

Voluntary Guideline for the Dietary Supplement Industry

No.3

Dietary Supplement Component Supplier Qualification

A Voluntary Guideline



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1.0 INTRODUCTION

In today's complex global supply chain, proper component **supplier**¹ qualification is essential for avoiding supply chain failures and maintaining traceability of products. There have been numerous public health crises in various industries regulated by the US Food and Drug Administration (FDA) related to contamination or **adulteration** of material along the supply chain.

For example, the drug industry has experienced contaminated heparin² and glycerin contaminated with diethylene glycol in cough syrup³ and toothpaste.⁴ The food industry has experienced intentional adulteration with melamine⁵ and *Salmonella* contamination.⁶ All of these examples were linked to numerous deaths. The dietary supplement industry has also experienced supply chain failures, including contaminated L-tryptophan,⁷ contamination of plantain with *Digitalis lanata*,⁸ and adulteration of weight loss and male sexual enhancement products with active pharmaceutical ingredients (APIs).^{9,10,11,12} These incidents stem from failures somewhere in the supply chain and highlight some of the difficulties associated with managing the global supply chain.

1.1 Purpose

This document serves as a *voluntary* guideline to assist manufacturers of dietary supplements (or other users of dietary supplement components) with compliance with the dietary supplement current good manufacturing practice (cGMP) requirements of the US FDA 21 CFR §111. The Component Supplier

¹ Key terms are highlighted in bold and the corresponding definitions are provided in the glossary located at the end of this document.

² Blossom DB, Kallen AJ, Patel PR, et al. (2008) Outbreak of adverse reactions associated with contaminated heparin. *N Engl J Med* 359:2674–84

³ Rentz ED, Lewis L, Mujica OJ, et al. (2008) Outbreak of acute renal failure in Panama in 2006: a case-control study. *Bull World Health Organ* 86:749–56

⁴ US FDA (2007 Jun 1) FDA advises consumers to avoid toothpaste from China containing harmful chemical [FDA news release P07–97]

⁵ Gossner CM, Schlundt J, Ben Embarek P, et al. (2009) The melamine incident: implications for international food and feed safety. *Environ Health Perspect* 117:1803–8

⁶ Hanning IB, Nutt JD, Ricke SC (2009) Salmonellosis outbreaks in the United States due to fresh produce: sources and potential intervention measures. *Foodborne Pathog Dis* 6:635–48

⁷ Varga J, Utto J, Jimenez SA (1992) The cause and pathogenesis of the eosinophilia-myalgia syndrome. *Ann Intern Med* 116:140–7

⁸ Slifman NR, et al. (1998) Contamination of botanical dietary supplements by *Digitalis lanata*. *N Engl J Med* 339:806–11

⁹ US FDA (2010 Jul 8) FDA public health alert: Que She weight loss capsules contain potentially harmful ingredients [FDA news release]

¹⁰ US FDA (2010 Jun 19) FDA warns consumers to avoid magic power coffee [FDA news release]

¹¹ US FDA (2009 Nov 5) FDA warns consumers on sexual enhancement products. Another dietary supplement is found to be contaminated with potentially dangerous ingredient [FDA news release]

¹² US FDA (2009 Jul 28) FDA warns consumers not to use body building products marketed as containing steroids or steroid-like substances. Agency issues warning letter to American Cellular Laboratories for marketing and distributing potentially harmful steroid-containing products [FDA news release]

Qualification Voluntary Guideline, referred to hereafter as “the guideline,” is intended to assist component **users** with the development of their own risk-based supplier qualification programs. These programs can be used to help establish the reliability of the component supplier’s **certificate of analysis** (COA), which may allow the component user to justify reduced testing of incoming **components**.¹³ The guideline also serves to educate component suppliers on the expectations for supplier qualification. Broad use of this guideline across the dietary supplement industry can play a key role in helping to maintain the integrity of the supply chain, ensure cGMP compliance, and help serve in protecting the public health.

1.2 Scope

This guideline may be applicable to all **dietary supplement components** used in the manufacture of a dietary supplement product. It provides recommendations to comply with the regulatory requirements of component supplier qualification and may be utilized by finished product manufacturers or other users of dietary supplement components to build the foundation for a supplier qualification program.

This guideline focuses on compliance with US regulations, but it also has international application, as components used in the manufacture of dietary supplements are sourced globally and are encompassed by many different government regulatory systems. When considering how to use this guideline, each component supplier, distributor, or component user should consider how the guideline might apply to its particular circumstance. The diversity of components and products and their uses, along with the global nature of the supply chain, make it so that some principles of the guideline may be more or less applicable to certain components or products than others.

1.3 Adopted Principles

Resources allocated to supplier qualification activities are finite. Thus, supplier qualification programs should be appropriately risk based, with the most resources allocated to those components or suppliers that pose the highest risk. The recommendations articulated in this guideline are based on the basic principles of **risk management**, as described by the International Conference on Harmonization (ICH).¹⁴

Supplier qualification (and requalification) is an ongoing, iterative, and cyclical process. Risk should be regularly reassessed based on the performance of the supplier and component, as should decisions on whether and how to mitigate that risk.

¹³ 21 CFR §111.75, Subpart E

¹⁴ ICH (2005) ICH Q9 Quality Risk Management Guideline. Available at:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128053.pdf>

1.4 Supplier Risk Management Principles

Risk should inform an organization's decision-making processes. Organizations manage risk by identifying, analyzing, and evaluating whether a particular business risk element should be controlled through the allocation of resources against the high-risk entity.

The application of risk management principles, as described by the ICH, to component supplier qualification is a logical approach to managing a very complex global supply chain.

For supplier qualification, risk can be defined in the following ways:

- Risk of a quality event (e.g., **out-of-specification** resulting in adulteration or **misbranding** of finished product)
- Safety risk to the component user or consumer
- Risk of disruption of service or supply

A risk management approach allows component users to apply finite resources to those component suppliers that represent the greatest risk. Allocating resources to medium- and high-risk suppliers and/or components on a case-by-case basis allows the user the flexibility to shift resources to maximize the potential to prevent a significant quality event (e.g., adulterated product in the market).

The application of risk management principles requires an understanding of the **probability**, **severity**, and **detectability** of a specific event. For more information on risk management principles, refer to the ICH Q9 Quality Risk Management Guideline.

1.4.1 Assessing Risk

Determining whether a particular component from a specific supplier intended for use in a dietary supplement presents a low, medium, or high risk requires careful consideration of factors with respect to both the component and the supplier and its **quality management systems** (QMS).

The same component sourced from different suppliers can present different risk profiles; conversely, the degree of risk may vary significantly between different components that are purchased from a single supplier who uses the same QMS to produce the different components.

