Questions to the Committee Concerning the Determination of Little/No Risk Drugs with respect to Product Quality

Regarding Drug Substances (See Table 1)

1. Is each of the identified attributes important in determining potential risk to product quality? Or are they the potential sources of product defects?

2. Are there other critical attributes which need to be considered?

3. Assuming all the attributes identified are critical, how can we best establish the acceptance criteria for each attribute ?

3a. Should the chemical structure of the drug substance be well characterized? If yes, what is the definition of "well characterized"? If not, please state the reasons. Also, should a drug substance with multiple chiral centers be excluded?

3b. How can a "Simple Synthetic Process" be defined?

3c. What should be the standards for "Adequate Specifications"? How should product specific (i.e., specific to a manufacturer's product) impurities be handled?

3d. With respect to physical properties, do you agree that when polymorph forms or micronization process (particle sizes) can be defined and controlled, these drugs could be included in the category of little/no risk? Are there other physical properties that can become a barrier?

3e. How can a "stable substance" be defined? By shelf-life? By chemical reactivity ?

3f. How many years of marketing history is considered sufficient?

Regarding Drug Products (See Table 2)

1. Is each of the identified attributes important in determining the potential risk to product quality? Or are they the potential sources of product defects?

2. Are there other critical attributes which need to be considered?

3. Assuming all the attributes are critical, how can we best establish the acceptance criteria for each attribute?

   3a. Should dosage forms other than immediate release oral solid, oral liquid, and simple sterile solutions (e.g., saline, dextrose, trace element salts) be excluded?

   3b. Should only products that can be manufactured by multiple processes be included (e.g., wet granulation and direct compression)? What are the criteria for defining a robust process?

   3c. What should be the standards for "Adequate Specifications"? How should product specific (i.e., specific to a manufacturer's product) impurities and degradants be handled?

   3d. How should a "stable product" be defined? By shelf-life? By the absence of drug substance and excipient interaction?

   3e. How many years of marketing history is considered sufficient?

Table 1. Drug Substance

Attributes	**Acceptance Criteria**
Chemical Structure	Well characterized, others (to be defined)
Synthetic Process	Simple process (to be defined)
Quality	Adequate specifications, known not to contain toxic impurities and others (to be defined)
Physical Property	Polymorphism? Particle Sizes?
Stability	Stable (to be defined)
Manufacturing History	10? Years on the market, others (to be defined)
Others	(To be defined)

Table 2. Drug Product

Attributes	**Acceptance Criteria**
Dosage form	Oral dosage form (IR), simple sterile solutions, others (to be defined)
Manufacturing Process	Easy to manufacture (to be defined), Simple sterile solutions excluding changes that may affect sterility assurance
Quality	Adequate specifications and others (to be defined)
Stability	Stable (to be defined)
Manufacturing History	10? Years on the market and others (to be defined)
Others	(To be defined)