Table 1: Example of Bottle packaging defects

Defect class	Example AQL	Example Defect
Critical	0.01% None or reject with 1[a]	• Incorrect or missing packaging material • Incorrect or missing bottle label • Objectionable foreign matter or incorrect product • Contamination (foreign material) • Wrong product insert/outsert or wrong revision • Incorrect/absence inner seal material • Non-functioning seal (misaligned, wrong dimensions) • Unengaged closure (squeeze and turn) Others (one site example): • Perforated bottle • Broken desiccant inside bottle • Bottle with flashing (impact personal injury) • Cotton/rayon/polyester outside the internal seal affecting sealing
Major	1.0%[b] (0.4- 1.5%)	• Short count (separate criteria may be developed, e.g. controlled substances) • Empty bottle • Obvious low or high fill (liquids)(separate criteria may be developed; e.g. controlled substances) • Bottle with leaks (liquids only) (lower AQL%) [d] • Damaged or dirty container (package integrity not compromised or not in contact with product) • Damaged or dirty inserts/outserts (higher AQL%)[d] • Missing or incorrect desiccant (lower AQL%) • Particulate matter in liquid product (lower AQL%) • Damaged product or closure (e.g. crimped or torn closure s) • Cotton /rayon/polyester present- none or double • Cotton/rayon/polyester - contaminated • Cotton/rayon/polyester- protruding from under seal[c] • Closure removal torque- out of specifications (lower AQL%) • Incomplete inner seal • Detached closure/foam liner (squeeze and turn) • Missing batch number or expiration date • Outsert or label not adhering completely • Wrinkle in label causing illegible print (lower AQL%)
Minor	2.5%[b] (1.5% - 4.0%)	• Loose bundles • Improper amount of cotton/rayon/polyester (if amount is specified) • Scratched closure • Color variation in closure

Footnotes:

(a) Setting AQLs of 0.01% may require larger sample sizes in order to claim that level of quality. Depending on batch and sample size, no critical defects ('None' or ' Reject with 1") may be the limit. Alternate

Applicability of Harmonizing Acceptable Quality Levels (AQLs)
Each application is suggested to be evaluated on a case-by-case basis to determine which defects are critical, major and minor, for that specific package or product line. Depending on the specific package and dosage form, some of the attributes or defects listed below may not be applicable, additional defects may be warranted, or the description of the defect further specified. Definitions of defects may vary from site to site, so the classification is highly dependent on the interpretation and specific definition of the defect. The concepts of AQL (Acceptable Quality Level) and UQL (Unacceptable Quality Level) may be non-uniformly applied in setting acceptance or statistical quality control criterion.

The "95 percent" level of high probability of acceptance may not be accepted at all gmp sites or for some dosage forms; It could be too low or high (4). Thus, it may be impractical to establish a uniform system of AQLs and/or UQLs for package defects. The uses of AQL and/or UQLs and their ranges are examples of statistically derived levels for acceptance or rejection. The basic requirements are that the acceptance criteria for sampling, testing and for acceptance levels be based on appropriate statistical quality control criteria. Sound statistical methodology should be applied to the procedures for testing of attributes that impact on the quality of drug products and the evaluation of the results to determine acceptance or rejection of the drug product lot.
An important aspect of AQLs and UQLs is the continuous learning and possible adjustments of defect descriptions and levels. Failure to meet established defect limits is investigated to determine the impact on validation. As events and history of the packaged product and process are gained, changes may be warranted. Re-evaluation of the attribute description (e.g. quantitative measurements enhanced or more specific description of the defect) and acceptability by the Quality Unit of that defect and corresponding acceptance criteria may be beneficial. Trending, quality incidents and investigations and statistical treatment of inspection data are a means to review the defects. Quality risk management tools may also be used to provide a basis for evaluating the potential impact of package defects.

Definitions of classifications:
Common defect classification criteria for critical, major and minor and its impact on the safety, regulations, use, consumer relations and company are shown in Appendix I.

Sampling Plans:
Typical sampling plans that can be used are General Inspection Level II (ANSI/ASQC Z1.4-1993), with Single, Normal Sampling Plan or ISO 2859-4 (10). Other sampling plans may be appropriate depending on administrative difficulty of the ensuing sample size, desired or given AQL, sample size of the available plan, packaging history and routine monitoring intentions.

Sample size of multiple plans is less than double sampling plans, which in turn is less than the single sample plans. Once determined, the total sample size is divided by the number of sampling intervals to determine the number of samples per interval (e.g. 200 bottles (sample size) /24 intervals = 9 bottles/interval).