Determining the inherent risk factors for both the component and the supplier is essential to understanding where the proposed transaction falls on the risk continuum. Component users weigh various factors and assess risk differently, depending on their particular situation and intended use of components. However, certain core risk assessment principles are universally applicable.

See Appendix A for examples of high-, medium-, and low-risk suppliers and components.

1.4.2 Risk Factors

Below is a brief list of general risk factors to consider when assessing risk of a supplier or component. These are described in more detail in Section 8.0.

Supplier considerations

- Country of origin
- Supplier regulatory history
- Supplier experience
- Supplier audit results

Component considerations

- Complexity of material
- Intended use of material
- Process complexity

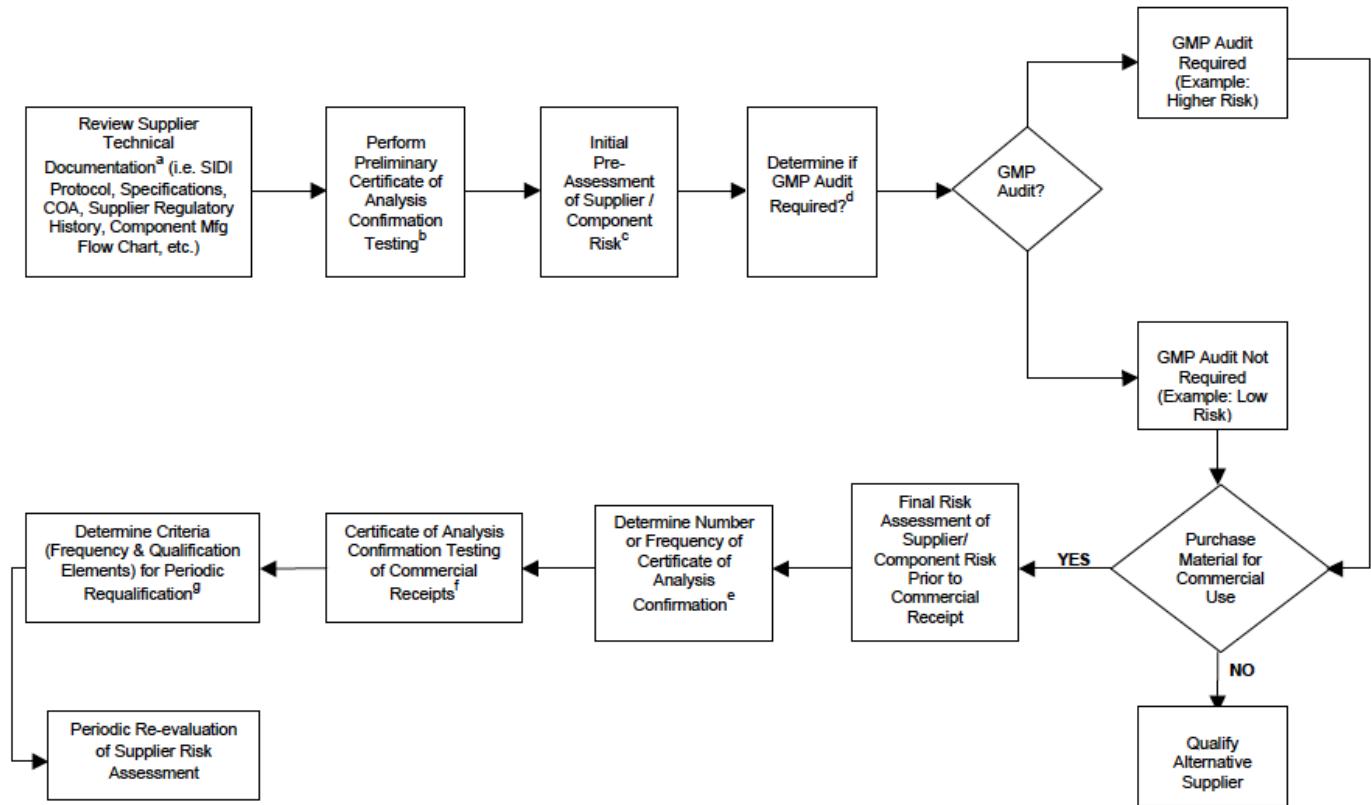
Documentation considerations

- Compendial status of material
- Supplier **specifications** (comprehensive versus superficial)
- Technical documentation (e.g., **SIDI™ Protocol** dossier)
- Claims substantiation

1.5 Supplier Qualification Process

The following flow chart (Figure 1.1) is intended to provide a high-level illustration of the main elements of the component supplier qualification process. These elements are described in detail in the following sections.

Figure 1.1 High-level supplier qualification flow chart*



*Qualification process may be terminated at any step or may return to a previous step in the process should evidence so warrant.

^aRefer to Section 2.0.

^bRefer to Section 4.2.

^cRefer to Section 4.2.1.

^dRefer to Section 3.0.

^eRefer to Section 4.2.3.

^fRefer to Section 4.2.2.

^gRefer to Section 5.0.

2.0 PRE-ASSESSMENT CRITERIA

The purpose of this section is to provide basic recommendations for the pre-assessment and pre-qualification of a component supplier itself, or in conjunction with a particular component that it manufactures or distributes. The objective of a pre-assessment is to obtain enough information to perform a preliminary risk assessment for a particular component or supplier. This pre-assessment may also be used to determine whether the component or supplier is suitable to move to the next stages of formula development or pilot production.

At this early stage, a pre-assessment largely entails gathering relevant documentation regarding a component or supplier; accordingly, this pre-assessment (including any questionnaire) *should not* be used by itself to qualify the component or supplier or to assess specific compliance with applicable cGMPs and other relevant regulatory standards. Verification of compliance with relevant regulations for suppliers and components should occur during the formal qualification phase and may include onsite activities not specified here.

The recommendations presented herein are intended to assist component users in understanding what information they can and should request from suppliers to support their risk management decision making and supplier/component qualification activities. Users may find that they require additional or alternative documentation or assurances other than the examples provided here based on their particular situation.

2.1 Pre-Qualification Documentation

The purpose of obtaining pre-qualification documentation is to perform an initial assessment of the supplier's QMS (see Section 3), their supply capability, and basic component information and specifications. There are various voluntary guidelines, protocols, and other documentation that can be used to perform this initial assessment. Examples of such documentation are provided below; however, component users may also choose to require additional types of documentation not discussed here.

2.1.1 Supplier Certificate of Analysis

One of the first and most critical steps in this pre-assessment is to request a COA from the component supplier (see Section 4).

