Considerations for setting specifications for excipients of natural origin.

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A specification for an excipient establishes the criteria to which the excipient should conform so as to be considered acceptable for the manufacture of medicinal products. A specification usually contains of a list of tests, references to analytical procedures and appropriate acceptance criteria for the tests described. If the substance meets the acceptance criteria when tested according to the listed or equivalent analytical procedures, then it conforms to specification.

Excipients derived from natural sources are remarkably diverse, ranging from non-volatile oils (palm, olive), volatile oils (anise, eucalyptus), gums (acacia, tragacanth, xanthan), proteins (gelatin, albumin), carbohydrates (starch, cellulosics, cyclodextrins), clays (bentonite, talc), waxes (candelilla, carnauba), juices (cherry), hydrocarbons (paraffin, mineral oil, microcrystalline wax), exoskeleton components (chitin) and secretions (shellac, acacia, yellow wax). They can be of plant (fruit, seed, stem, flowers), animal and insect (wool, egg yolks, resinous secretions), mineral or of human or recombinant (albumin) origin. Furthermore, some of these products can be processed further such as be refined, hydrogenated, bleached, de-polymerized, hydrolyzed (by enzymes, heat or chemicals) or denatured.

Some representative general attributes or criteria which could serve as specifications for such compounds may constitute (for fats and oils) identification tests, fatty acid composition (FAC), saponification value, iodine value, maximum unsaponifiable matter, acid value, peroxide value, heavy metals, melting point, free fatty acids and water. Specifications for natural polymers may constitute identification tests, microbial limits, loss on drying, acidity/alkalinity, heavy metals, water absorption, viscosity and molecular weight.

Setting specifications for excipients derived from natural sources presents challenges for several reasons:

1. Due to natural, seasonal and/or geographical variations in composition of the material, it may be necessary to specify wide ranges of attributes acceptable from

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the viewpoints of safety, functionality and cost effective extraction. Additional controls may be required so that there is reasonable assurance of the excipient not being adulterated, not processed improperly or incompletely, and assuring fitness for purpose in specific applications.

2. Functionality and/or safety of the excipient can be influenced by seemingly non-related/obvious attribute(s). For example, metal ions bound to allostearic site(s) in proteins can influence the properties at catalytic site(s). Quantification of metal ion binding compromised folding variants of such proteins hence represents an important specification for consistent functionality.

3. The distribution of repeat units and/or functional groups on a polymer of natural origin or processed chemically can significantly affect crystallinity or the proportion of crystalline to amorphous regions. Non-random distribution of functional groups and/or 'block polymeric regions' can alter functional attributes of the excipient such as rheology, swelling characteristics and emulsification efficiency. Therefore, standard specifications may not adequately control lot-to-lot variability or functional properties. It is possible to measure a 'randomness index' of functional groups or blocks using nuclear magnetic resonance spectroscopy.

4. Advances in genetic engineering and biotechnology have made it possible for plant species to produce material, in particular, oil of predetermined fatty acid composition tailored for specific markets. For example, canola and soybean oils can now be 'designed' to contain a lesser proportion of saturated fatty acids. In the absence of a link between the species and the general make up of the oil it produces, it becomes increasingly difficult to set nomenclature specific specifications.

Incorporation of compositional profiles makes it economically and technically difficult to conform to by artificial means. For example, the preference for natural biochemical processes to link saturated fatty acids to positions 1 and 3 and unsaturated fatty acids to position 2 of glycerol can be exploited via the lipase test to detect the presence of esterified oils in pressed oils. The direct correlation between the ratio of 1,2 and 1,3 diglycerides with free acidity that occurs naturally can be used to detect fraudulent de-acidification. An increase in the content of trans-isomers can be used as a test to detect adulteration by de-sterolized foreign oil. The determination of the composition and content of sterols from unsaponifiable matter serves as a further test for adulteration..

For proteins where quantification of nitrogen serves as a primary ID or assay, testing for the ratio of this element to other elements or functional groups in the molecule provides a better characterization in conjunction with detecting adulteration. This paradigm of testing ratios of two or more elements and/or functional groups may be extended to natural polymers and 'small molecule' natural substances as well. Such tests for selected attributes, particularly when used in combination, provide a robust and unique specification for that material.

Specifications for a particular material can change over time. Such changes usually occur because improved quantification techniques turn out to be more universal in application, more sensitive, and able to detect multiple analytes simultaneously. Changes to specifications are also necessary to enhance their usefulness in preventing economic adulteration. Some examples may include the dilution of expensive vegetable oils with cheaper oils or the

addition of lower grades to virgin grades. Another example is the spiking with desterolized oil that is likely to be higher in trans-isomer content. Because there is no a' priori method of knowing whether adulterants will be non-toxic, economic and unsafe adulteration may not be mutually exclusive and specifications must change to address ever more insidious methods of adulteration.

Setting, non-onerous and relevant specifications for excipients derived from natural sources is further complicated by the fact that precedents for setting specifications for such novel materials are few and the range of properties that are critical to their functionality are greater. Since these excipients have the potential to influence clinical outcomes, it may be that the number of attributes required to set specifications could be considerably greater. Some examples of such attributes include the determination of three dimensional structure (tertiary and quaternary), molecular weight and polydispersity, randomness index of substituted or block-polymeric domains, pattern and degree of glycosylation, isoforms, covalent aggregates, allosteric substrate compromised folding variants, and free thiols.

Excipients of natural origin pose a special challenge in setting specifications. More work needs to be done in this field.