Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion:
This document provides recommendations when developing specifications for the design of Direct Impact Compressed Air, Pressure Swing Adsorption (PSA) and Cryogenic Nitrogen Systems used in the manufacture of Active Pharmaceutical Ingredients (APIs) and Drug Products (DPs).

It is desirable that the quality of the compressed air and nitrogen is assured through adequate design, appropriate controls (e.g. change control, procedures), and routine maintenance of the system. If these controls are in place, direct-impact compressed air and nitrogen systems typically do not require analytical testing to be conducted. Routine release testing (e.g. identification testing) of vendor supplied compressed air or nitrogen shipments may still be needed for release of these incoming raw materials. This release testing is outside the scope of this document. The development of specifications for compressed air and nitrogen systems is typically conducted during the engineering design phase of the system, with documented verification of the systems' suitability for intended use conducted during commissioning and qualification.

The scope of this document is applicable to systems that have direct impact on product quality (e.g. product contact). Indirect and no impact systems are outside the scope of this document. If it is determined that testing of a system is necessary, the limits for the testing should be suitable for the intended use of the gas. Commonly used limits and references for test methods are include in Table 1.

It does not include recommendations for the location, frequency or number of samples for this testing. These considerations may depend upon the results of a risk assessment to target the sampling commensurate with the risk.

A system level impact assessment is performed to determine which systems are considered direct impact. Examples of applications that are often considered direct impact may include:

- Air used to spray tablet coatings.
- Air and nitrogen used to dry product, product contact equipment surfaces, vials or ampoules.
- Air and nitrogen used to clean and dry product-contact equipment surfaces.
- Air and Nitrogen used to suspend API during micronizing or milling steps.
- Nitrogen used to blanket API vessels.

System Control Considerations
It is desirable that the assurance of quality of the air or nitrogen is controlled through adequate engineered design, operation and maintenance of the system. If this is accomplished, compressed air and nitrogen systems typically do not require routine analytical testing to be conducted. If testing of the system has been determined to be necessary (e.g. due to invasive maintenance work), then the recommendations below and in Table 1 may be considered.

Viable and Non-viable Particulates