Depending on what may be included on a component supplier COA, component users may have to request more information from suppliers if the measured parameters are insufficient or do not address items critical to support the component user's needs or cGMP compliance requirements. Certain components may have generally known contaminant issues that should be addressed in a supplier COA but may not be; accordingly, component users should request that this contaminant testing be added to the COA.

The component COA must include results of tests or examinations characterizing the identity, strength, purity, composition, and limits on contaminants, as applicable. The tests or examinations may be physical, chemical, organoleptic, or microbiological. For more detailed information on the contents of a COA, refer to the SIDI Work Group's Voluntary Certificate of Analysis Guideline.¹⁵

2.1.2 Standardized Information on Dietary Ingredients (SIDI™) Protocol

The SIDI™ Protocol is a voluntary guideline developed jointly by several dietary supplement trade associations and industry representatives, with the purpose of facilitating the communication of basic supplier and component information between component suppliers and component users. The protocol provides guidance on the type and scope of information to include in the form of an information package or dossier, for both botanical and non-botanical dietary supplement components. In addition, the protocol covers information such as specifications and COA, as well as regulatory, manufacturing, and facility information. As part of the pre-assessment criteria, this information helps to inform the initial risk assessment of the supplier and/or component. For component suppliers who have constructed SIDI information packages and have them readily available, component users should request a copy. If a supplier does not have a SIDI information package or dossier available, templates are available to guide component suppliers.¹⁶

2.1.3 Excipient Information Protocol

Similar to the SIDI™ Protocol in objective and format, the International Pharmaceutical Excipients Council (IPEC) has developed the Excipient Information Protocol (EIP) to provide information specifically for excipients. This protocol provides information that may be used in dietary supplement, food, and pharmaceutical applications.¹⁷

2.1.4 Supplier Questionnaire/Self-Audit Assessment

Depending on the supplier, the component, and both the component and the finished supplement's intended use, the component user may decide to develop its own questionnaire or assessment document. This information may be used in conjunction with other guidelines and protocols such as the SIDI™ Protocol. A component user's self-generated product or audit questionnaire should not replace the need for a more detailed risk analysis, and also should not replace the formal risk assessment discussed in Section 1.4 and in the ICH Q9 Quality Risk Management Guideline.

¹⁵ SIDI Work Group (2010) Certificate of Analysis for Dietary Supplement Components: A Voluntary Guideline. Available at: <http://www.sidiworkgroup.com>

¹⁶ Templates are available from the SIDI Work Group at: <http://www.sidiworkgroup.com>

¹⁷ Templates are available from IPEC Americas at: <http://www.ipecamericas.org>

2.1.5 Government and Regulatory Enforcement History

Publicly available documents can offer information related to components and suppliers in several key areas of regulatory compliance. This may provide preliminary indicators of a supplier's performance in terms of quality and supply, as well as the suitability of a specific component for use in a particular component user's application. Examples of publicly available government enforcement activities include FDA establishment inspection reports,¹⁸ enforcement reports,¹⁹ warning letters,²⁰ lists of recalls/market withdrawals/safety alerts,²¹ Federal Trade Commission (FTC) actions,²² and import alerts initiated by the FDA.²³ This information may be located on searchable government websites and/or may be located using services that routinely conduct Freedom of Information Act (FOIA) searches and have established archives of commonly requested information. Companies may also make their own FOIA requests to the FDA.²⁴ The FTC also provides guidance on making FOIA requests to the agency in its Freedom of Information Act and Privacy Handbook.²⁵

For international component suppliers, searches for publicly available information may need to be conducted using international databases. Supplier and site compliance information and standards can vary significantly by country. Component users should self-affirm that they understand and accept differences in compliance standards, language and nomenclature when dealing with international regulatory authorities.

2.1.6 Third-Party Certifications

Third-party certifications of a supplier's QMS, manufacturing facility or facilities, and/or component may provide sufficient information to determine a supplier's capabilities and/or risk profile. The component user should take care to understand the relevance, requirements, limitations, independence, and credibility of the certification, and should have some knowledge of the certifying organization. Third-party certification alone may not provide adequate information on which to form a determination of a components risk profile, and more information may be required. Examples of third-party certification or verification services include the International Pharmaceuticals Excipients Auditing, Inc. (IPEA), Natural Products Association, International Organization for Standardization (ISO), Safe Quality Food Institute (SQF), NSF International

¹⁸ Commonly requested establishment inspections reports are available at:

<http://www.fda.gov/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/default.htm>

¹⁹ Available at: <http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm>

²⁰ Available at: <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>

²¹ Available at: <http://www.fda.gov/Safety/Recalls/default.htm>

²² FTC actions may be searched at: <http://ftc.gov/os/index.shtml>

²³ Available at: <http://www.fda.gov/ForIndustry/ImportProgram/ImportAlerts/default.htm>

²⁴ US FDA. How to Make a FOIA Request. Available at:

<http://www.fda.gov/RegulatoryInformation/FOI/HowtoMakeaFOIARequest/default.htm>

²⁵ FTC. Freedom of Information Act and Privacy Handbook. Available at:

<http://www.ftc.gov/foia/foiahandbook.pdf>

(NSF), and US Pharmacopeial Convention (USP) Verification Programs for Ingredients (DIVP).²⁶

2.1.7 Regulatory Status of the Component

The legal status of the component should be determined prior to use. Initial investigational approaches used to establish the regulatory status should be based on the component's intended use (e.g., as a dietary ingredient or excipient). Components intended to function as dietary ingredients must be further evaluated to establish their dietary ingredient status and suitability for use in dietary supplements pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA) §201(ff).²⁷ Written documentation may be required to support certain positions or assertions of regulatory status. Products intended to be used as non-dietary ingredient components (e.g., excipients) must have a legal basis for use in dietary supplements. This includes approved food additives, substances Generally Recognized as Safe (GRAS), or other regulatory standard.²⁸

²⁶ IPEA, <http://ipeainc.com/>; Natural Products Association, <http://www.npainfo.org/>; ISO, <http://www.iso.org>; SQF, <http://www.sqfi.com>; NSF, <http://www.nsf.org>; DIVP, <http://www.usp.org>

²⁷ FDCA §201(ff), 21 U.S.C. §321(ff)

²⁸ "...any substance, other than a 'dietary ingredient,' the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of the dietary ingredient or dietary supplement, must be:

- Authorized for use as a food additive under §409 of the act, or
- Authorized by a prior sanction consistent with 21 CFR 170.3(l), or

If used as a color additive, subject to a listing that, by the terms of that listing, includes the use in a dietary supplement, or Generally recognized as safe (GRAS) for use in a dietary ingredient or dietary supplement. Any claim that a substance is GRAS, other than a dietary ingredient within the meaning of §201(ff) of the act, must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or dietary supplement..."

