Un-characterized and *un-characterizable* attributes of macromolecular excipients.

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Macromolecular excipients are unique in that each (macro)molecule or polymer chain can chemically differ significantly from another. However, these differences may not be detected across different lots or different samples because the analytical methods used to characterize such samples typically can only detect the *average* of the different individual molecular chemical attributes. As an example, the percent substitution of hydroxypropyl groups in the macromolecular excipient, hydroxypropyl cellulose (HPC), is the *average* molar ratio of hydroxypropyl groups to anhydroglucose groups in the sample. This result does not preclude one subpopulation of polymeric HPC chains being sparsely substituted (with HP groups) and another subpopulation of polymeric chains being densely substituted. As a result, it may be possible that different lots of macromolecular excipients that nominally conform to certain set specifications (degree of substitution, molar substitution, % content of hydroxypropyl groups) may yet contain subpopulations, whose chemical attributes may differ widely from the average, and also differ widely from subpopulations in other lots. Such a scenario can *always* exist in the case of macromolecular excipients derived, harvested or modified from natural sources such as the cellulosic polymers and their derivatives, gums, starch, gelatin etc. This is especially important when the excipient manufacturer changes the source of raw material used to manufacture the excipient and/or the manufacturing process, when lots are procured from different manufacturers, or when different grades of raw material are mixed together. Finally, because the most widely used excipients (by volume) are produced using continuous processing, some process variability over time is inevitable. As an example, the complexity of analysis of a naturally occurring macromolecule, Inulin, can be ascertained by a read of the review by Barclay *et al.* which appears in this issue.

Analytical method limitations (for macromolecules), thus force the categorization of such attributes as being 'un-characterizable'. Such un-characterizable attributes, as related to an individual polymer chain or macromolecule, may also include the following:

1. The molecular weight between crosslinks (in the case of crosslinked polymers such as carbomers) may affect the release rate profile of embedded active molecules.

2. Where the final step in manufacture of the polymer involves deacetylation to various degrees, such as in the case of Chitosan and Polyvinyl alcohol, the positional 'randomness' of residual acetyl groups on the polymer backbone may affect aggregative or surface active properties or propensities of the final product.

3. The length of a 'block' in a block copolymer (such as the polyoxyethylenepolyoxy-

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propylene block co-polymer) may affect surfactant associated properties.

4. The ratio of different sugars in the polymer backbone or the degree of branching (such as in the case of polysaccharides) may affect multiple functional properties including viscosity, agglomeration profile, shear thinning (or thickening) behavior and propensity to degrade.

Un-characterized attributes, on the other hand, include those attributes which are not specified in the compendia and which the end-user may not test routinely on incoming raw material. For example, several macromolecular monographs do not yet specify the molecular weight, molecular weight distribution or polydispersity, yet these attributes can play a major role in several performance related properties. The polydispersity index, for example, can potentially be used as a first approximation surrogate for the uniformity of hydroxypropyl substitution between polymer chains.

Because quality-by-design (QbD) product development processes typically gather data using a representative range of excipient lots and because a dosage form will typically incorporate millions of individual polymer chains, the limitation of being able to determine only an *average* for a given excipient attribute (uncharacterizable attributes), at first glance, may not seem detrimental to product quality and/or performance and may assume lesser significance. On the other hand, the certainty that excipient lots used to generate QbD data will indeed be representative of the range becomes questionable precisely because some chemical attributes of the excipient macromolecule are un-characterizable at the molecular level.

This should not be construed as a proposition to impose new guidelines or regulations for excipients to be characterized by analytical methods that do not yet exist (or are limited in what they *can* characterize), or to devise new paradigms for failures that can (or paradoxically, cannot) be attributed to such "uncharacterizable attributes" of macromolecular excipients, because such failures may admittedly be few and far between. It is highly desirable that Industry and Academia co-operate to discover and develop analytical methods for such uncharacterizable attributes.

Having said that, there can be no doubt that, it is necessary to better characterize excipient macromolecules. If differences in performance are construed as originating from differences in un-characterizable and/or un-characterized attributes, a thorough understanding of macromolecular excipient composition and how it relates to performance is preferable to indirect assessment via physical tests that may only relate to restricted applications of the excipient, or to QbD analysis, where the 'edge of failure' may be highly correlated with such un-characterizable attributes. To quote a statement attributed to Lord Kelvin "I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it, but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind…". In the case of macromolecular excipients, monograph modernization to include as yet un-characterized attributes, and attempts to better characterize the material on a molecular level perhaps using 'derivative functions' of the average attribute value(s) may yet obviate the need for performance related testing.