Certificates of Analysis

What is that piece of paper and what role does it play in GMP compliance?

By Paula Brown

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A very common question asked by manufacturers, suppliers and contract laboratories is: "what should be on a certificate of analysis?" Let's start from the beginning by defining a "certificate of analysis" or "CofA."

Alas, that modern mainstay of electronic information, *Wikipedia*, is silent on the topic. A Google search, however, turns up hundreds of examples of actual certificates but surprisingly few definitions. A useful starting point might be an online bank glossary, which states: "Certificate of Analysis: A document usually issued by an inspection firm attesting to the quality or purity of exported commodities. The document is often required either by the importer or by government regulation in the importing country."

According to a Pharmaceutical Validation Blog, "…the Certificate of Analysis of a Drug or Formulation gives the exact details about its quality and compliance to specifications and is a document relating specifically to the result of testing a representative sample drawn from the specific batch or lot of material it is purported to represent." The CofA is the documented evidence of the quality control testing carried out on the drug or formulation. In short, a CofA is a piece of paper that certifies something. Since it's a certificate of analysis, that is what it certifies, an analysis.

Turning to the dietary supplement GMP regulations is not overly helpful, as FDA stated in the preamble to the final rule that it would decline to define CofAs. Although a parenthetical comment in the preamble, which lacks the force of law, notes a CofA is a document, provided by the supplier of a component prior to or upon receipt of the component that documents certain characteristics and attributes of the component." Section 111.75 titled "What must you do to determine whether specifications are met?" says you must test or examine everything to see whether or not specifications are met, but the final rule also says you can rely on a CofA in lieu of testing or examination. Despite the lack of a full definition Section 111.75(a)(2)(ii)(B) does require that a CofA include several features: a description of the test or examination method(s) used; limits of the test or examinations; and actual results of the tests or examinations.

Now, imagine you are a manufacturer and are required to have specifications and test results, but you do not have a lab. That is where the CofA becomes important. If you want to buy that low cost raw material but have to show the FDA that it meets your high standards, then you need to get a CofA that proves your standards were met. No lab, no CofA, FDA can shut you down.

Keep in mind a CofA may play many roles and the GMP standards require that manufacturers set and test against specifications for pretty much everything from raw materials (including bottles, labels, the cotton used in the bottles, colorants, the excipients and dietary ingredients) to outgoing finished products. Also remembering that the GMP applies to manufacturers and not to farmers or raw material suppliers, the question "what should be on a certificate of analysis?" should be directed inward rather than outward.

Section 111.70 of the GMP, "What specifications must you establish?" tells you (111.70 (b)) that for each component you use in the manufacture of a dietary supplement, you must establish component specifications as follows: (1) You must establish an identity specification (remember a CofA alone will not work for identity); (2) You must establish component specifications that are necessary to ensure that specifications for the purity, strength and composition of dietary

supplements manufactured using the components are met; and (3) You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement. So to answer the question, "What should be on a CofA?" The answer is that the CofA should demonstrate all the specifications have been met.

While there are certainly industry standards that may be covered by a generic CofA, remember the information on that piece of paper has to certify your specifications for quality have been met. If you choose to accept somebody else's specifications as yours, then be prepared for the possibility that a change of supplier could mean the CofA they provide is different. If that's the case, you have just changed your specifications (whether you wanted to or not) and you're going to have to go back through ALL your GMP paperwork, including your master batch records, and make changes to reflect that change. You're better off communicating to your supplier your specifications. If they won't cooperate or cannot meet these specifications, I suggest you find another supplier.

There are several major pieces of information that must be on every CofA: the specifications and their acceptance criteria, the names of the tests used for each specification, and the results of those tests. (Remember too that the burden is on the manufacturer to demonstrate the tests used have to be scientifically valid.) This information must be provided for each batch or lot number. CofAs with no batch or lot numbers, with the same photocopier stripes as the last seven certificates, or with the exact same numerical test result values to four significant figures, are not acceptable.