3.0 SUPPLIER CAPABILITY/AUDIT ASSESSMENT

The intent of this section is to provide basic recommendations for assessing in detail a dietary supplement component supplier's QMS and to determine compliance with applicable cGMPs and other standards. This is one element that should be used to assess supplier (or component) risk and to help fulfill the requirement for supplier qualification that justifies reliance on the supplier's COA.²⁹

The recommendations provided in this section are based on the principle that information from an onsite audit should be obtained from component suppliers at a certain frequency, the determination of which should be based, in part, on the risk posed by the supplier and/or component, as well as past performance. If audit findings are considered significant to the user of the component, then consideration should be given to establish the component supplier as conditionally qualified. Paper audits, vendor questionnaires, SIDI protocol information packages, and the like do not provide the same level of detail or information provided by onsite audits; except in certain low-risk situations, these data may not be adequate on their own to serve as the basis for supplier qualification.

3.1 Supplier Quality Management System Review

All component suppliers should have a formal QMS that establishes how critical elements of quality and compliance are managed at the site of manufacture and, if applicable, through a corporate governance system. Basic elements of a QMS include the following:

- Management oversight of quality
- Facility and equipment operating systems
- Material management systems
- Production and control systems
- Packaging and labeling systems
- Laboratory control systems

Component suppliers and component users are encouraged to consult QMS standards and guidelines, such as those provided by the ISO³⁰ and the SQF.³¹ These standards are not specific to any one industry or discipline and may be used by companies to develop their own QMS.

²⁹ 21 CFR §111, Subpart E §111.75 (a)(2)(ii)

³⁰ ISO. ISO 9000 Quality Management. Available at: http://www.iso.org/iso/iso_9000

³¹ Safe Quality Food Institute. SQF 2000 Guidance. Available at: <http://www.sqfi.com/wp-content/uploads/2000-Guidance-General.pdf>

3.2 Auditing Technique Recommendations

An appropriate risk-based supplier qualification program is based on the principle that most component suppliers' manufacturing facilities should be audited with some predetermined frequency, depending on the risk posed by the component and/or supplier, as well as past performance. These onsite audits should be facility-specific, and the reports generated from such audits can be used to confirm the component supplier risk assessment rating (see Section 1.4.1) and serve as back-up support for reduced component testing (i.e., reliance on the component COA).

Several different auditing techniques can be utilized by or for the component user, each with strengths and limitations. Users may audit a component supplier's facility or facilities using their own internal qualified personnel, rely on an independent third-party audit and/or third-party certification, enter into a formal or informal shared audit program³², or utilize a combination thereof. The component user should decide which technique is most appropriate for a given component/supplier based on the risk posed by the component and/or supplier, past performance, cost, capability and availability of resources, and intended use of the component.

Some form of onsite facility-specific audit information should be obtained for most components and suppliers. An exception might be, for example, a low-risk commodity component defined by compendial specifications from a supplier with a favorable history of compliance (i.e., minimal regulatory enforcement action). The absence of audit information for a high-risk supplier and/or component further increases the risk and makes mitigation more difficult. In contrast, the availability of a comprehensive audit report may allow one to lower risk. At a minimum, facilities should be audited against legally applicable cGMPs.

3.2.1 Direct cGMP Audit

A direct audit by the component user provides the greatest assurance that the component supplier's capabilities and practices meet the component user's needs, and represents the most direct way to assess and mitigate risk. Users may request information that is specific to their needs and intended use of the component. Completion of a SIDI protocol dossier or pre-audit questionnaire may help to identify potential gaps that will contribute to an improved onsite audit (see Sections 2.1.2 and 2.1.4). A limitation is that direct cGMP auditing can be resource intensive and may be the most costly to execute and maintain.

3.2.2 Independent Third-Party Certification

Third-party certification of a component supplier may or may not generate an audit report accessible to the component user. In cases in which the audit report

³² Formal audit programs may involve an audit report bank and standards for auditors.

is not available to the component user, the component user relies on the merits of the certifier to assure the component supplier's capabilities. In cases in which the report is available to the component user, third-party certification may provide better information than a direct audit due to the greater depth and length of the audit than that provided to an individual company. Third-party certification for risk and/or capability assessment programs that are accredited by a recognized independent accrediting body such as the American National Standards Institute (ANSI),³³ the International Organization for Standards (ISO),³⁴ or a similarly qualified accrediting body may provide higher reliability than those programs that are not accredited.

3.2.3 Independent Third-Party Audit

If component users lack the capability or resources to conduct audits, they may rely on independent third-party audits. Limitations may include general audit reports that may not address all of a component user's specific needs and questions, thus providing less assurance about the specific component suppliers' QMS and capabilities that are specific to the component user's particular applications. However, these types of audits can provide valuable information about a supplier's ability to meet the key cGMP criteria needed for the use of the component in dietary supplements.

3.2.4 Shared Audit Information

Sharing audit information from the onsite audit of a single component supplier/facility among multiple component users represents a cost-effective technique for obtaining important information on a supplier's capabilities. Both formal and informal, this technique is based on the same basic concept of sharing among component users of both the cost of the audit and the audit information generated. This technique can be convenient for multiple component users of the same component and convenient for the component supplier whose facility is subjected to fewer overall audits. Similar to third-party audits, the component user is not physically present in the supplier's facility and the audit report may lack detail specific to the component user's needs. The IPEA is an example of a formalized shared audit program established for the excipients industry.³⁵

3.2.5 Auditor Qualification

Irrespective of the audit technique(s) implemented by the component user, auditor competency is central to the quality, integrity, and value of the generated audit report. Education, training, and experience are the 3 most important criteria

³³ ANSI, <http://www.ansi.org/>

³⁴ ISO, <http://www.iso.org>

³⁵ IPEA, <http://www.ipeainc.com/>. This example of a formal shared audit program is administered by an independent party.

for determining auditor compliance. Auditors should have documented experience in dietary supplement and food cGMPs and experience in auditing dietary ingredient and other dietary supplement component facilities. Where possible, auditors should be chosen who have been certified or accredited by an independent body. In some cases, an auditor may require unique subject matter expertise to address unique processes (e.g., aseptic packaging) by which dietary supplement components are manufactured. Regardless of qualifications, the auditor should understand the differences in regulatory expectations and standards of evidence for the dietary supplement industry versus other industries (e.g., the pharmaceuticals industry).

