Establishing purity is a first line defense in making sure product specifications are met.

By Paula Brown & Joseph Betz

This month’s column was co-authored by Dr. Joseph Betz, Office of Dietary Supplements, U.S. National Institutes of Health. He can be reached by E-mail: BetzJ@od.nih.gov.

Paula Brown, Program Head of the Natural Health Product Research Group (NRG) at BCIT, directs a multi-disciplinary research facility providing fundamental investigations on product quality, safety and efficacy. In establishing NRG, Ms. Brown has created the capacity to support industry through the entire continuum, from grower to manufacturer, ensuring product integrity is maintained. An active volunteer, she is a founding member of the NHP Research Society of Canada, a nonprofit group dedicated to supporting and promoting scientifically rigorous research and education on NHPs. Ms. Brown is also General Referee for the AOAC Dietary Supplements Methods Committee. She can be reached at BCIT, 3700 Willingdon Avenue, Burnaby, BC, Canada, V5G 3H2, E-mail: pbrown@bcit.ca; Website: www.bcit.ca/appliedresearch.

‘What’s in a name? That which we call a rose / By any other name would smell as sweet’—William Shakespeare, Romeo and Juliet, act II, sc. ii

Were you to buy a dozen roses and get them home to find 11 roses and a daisy, what would your reaction be? Embarrassment? Outrage? I paid for a dozen roses! Worse, what if you were violently allergic to daisies? This is no longer a simple economic deception, now there’s a health hazard. Let’s step back a bit. What if you had bought 12 dozen roses, and there was one daisy. Not so bad from an economic perspective, but still a health hazard for the unlucky allergic individual.

In the first case, the bundle contained 92% roses and only 8% not roses, yet we would have little difficulty recognizing it was not the commercial entity known as “a dozen roses.” In the second case, the gross of roses contained 99.3% roses and 0.7% not roses. Is it still a gross of roses? If we were florists, would we accept this lot of flowers from our wholesalers? Now let us switch to the world of dietary supplements. What if you were a bulk purveyor of rose petals, rose hips or (shudder) powdered bulk floral rose parts and were buying 10 kilograms of raw material?

‘Rose is a rose is a rose is a rose.’—Gertrude Stein (1874-1946) Sacred Emily

Except, of course, when it isn’t a rose. Nothing in nature is 100% pure. Purity as percent of an extraneous plant or other foreign material is a tricky concept. On the macroscopic level, were you to be handed a single red rose, you’d have little difficulty identifying it as such. However, on another level the question might not be so easy; for example, was the rose treated with pesticides? Are there residues present? How about that aphid working its way up the stem? One could easily conclude that the rose is still a rose and that extraneous matter has nothing to do with its identity, but under the new dietary supplement GMPs, if you wished to grind it up, you’d need a descriptor for extraneous material. In this case, that descriptor would be referred to as the purity specifications.

The dietary supplement GMPs require that specifications be set for identity, purity, strength, and composition, and that methods employed to test against specifications be scientifically valid. Approaches to these requirements include panic, writing your own specifications and establishing appropriate tests, or adopting specifications and tests set out by other organizations. Compliance with specifications in official compendia is voluntary, but can aid in writing specifications or provide a framework for quality control if adopted as published.

‘All June I bound the rose in sheaves, Now, rose by rose, I strip the leaves.’—Robert Browning, One Way of Love

Virtually all modern pharmacopeias set specifications for undesirable contaminants (mycotoxins, microorganisms, pesticides and toxic elements). Each monograph defines permissible limits for adventitious agents, and pharmacopoeia generally devote one or more general chapters to laying out detailed protocols for determining whether specifications are met. For instance, the subsection on purity in the Japanese pharmacopoeia monograph for “ephaedra herb” states, “The amount of the woody stems contained in Ephedra Herb does not exceed 5.0%.” And in a subsection labeled Foreign Matter, “that Ephedra Herb does not contain stems of Equisetacea or Gramineae plants, or any other foreign matter.” These specifications define the identity of the material, “Ephedra Herb,” and include not only the plant but also the plant part. Interestingly, not all botanical monographs set purity specifications; perhaps because purity problems do not exist or no one has collected data on common foreign matter for those plants.

Specifications will depend on several factors. One is cost. How clean can one expect a good quality material to be and still be affordable? Another is safety. If
the weed is digitalis, manufacturers shouldn’t tolerate much or they’ll poison their customers. A few grass stalks, on the other hand, are probably not going to cause adverse toxicological or economic effects. There’s also a “yuk” factor that may be aesthetic or pose a genuine public health threat. A few aphids are probably okay as long as the consumer doesn’t see them. “Yuk!” However, dung beetles or carrion flies would probably attract the attention of FDA since both can be disease vectors.

