Inclusion of relevant tests in the Pharmacopoeia to improve supply chain integrity.

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Editorial

Raw material compliance with compendial specifications, and supply chain integrity, are necessary but insufficient requirements for patient safety. The former ensures the identity of the material, absence of toxic and unsafe components, and fitness for the intended route of administration. The latter ensures that the material has been manufactured and distributed in accordance with Good Manufacturing and Distribution Practices. However, compliance with compendial specifications alone does not guarantee 'excipient pedigree'. As evidenced by the FDA Monograph Modernisation Initiative, for some excipients, compendial ID tests and assays can themselves be inadequate. Neither compliance, nor supply chain integrity, can ensure fitness for purpose in a particular application.

Because the Kjeldahl compendial methods for the determination of total nitrogen are not specific to the raw materials, compliance with the specification for nitrogen content could be artificially enhanced by economically motivated adulteration with nitrogenous materials such as melamine, a compliance enhancing additive, but injurious to patient safety. Complementing the Kjeldahl method with a more protein-specific method such as Ninhydrin provides a better likelihood of detecting adulteration with non-protein nitrogen sources such as melamine or cyanuric acid. Tests that can quantify ratios of two or multiple functional groups in the same molecule, such as the ratio of carboxylate to amino acid in proteins, provide a good conceptual starting point for designing better and more specific identification tests to make it harder to adulterate the material.

Unfortunately the hastily assembled list of at-risk materials subject to the absence of melamine testing does not distinguish between those materials where a lower nitrogen content is the mark of quality (e.g. guar), from those where the desired higher nitrogen content drives economically motivated adulteration.

Oversulfated chondroitin sulfate is another compliance enhancing additive which when added to heparin can be fatal for the patient. Such economically motivated adulteration exploits the reliance on current inadequate specifications alone without ensuring supply chain integrity.

Could better specifications tests deter economically motivated adulteration? As an example, consider fats and oils, which can be adulterated in a number of ways, including but not limited to:

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1. Decamphorated eucalyptus oil (source adulteration)

2. De-acidified oils (mislabeled, fraudulent increase in shelf life)

3. De-sterolized oils (mislabeled, adulteration)

4. Mixed or fractionated grades (grade adulteration)

5. Phorbol esters from *Jathropa curcas* seed oil (biofuel feedstock or constituents used as pharmaceutical excipients or adulterants)

6. Addition of cheaper volatiles to essential oils (constituent adulteration)

How might compendial specifications be improved to detect adulteration in this class of excipients? Some possibilities include quantifying the ratio of constituents, including the ratio of sterols obtained from unsaponifiable matter. These may be specific to a particular species, be a characteristic of the refining process (Stigmastadienes form from sterols during refining) or indicate adulteration with similar oils. For oils whose triglyceride compositions significantly overlap, stable isotope $^{13}C/^{12}C$ ratio mass spectrometry has been shown to detect adulteration, as do chemometric methods. Other options might include the pattern of minor constituents, the ratio of saturated fatty acids on the 2-carbon position relative to those at the 1 and 3 positions of triglycerides, and the determination of molecular weight (as opposed to viscosity).

Developments in chemometric methods enable source identification for naturally sourced excipients using principal components analysis (PCA) or similar dimensionality reduction techniques. Enantioselective gas chromatopgraphy may be used to detect the addition of cheap volatiles to essential oils (such as the addition of linalool and linalyl acetate to bergamot or lavender oil).

For persistent contaminants such as diethylene glycol it may be necessary to include a specific contaminant test as part of the mandatory ID testing of at-risk materials in order to ensure patient safety. However, while effective against known contaminants, this approach cannot protect against the next compliance enhancing additive, chosen to dupe those who still rely on inadequate specification alone (cheapest source) and do not ensure the integrity of their supply chain. Global registration of all excipient manufacturers under FDASIA is a good complement to counter this weakness.

As recognized by the FDA Monograph Modernisation Initiative a better approach would be to improve the specificity of raw material ID tests and assays, in tandem with tightening supply chain security, rather than bolting on an accumulation of specific contaminant tests after the event. Improving compendial identification tests are key to shifting from a reactive to a proactive deterrence of raw material adulteration. Developments in spectral analysis, chemometrics, or simply using a combination of tests e.g., the functional group ratio test proposed above provide an attractive combination of portability, in-field utility, rapid analysis and increasing specificity for ID testing. Simultaneously it would be more difficult to, engage in economically motivated adulteration, divert or counterfeit materials, and additionally it would strengthen the supply chain integrity.

Because current compendial methods are not sufficiently robust, specific or rapid enough for many excipients, compliance with specifications is a complement, not a substitute for supply chain security. Compliance with specification is the goal of those practicing economically motivated adulteration and is the Achilles heel of inadequate supply chain integrity. Reliance on specification alone, a lowest common denominator approach, inevitably leads to introduction of undesirable materials in the supply chain. Multiple and more specific tests will hinder economically motivated

adulteration. As recognized by FDASIA, other aspects of supply chain security, such as registration, qualification and on-site auditing of vendors are necessary. Over reliance on current pharmacopoeial compliance not only jeopardizes the supply chain but also contributes to the relatively low manufacturing performance of the pharmaceutical industry compared to other regulated sectors. Fitness for purpose in a particular application would also benefit from improved specification as well as supply chain security. Specifications should be improved, supply chain oversight tightened, and *caveat emptor*!