3.3 GMP Audit

Aspects of GMPs against which component users may evaluate component suppliers are variable. At a minimum, component suppliers must adhere to cGMPs for food (21 CFR §110). However, there are substantial differences between 21 CFR §110 and 21 CFR §111 that should be addressed to ensure that component suppliers are appropriately meeting the needs of component users. There are a variety of applicable cGMP audit checklists available, including the International Food Additives Council (IFAC) Good Manufacturing Guide for Food Ingredients,³⁶ as well as USP³⁷, NSF³⁸, and NPA audit checklists.

³⁶ IFAC (2010). IFAC Good Manufacturing and Quality Assurance Guide for Food Ingredients 2010. Available at: <http://www.ifacmem.org/> for IFAC members only. IFAC plans to provide open access in the near future.

³⁷ USP (2011). United States Pharmacopeia Dietary Ingredient Verification Program Manual for Participants. Available at:

http://www.usp.org/sites/default/files/usp_pdf/EN/USPVerified/divpparticipantguidelines.pdf

³⁸ To be available on the NSF website at <http://www.nsf.org>.

4.0 CERTIFICATE OF ANALYSIS CONFIRMATION RECOMMENDATIONS

In order to rely on the component COA to determine that established specifications have been met, the component user must verify the minimum required information (test results, specification limits, and methods) on the COA.³⁹ The intent of this section is to provide recommendations for meeting the requirement of COA confirmation to establish a basis for reduced testing on incoming components according to 21 CFR §111.75(a)(2)(ii):

- (A) You (must establish) the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations [§111.75(a)(2)(ii)(A)].
- (B) 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 [§111.75(a)(2)(ii)(B)].

4.1 Preparation of the Certificate of Analysis

The SIDI Work Group's voluntary COA guideline provides recommendations for the content and format of COAs for dietary supplement components.⁴⁰ This voluntary guideline assists component manufacturers and component users in understanding the industry expectations related to the preparation of component COAs.

4.2 Certificate of Analysis Testing Recommendations

COA testing confirmation can be divided into 2 basic phases: **pre-commercial** and commercial. The scope, amount, and frequency of testing depend on the specifications established for the component and the risk posed by the component and/or supplier (see Section 1.4). If applicable, component specifications may conform to available compendial standards.

The component supplier's COA may include the results of tests or examinations that do not pertain to specifications established by or relevant to the component user. Conversely, component users may have predetermined specifications for a component that are not included on the supplier's COA. Where practical, supplier and component user tests or examinations and specifications should be aligned. Refer to the voluntary COA guideline for component COA recommendations⁴¹. The pre-commercial evaluation of the component supplier's COA and commercial confirmation of the reliability of the COA should involve those test results or examinations that pertain to specifications relevant to and established by the component user.

³⁹ §111.75(a)(2)(ii)(A)(B)

⁴⁰ SIDI Work Group (2010). Certificate of Analysis for Dietary Supplement Components: A Voluntary Guideline. Available at: <http://www.sidiworkgroup.com>

4.2.1 Phase 1 Testing (Pre-Commercial)

Phase 1 testing should be performed early in the evaluation of the component and/or component supplier and may coincide with the supplier capability assessment (see Section 3) and other aspects of component supplier qualification. Therefore, although the scope and amount of phase 1 testing will depend, in part, on the risk posed by the component and/or supplier, the test data may also be used to assess risk.

Pre-commercial test results on prototype non-commercial component **batches** should be reconciled and evaluated against commercial batches when they become available.

4.2.2 Phase 2 Testing (Commercial)

Phase 2 testing should occur following pre-commercial qualification of the component supplier. Testing must be performed to confirm those test results from the component supplier's COA that pertain to the component specifications established by the dietary supplement manufacturer or component user per the requirement listed in §111.75(a)(2)(ii)(A). Laboratory testing can be done internally by qualified personnel or by a qualified third-party laboratory. After commercialization, a component specification may be evaluated and amended as necessary to reflect true process capabilities.

The amount (number of batches) and scope of testing should be based on the established risk posed by the component and/or supplier. The use of pre-commercial qualification activities should only be applied to commercial qualification if the component is representative of true commercial production.

4.2.3 Certificate of Analysis Confirmation Recommendation

Phase 1 and phase 2 testing should be appropriately risk based and, at a minimum, follow the recommendations listed in Table 4.1. These recommendations represent a guideline for determining the number of different batches that should be tested. Individual dietary supplement manufacturers or component users may choose to perform their own frequency of testing, commensurate with their resources and risk tolerance. For components manufactured via continuous processes, the batch should be defined based on time or defined quantity or some other quantitative measure.

Table 4.1 Recommended protocol for COA confirmation⁴¹

Risk Profile	Confirmation Recommendations Prior to Reliance on COA
Low-risk supplier/component	<ol style="list-style-type: none"> 1. Test a minimum of the first 3 different consecutive component batches received 2. Evaluate data to verify that test results are consistent with the information provided on the COA and within measurement uncertainty expectations.⁴² 3. Test additional batches if discrepancies are identified. Testing additional batches may be limited to a subset of specifications (e.g., strength) that is misaligned.
Medium-risk supplier/component	<ol style="list-style-type: none"> 1. Test a minimum of the first 5 different consecutive component batches received. 2. Test additional batches for identity, strength, purity, composition, or contaminant attributes that apply to risk factors identified in a cGMP audit and documentation review as applicable. 3. Evaluate data to verify that test results are consistent with the information provided on the COA and within measurement uncertainty expectations. 4. Test additional batches if discrepancies are identified. Testing additional batches may be limited to a subset of specifications that is misaligned.
High-risk supplier/component	<ol style="list-style-type: none"> 1. Test a minimum of the first 10 different consecutive component batches received. 2. Test every batch received for identity, strength, purity, composition, or contaminant attributes that apply to factors identified in a cGMP audit and documentation review as applicable. 3. Evaluate data to verify that test results are consistent with the information provided on the COA and within measurement uncertainty expectations. 4. Test additional batches if discrepancies are identified. Testing additional batches may be limited to a subset of specifications that is misaligned.

⁴¹ These are recommendations only. Each individual company should base COA confirmation on its own supplier/component risk assessment and risk tolerance.

⁴² 21CFR101.9(g)

4.2.4 Economically Motivated Adulteration

During phase 2 testing and periodic reconfirmation, special attention should be paid to components at risk for **economically motivated adulteration** (EMA). Enhanced vigilance in the form of increased testing and more rigorous qualification may be necessary for components prone to EMA, such as proteins, oils, and botanicals (whole plants and extracts). Users should consult their respective component suppliers for information, including analytical methods, to detect and differentiate components susceptible to EMA. Additional information resources, including analytical methods used to detect certain known or suspected adulterants, have been developed for some components and are publicly available.⁴³

In addition to following the protocol in Table 4.1 that corresponds to the risk profile of the supplier and component, users should consider testing every batch received for adulterants potentially added or substituted for economic gain. This also would include testing for requirements for contaminants (e.g., heavy metals, pesticides) when historical values demonstrate a likely presence.