‘I am not the rose, but I have lived near the rose.’—Geoffrey Chaucer, The Roman Iliad

When we purchase our supplements from nice, clean retail outlets, it is easy to forget the herbs in those pristine bottles grew in dirt, and dirt is loaded with microbes. Raw herbs are teeming with mostly harmless environmental bacteria; however, pathogens in the environment can be introduced during handling and processing. That’s why all GMPs require employees to wash their hands and why compliance with Good Agricultural Practices (GAPs) is a good idea. Processing may dramatically reduce bacterial counts, but there are likely to be some residual microorganisms. Steps must be taken to keep bacteria from being reintroduced into the product stream and to prevent their proliferation in processed products.

Recommendations by compendia for acceptable microbial loads range from too stringent to not stringent enough. This is probably due to a lack of real world data on the expected microbial load for clean, high quality material. One common specification in the FD&C Act and in various compendia is zero tolerance for pathogens. In writing the GMPs for dietary supplements, FDA properly mandated that specifications be set and testing be performed for potentially harmful impurities when there is reason to believe such testing is necessary.

There is no blanket requirement to test mycotoxins—natural toxins produced by several species of common fungal genera such as Aspergillus, Penicillium and Fusarium. They may occur as endophytes within plants in the field or as spoilage microorganisms, proliferating during improper storage. Presence of the fungi may indicate mycotoxin presence, but in many cases the commodity itself can inhibit production. The burden is placed on the manufacturer to determine whether or not mycotoxins are likely to be a problem in their raw material.

‘Life is like a rose garden - Watch for the thorns and keep the pest dust handy’—Anonymous

The topic of pesticides is both difficult and easy. For all practical purposes, the presence of virtually any pesticide in herbal material renders the herb adulterated. See? Easy! Provisions in the FD&C Act state that poisonous or deleterious substances added to food are subject to food additive regulations that set limits or tolerances for their presence. Pesticide tolerances are set by the U.S. Environmental Protection Agency (EPA), and are specific to both the commodity and the pesticide. For example, quintozene is a perfectly legal pesticide for broccoli within EPA tolerance limits. However no EPA tolerance was ever established for quintozene in ginseng, and in the absence of a set limit federal law mandates zero tolerance.

This situation puts manufacturers in a bind since few tolerances for herbs in commerce exist. The unfortunate part of the pesticide dilemma is that EPA sets tolerances based on toxicological and other data as submitted to EPA by those interested in establishing the tolerance of a particular pesticide for a particular crop. For large commodities that use billions of dollars worth of pesticide, the pesticide companies themselves commission the toxicology studies so they can sell more pesticide. For minor commodities, like most herbs, no one is willing to bear the research expense to establish the tolerance.

‘The rose distils a healing balm’—Thomas Moore, Odes of Anacreon, Ode LV

Help is on the way. One way to avoid introducing adulterated product into the marketplace is to be in compliance with tolerances. The key is to have tolerances with which to comply. The U.S. and Canada are currently pursuing an approach to setting tolerances called “Crop Grouping.” This approach establishes maximum residue limits for groups of crops based on residue data from representative commodities, thereby enabling development of pest control options for many crops, while facilitating trade in those commodities.

Goals of the initiative include updating the crop group regulations to incorporate more than 500 “orphan crops” (both domestic and imported), and developing new crop groups to facilitate harmonization and simplification of commodity terminology for establishing tolerances. Key organizations in this effort include the American Spice Trade Association, the Canadian Coalition for Herb, Spice and Natural Health Products, and the IR-4 Project at Rutgers University.

‘Discipline trains you to put up with disappointments, every rose has a thorn.’—Sri Sathya Sai Baba

One of the biggest thorns in the supplement industry’s side has been media attention focused on a nauseatingly large number of “herbal” formulas found to contain pharmaceutical adulterants. These include numerous recalls involving male sexual enhancement products illegally adulterated with sildenafil, or worse, with bathtub knockoffs whipped up by cowboy chemists, dried botanicals for undeclared sulfites, weight loss formulas containing undeclared sibutramine, and sleep aids with diazepam derivatives. But those of you who deal in nutrients or pure chemicals, and who have chuckled at the trials and tribulations of the herb people, should remember one word—tryptophan.

‘When you accept the rose, you must also accept the thorns.’—Karim

The above quote refers to the nature of botanical dietary supplements and purity challenges therein, but also to compliance with dietary supplement GMPs. The GMPs require that manufacturers take steps to ensure that they do not introduce impurities into products. FDA doesn’t require that you test finished products for the presence of cleaning fluids, floor wax or rodenticide (you get the picture), but your factory and your production line had better be designed and maintained in a way that this stuff cannot be introduced into the process stream. Process control and GAPs are to purity as supply chain control is to identity—the first lines of defense for ensuring specifications are met.