You cannot accept just any old piece of paper. Under final Section 111.75(a), a manufacturer may rely upon a CofA from its supplier of a component, provided that certain criteria are met, including the following: (1) The firm first qualifies the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations; (2) the certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations; (3) the firm maintains documentation of how it qualified the supplier; (4) the firm periodically reconfirms the supplier's certificate of analysis; and (5) the firm's quality control personnel review and approve the documentation setting forth the basis for qualification (and requalification) of any supplier.

Basic Anatomy of a CofA

Having now discussed both the broad requirements (specifications, tests, test results, batch numbers) that should be on every CofA, and remembering there are different types of CofA (incoming dietary supplement components, finished products, reference materials, etc.), we can move on to the CofA template. According to the bloggers cited at the beginning of this column, a basic template includes a header, a body, certification and compliance statements and a footer. (*See Table 1.*)

The header should have the term "Certificate of Analysis"; the name, address, and phone number of the company providing the certificate, as well as those of the manufacturer for whom the certificate is intended; the name of the material or formula being certified; and the category into which it fits (dietary component, dietary ingredient, in-process control, finished product).

The body of a CofA should include the lot/batch number to which the certificate applies, the date of manufacture or production of the material being certified, the product code or number, the expiration date (if there is one), the recommended re-evaluation date (if required) and a stability statement (if required). Within the body is the heart of the CofA, the analysis section. It should include the name of the specification, the acceptance criteria for determining whether or not the specification has been met, the name of the test(s) used with references and the test results along with test method tolerances. The results section contains the data and/or observation. Words like "passes" or "complies" are not recommended, as they are not clear and do not describe the observation/data that lead to such a determination. Any substance that is tested against specifications laid out in a pharmacopeial or other compendial monograph must list all tests from the monograph and the results.

The certification and compliance statements section provides an affirmative statement that the material complies with the intended specification (e.g. a pharmacopeial standard or the specifications laid out in a master batch record for the product) along with a reference to the specification (e.g. USP 34/NF 28, In-House Specification #XXXX for Finished Product #YYYY). If the reference is an in-house specification, this should be noted, and a copy of the written specification, with the associated tests, should be a part of the manufacturer's GMP paperwork.

Finally, the last part of a CofA is the footer, which includes the name and title of the analyst(s) who performed the analysis/analyses, the name of the person who approves or authorizes the findings presented in the certificate, their respective original signatures and the date of approval. The footer should also include the page number and the total number of pages associated with the CofA and various significant dates, such as the date of manufacture, the expiration date (if applicable), the analysis date(s) and the batch release date for the certified material.

While this discussion has focused primarily on incoming components, including dietary ingredients, recall that Sec.111.35(g) requires testing of each batch of finished product when possible (and justification for not testing when not possible). FDA has made it clear in the preamble that the manufacturer can test, examine, rely on a certificate of analysis (other than to verify the identity of dietary ingredients), or, in the case of a specification that is exempted from periodic testing of a finished batch, rely on other information that ensures that such an exempted product specification is met. NW

References furnished upon request.

Table 1

ITEMS THAT BELONG ON A CofA:

- "Certificate of Analysis"
- Name/address/phone number of supplier and manufacturer
- Name of raw material/finished product
- Category: (component, ingredient, in-process, finished product)
- Lot/Batch number
- Date of manufacture (of material being certified)
- Product Code or Number
- Expiration date of certified material (if applicable)
- Re-evaluation date (if applicable)
- Stability statement (if required), e.g. store at -80°K
- Test name(s)—note may include physical descriptions, chemical tests for contaminants as well as desirable characteristics—chemicals like caffeine will require only a few specs and tests, botanicals and extracts will require more
- Test reference(s), e.g. USP 28/NF 34
- Test results—actual values as well as the pass/fail designation
- Acceptance Criteria—usually something along the lines of "not less than x, or not more than y"
- Certification of compliance—something like "this material complies with the specifications set forth in XXXX (e.g. USP 34/NF 28, In-House Specification) for the manufacture of Finished Product QQQQ as described in Master Batch Record VVVV"
- Printed name(s) and signature(s) of analysts
- Printed name and signature of Approver
- Page number and total pages, e.g. page 1 of 5
- Date of manufacture of the material being certified
- Expiration date (if applicable)
- Analysis date(s)
- Batch release date for the certified material