⁴³ US FDA (2009). Guidance for Industry: Pharmaceutical components at risk for melamine contamination. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175984.pdf>

Foster S (2011) A brief history of adulteration of herbs, spices, and botanical drugs. *HerbalGram*. 92:42–57. Available at: <http://cms.herbalgram.org/herbalgram/issue92/FEAT-HxAdulteration.html>

ABC-AHP-NCNPR Botanical Adulterants Program. Available at:

<http://abc.herbalgram.org/site/PageServer?pagename=Adulterants>

American Herbal Products Association. AHPA Guidance Policies: Known Adulterants. Available at: http://www.ahpa.org/Default.aspx?tabid=223#section_known_adulterants

Dietary Supplements Analytical Methods and Reference Materials (AMRM) Program. Analytical methods for dietary supplements. Available at: <http://ods.od.nih.gov/research/AMRMAalyticalMethods.aspx>

AOAC International. Official Methods of Analysis. Available at: <http://www.eoma.aoac.org/>

USP. Food Chemicals Codex. 8th ed. Available at: <http://www.usp.org/products/FCC/>

USP. Food Fraud Database. Available at: <http://www.foodfraud.org>. Contains compilation of the most fraud-prone ingredients in the food supply, analytical methods of detection and type of fraud reported from 1980 to 2010.

5.0 SUPPLIER/COMPONENT REQUALIFICATION CONSIDERATIONS

Suppliers and/or components must be periodically requalified and if the supplier relies on the supplier's COA results, the COA must be reconfirmed on a periodic basis.⁴⁴ The scope and frequency of requalification depends on the risk posed by the supplier/component and the supplier's performance over time.

Low-risk suppliers or components may be subject to less frequent and less extensive requalification, whereas higher-risk suppliers or components may require frequent and extensive requalification procedures. The particular approach to requalification will also depend on the supplier's performance as well as the nature and extent of any deficiencies, failures, or quality events.

Changes, deviations, or failures by the supplier in key areas may necessitate requalification (at a minimum, COA reconfirmation) or may increase the risk posed by the supplier, in turn requiring more frequent requalification.

The combination of low-risk suppliers/components and strong performance history (see Section 6.1.2 for information on performance criteria) may allow a supplier to be requalified via paper audits (i.e., SIDI protocol dossier) in addition to reconfirmation of the COA.

5.1 Certificate of Analysis Reconfirmation

Dietary supplement manufacturers who choose to rely on a supplier's COA results in lieu of their own testing are required to periodically reconfirm the results of the component supplier's COA.⁴⁵ The frequency of COA reconfirmation depends on a combination of factors, including the risk posed by the component and/or supplier, the performance of the supplier, the number of batches of the given component sourced from the supplier over a given period of time, and any mitigation strategy.

In general, COAs from higher-risk components and/or suppliers should be reconfirmed more frequently compared to low- or medium-risk components and/or suppliers. Conversely, the relative frequency of reconfirmation may be influenced by the number of batches of the component sourced annually. Figures 5.1 and 5.2 are general representations of the relationship between COA reconfirmation and supplier/component risk, respectively.

⁴⁴ §111.75(a)(2)(ii)(D)(E)

⁴⁵ §111.75(a)(2)(ii)(D)

