derived ancillary (raw) materials that could be intentionally added to the preparation or present as by-products from the manufacturing process. Similarly, cells can be further divided according to user-defined criteria. Each component can then be examined individually and with respect to other components, particularly when designing an appropriate assay in which multiple components may contribute to a measured response.

Ambiguities associated with applying criteria to a heterogeneous cell population (illustrated as gradients in Figure 1) make the process for clearly defining the cell components critical. A cell population can be defined by its genomic profile, function, morphology, viability and specific biomarker, for example. As such, the quality attribute should be defined explicitly to reflect the specific cell population of interest, particularly when a quality attribute has multiple possible definitions. The user may have to establish specifications for deciding whether a cell is or is not a part of the defined population, particularly for

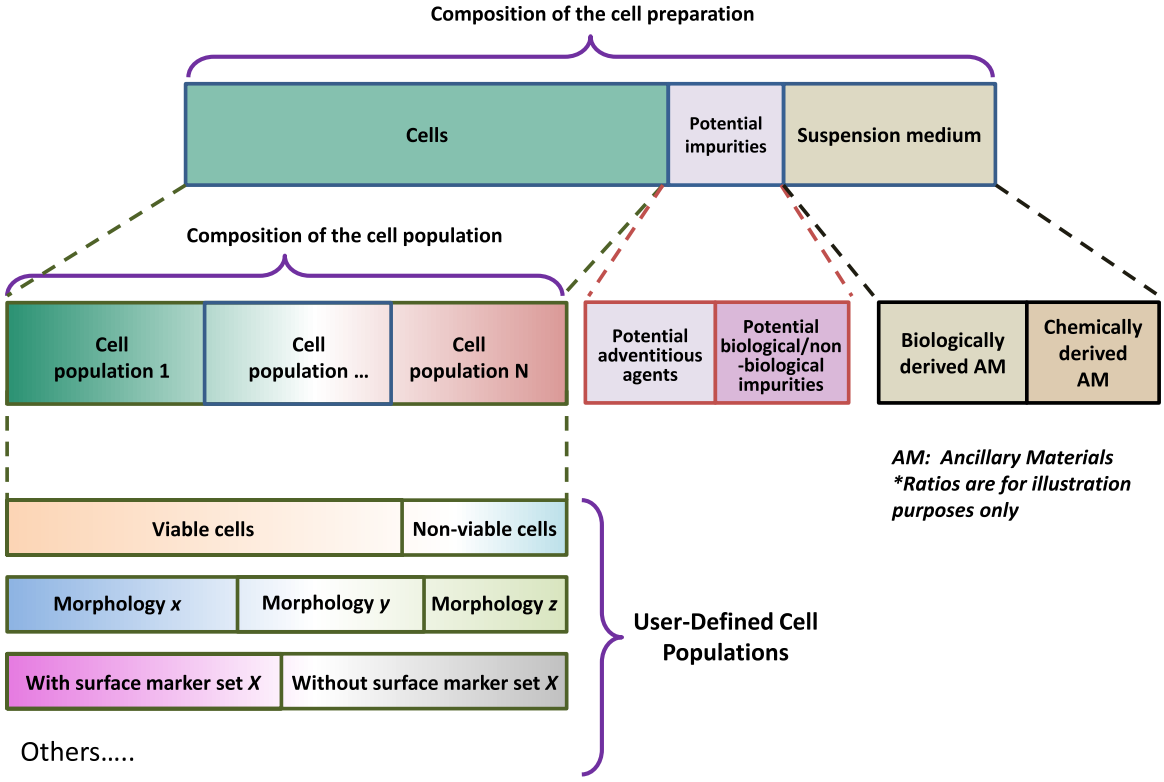

Figure 1. Establishing clearly defined and quantifiable components and sub-components for a cell preparation at a given time.