

$U_k$  =  $k$ th unlisted component (an inactive substance);  
 $n$  = number of unlisted components per batch;  
 $R_k$  = required tests for unlisted component  $k$ ;  
 $S$  = number of shipments (or lots) of ingredients and unlisted components;  
 $B$  = number of batches produced;  
 $H_1$  = 1th inprocess potential defects;  
 $R_1$  = required inprocess tests per batch for potential defect  $H_1$ ;  
 $o$  = number of potential inprocess defects per batch;  
 $z$  = number of ingredients identified per quality test.

- Number of tests: Evidence and distributions. The quantity and quality of evidence on the variables used to estimate the number of required tests varies greatly. In this section, we explain the evidence and assumptions we used to construct the formulas for the number of tests.

- Number of ingredients. We based our measure of the number of dietary ingredients per product on a sample of almost 3,000 dietary supplement labels (Ref. E46). Although some dietary ingredients may be missing from the labels and some listed dietary ingredients may be missing from the products, the ingredient list represents the best evidence we are likely to have on what dietary ingredients are used in dietary supplements.

- Number of ingredients per batch. According to the sample of listed ingredients (Ref. E46). Vitamin and mineral products contain about 13 listed ingredients. Other dietary supplements, mainly herbals, contain about four.

- Number of tests per ingredient lot. The option for more restrictive CGMP regulations would require that virtually all dietary ingredients be tested for identity and defects at some stage between harvesting the raw product and the beginning of the production of the final product. We assumed one identity test per ingredient lot. The number of tests for defects depends on the number of possible defects, which can include: Filth; Microbial pathogens; Chemical hazards, including pesticides; Insects; Physical hazards, such as metals; Natural toxins, such as aflatoxin; and Inadequate purity, quality, strength, or composition.

The number of potential defects is potentially unlimited. As a practical maximum, however, few products would have more than five potential defects. In the calculation of ingredient testing costs (part of the option for more restrictive CGMP regulations), we assumed that the average number of

tests per listed dietary ingredient would be between one and six: One identity test for identity, purity, strength, quality, and composition and zero to five tests for defects.

- Number of unlisted components. Dietary supplements are manufactured using solvents, binders, and lubricants that may not show up in the final product. An industry source (Ref. E47) says that four to six unlisted components are typical per product, although fewer are certainly possible. The minimum number is zero. We assumed that the number of unlisted components would be zero to six, with four the most likely.

- Number of tests per unlisted components. The unlisted components tend to be manufactured products, such as solvents. Therefore, one identity test would likely be sufficient.

- Number of shipments (or lots) of ingredients and unlisted components. We have no direct evidence on the number of shipment lots of dietary ingredients and components. We also have no evidence on the number of shipments per lot or on the number of shipments per batch. The increasing use of just-in-time inventory practices indicates that one shipment lot of components per batch may be the rule for some products and some producers. It is costly and difficult to store ingredients for an extended time, so establishments tend to buy more and smaller lots of components rather than a few large lots and storing them in bulk over an extended period (Ref. E48). Crude botanical and other ingredients are inherently unstable and may lose their quality in even a short time unless costly temperature, humidity, and light controls are in place (Ref. E49). We also know, however, that some dietary ingredient suppliers produce large amounts and then ship out smaller packages. For dietary supplements produced using part of a large production run of a dietary ingredient, the number of batches per lot could be large. Also, some producers buy a single shipment lot of a raw material and use it in many batches. We assume that as many as 12 batches per shipment lot of dietary ingredient is a plausible maximum. In the cost calculation, we assumed that 1 was minimum and 12 the maximum number of batches produced per lot, with 6.5 the average.

- Number of batches produced. We have survey results (Ref. E2) on the number of batches produced per establishment. According to the survey, very small establishments produce an average of 223 batches per year, small establishments produce an average of 554 batches per year, and large

establishments produce an average of 309 batches per year.

- Inprocess potential defects. Inprocess defects involve many of the same potential defects that can occur in components. The more restrictive CGMP option requires inprocess tests at all points where contamination or other defects can occur. Filth, chemicals, microbial pathogens, physical objects, and insects can be introduced into the product during manufacturing. In addition, purity, quality, strength, and composition can be compromised.

- Number of potential inprocess defects. Some processes may have no control points, steps, or stages that involve the potential for defects. If certain manufacturing processes in the production of a dietary supplement can be carried out without being subject to potential defects, no inprocess tests would be required for those processes. We therefore assumed that zero inprocess tests would be the lower bound requirement. For the upper bound, we assumed that no products would have more than five potential control points or steps that could lead to defects. We believe that most production processes will have fewer than 5 control points, so we assumed an average of 2.5 control points requiring inprocess tests for defects.

- Number of required inprocess tests per control point. We assumed one test per defect per control point.

- Number of ingredients identified per quality test. We had no direct evidence on the number of identity tests per final dietary supplement. For the maximum, we assumed that the number of tests would equal the number of ingredients. The number of ingredients identified per test varies from less than one to a very large number. We assumed that for vitamins and minerals, the minimum number of identity tests would be one and the maximum would be 30, with 2 the most likely. Botanical and herbals are less easily characterized than vitamins; so identifying large numbers of ingredients with a single test would be highly unlikely. We assumed that one to two ingredients would be identified per test for herbal products.

- Number of final product tests per batch. We had no direct evidence on the number of quality tests per final dietary supplement. After adjusting for the possibility of multiple results from a single test, multiple ingredients in single products, and the differing number of ingredients in herbal and vitamin products, we estimated that the proposed rule would require about three tests for identity, purity, quality, strength, and composition for each batch of final product. These are the