Figure 5.1 Supplier/component risk: time model

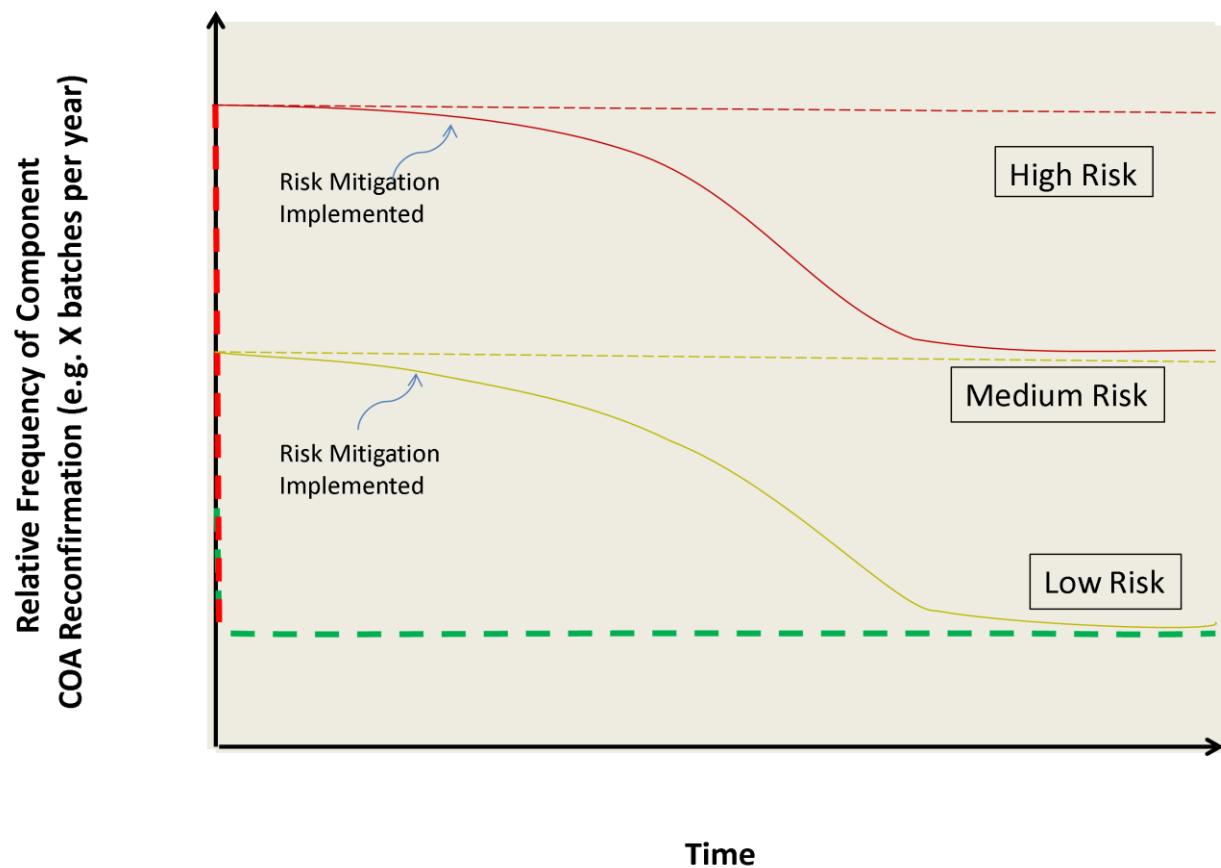
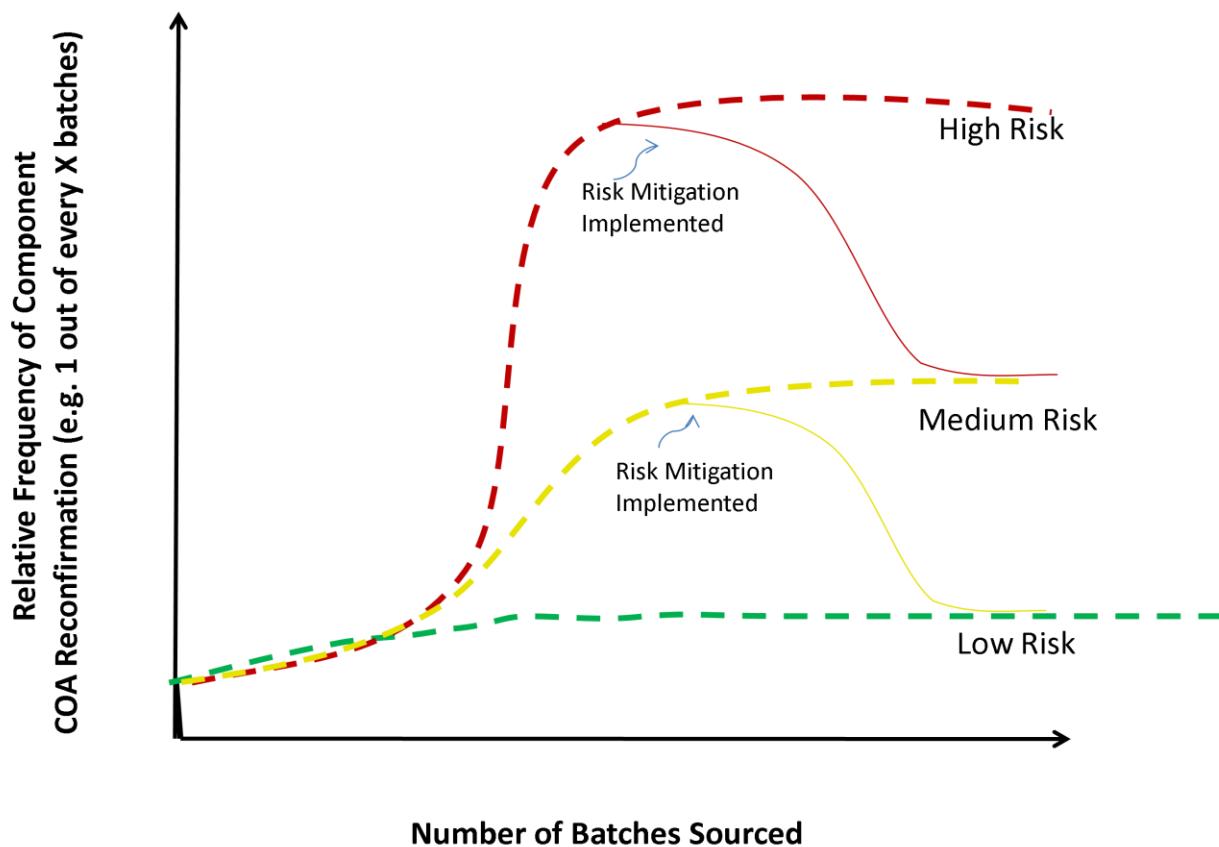


Figure 5.2 Supplier/component risk: volume-based model



5.2 Audit

Auditing frequency and audit depth depends on the risk posed by supplier/component and on past supplier performance. In addition, the complexity of the component and its intended use should be considered.

Three scenarios to consider are:

- Routine auditing on initial risk assessment of supplier/component
- For cause auditing due to special cause event
- Routine risk-based auditing for requalification as necessary

5.3 Change Control

Notification of changes to a component or its specifications may necessitate requalification (or reduced requalification), depending upon the nature and extent of the changes. Lack of **change control** and change notification can serve as an impetus for immediate requalification or may serve as grounds for disqualification (see Section 6). Users should pay particular attention to supplier/component

changes in component composition, component manufacturing processes, raw material sources, and component specifications.

The decision to requalify (e.g., re-audit, COA reconfirmation, and so forth) depends on the component user's needs and the type of change being made.

5.3.1 Significant Changes

Certain changes to the component may necessitate reconfirmation of the COA. Significant changes that also affect the dietary supplement's adherence to specifications for identity, strength, purity, composition, and limits on contaminants may necessitate COA reconfirmation. Depending on the circumstances, this could be limited to a single batch confirmation or multiple batch confirmations depending on the nature of the change. Minor component changes may only necessitate reconfirmation of a particular specification on the component COA.

Although the impact of the change will need to be evaluated on a case-by-case basis, the following types of changes are generally considered significant:

- Starting materials
- Raw material formula
- Specification limits
- Process modification
- Manufacturing site change
- Production scale
- Major equipment changes (new technology)
- Packaging changes (lower barrier resistance)

For more detailed information on what constitutes a significant change, consult the IPEC Significant Change Guide.⁴⁶

5.3.2 Critical-to-Quality Specifications

A **critical-to-quality (CTQ) specification** for a component is a specification that if not met would likely result in the finished dietary supplement being adulterated or misbranded if the component is used. Changes to CTQ specifications should be considered significant changes. Examples, dependent on intended use, are as follows:

- Identity
- Strength
- Purity
- Composition
- Limits on contaminants

⁴⁶ IPEC Americas (March 2009) Significant Change Guide for Bulk Pharmaceutical Excipients. 2nd Rev. Available at: <http://www.ipecamericas.org>

Failure to meet one or more CTQ specifications may require requalification via COA reconfirmation or cGMP audit. Depending on the scope of a change, the reconfirmation may focus on a single specification or multiple specifications.

5.3.3 Change Notification

Component suppliers should provide notification of any significant changes to the component user based on an agreed-upon change notification process. A source for more information on change notification is the IPEC Americas Significant Change Guide.⁴⁷

6.0 SUPPLIER/COMPONENT DISQUALIFICATION

Under certain circumstances, the component user may need to consider the disqualification of a component and/or supplier. Considerations for disqualification should be risk based and balanced against considerations for risk mitigation. Depending on the risk posed by the component or supplier, component users should employ a flexible risk mitigation strategy, allowing time to mitigate the problem(s) posed and/or to qualify a new or additional component source.

- a) *Existing Qualified Supplier:* The disqualification decision should be fact based. For example, the supplier provides material that is reported as compliant to component user specifications; however, confirmation testing shows that test results are out-of-specification. The supplier is not willing to investigate or apply **corrective action** to determine the root cause of the data integrity issue.
- b) *Potential Supplier:* The decision not to select a potential supplier is a risk management-based decision. If the supplier is not willing to engage in mitigation and/or corrective action efforts, then a decision should be considered whether to continue with the supplier qualification process.

6.1 Recommendations for Disqualification

6.1.1 Potential Disqualification Criteria

Components and/or suppliers may be disqualified (i.e., eliminated as an existing component/supplier or from consideration as a potential component/supplier) for one reason or a combination of reasons, depending on the circumstance, the area of deficiency, and the severity or impact of the deficiency. The deficiency or failure may raise the component and/or supplier risk such that they cannot be qualified. The component user should decide at this point whether to accept the risk, attempt to mitigate the risk, or disqualify the component/supplier.

Disqualification criteria may be based on the following basic areas of consideration:

- Supplier performance (existing qualified suppliers)
- Legal/regulatory action (new suppliers/qualified suppliers)
- Special cause event (new suppliers/qualified suppliers)

6.1.2 Supplier Performance

Supplier performance deficiencies might include critical cGMP audit observations, failed COA confirmation tests, change control system failure, and so forth.

6.1.3 Legal/Regulatory Actions

Legal/regulatory actions include consent decrees, warning letters, seizures, injunctions, criminal prosecution of management, falsification of documentation, and enforcement actions/disputes with regulators.

6.1.4 Special Cause Event

A special cause event is specific to a quality failure that cannot be overcome through risk mitigation by the component supplier or the component user. When risk mitigation is unable to bring the component into compliance or if use of the component would render the finished dietary supplement adulterated or misbranded, disqualification of the supplier/component may be warranted.

6.2 Risk Mitigation

Under certain circumstances, a component user may choose to mitigate the risk posed by a deficiency or failure in one or more of the above areas by assisting the supplier and/or by directly addressing the problem. This may include activities such as performing certain tests or examinations that the supplier is incapable of or unwilling to perform, auditing functions, specific actions intended to mitigate the identified ingredient risks, or other activities. Risk mitigation may be an alternative to supplier/component disqualification.

7.0 COMPONENT AND SUPPLIER RISK ASSESSMENT CRITERIA

The following criteria for high-, medium-, and low-risk components are provided to serve only as a guide. When determining component risk, it is important to assess critical characteristics and attributes for the component that are necessary for a comprehensive risk assessment. Some of the component characteristics and attributes that may be used to assess risk are included in Table 8.1.

The elements provided herein are not intended to be an all-inclusive list of risk factors. Likewise, a factor listed may not necessarily apply to a component or supplier if risk has been mitigated for that critical factor. For example, components of complex composition are not always high-risk if the supplier has data to demonstrate that its process is consistently operating in a state of control. Risk factors for both component and supplier need to be assessed in totality and weighted based on intended use.

7.1 High-Risk Component

- Complex composition or produced using a complex process, or a combination thereof.
- Known or suspected to be susceptible to EMA, such as components in high-risk categories that the FDA has identified as adulterated or at high risk for adulteration.⁴⁷
- Challenging to manufacture and does not consistently meet specifications for identity, strength, purity, composition, and limits on contaminants.

7.2 Medium-Risk Component

- Complex composition or produced using a complex process, or a combination thereof.
- Challenging to manufacture and does not consistently meet specifications for identity, strength, purity, composition, and limits on contaminants.

7.3 Low-Risk Component

- Simple composition (e.g., a pure material) and produced by a well-established process and is defined by official compendia or by regulation.
- High probability of consistently meeting established specifications for identity, strength, purity, composition, and limits on contaminants.

The following definitions for high-, medium-, and low-risk suppliers are provided to serve only as a guide. When determining supplier risk, it is important to assess

⁴⁷ US FDA. Tainted Products Marketed as Dietary Supplements. Available at: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm236774.htm#2>

critical characteristics and attributes inherent to the supplier. Some of the supplier characteristics and attributes that may be used to assess risk are included in Table 8.2. Identification of and number of critical and major deficiencies will have an impact on risk ranking.

7.4 High-Risk Supplier

- Lack of or poorly defined QMS.
- Previous history of releasing a component that has failed to meet one or more specifications for identity, strength, purity, composition, and limits on contaminants.
- Subject of recalls or official regulatory enforcement action (e.g., warning letters, consent decrees, etc.)
- Several major deficiencies identified during cGMP inspection.

7.5 Medium-Risk Supplier

- Modest QMS that is lacking certain key elements.
- Few number of major deficiencies identified during cGMP inspection.
- Several gaps identified in review of documentation such as component specifications.

7.6 Low-Risk Supplier

- Robust QMS that has a high probability of detecting internal failures with the component or process prior to release.
- Unlikely to release a component that does not meet specifications for identity, strength, purity, composition, and limits on contaminants.
- No history and unlikely to face official regulatory enforcement action.
- No major deficiencies identified during cGMP inspection.

8.0 COMPONENT AND SUPPLIER RISK FACTORS

The tables that follow include some of the component and supplier characteristics that may be used in a risk assessment. This list is not intended to be all-inclusive. Some of the characteristics and/or factors could be listed in one or more categories of risk depending on the intended use of the component.

Table 8.1 Component characteristics and factors for assessing risk

Low Risk	Medium Risk	High Risk
Comprehensive COA	Minor gaps identified in COA that require consistent follow-up with supplier	COA based on historical data and/or input values or missing key information (e.g., values for agreed-upon specifications)
Compendial grade material	No compendial monograph, but identity, strength, purity, and composition well characterized and consistent with material complexity	No compendial monograph or established specifications
Stability studies conducted on component	Some stability due diligence performed	No stability data
Limits of storage studies conducted on component	Some limits of storage studies performed	No limits of storage studies performed
Component is a single, purified substance	Component has simple composition with only incidental use of processing aids	Component is of complex mixture consisting of many different ingredients
Component is a free-flowing powder in a simple matrix, with visual confirmation of particle size self-evident	Component is granulated into a complex matrix in which particle size distribution can be critical to performance	Component is composed of a complex matrix or mixture (i.e., proprietary dietary ingredient blends)
Supply chain is fully traceable to original starting materials and/or agriculture commodities	Supply chain is somewhat traceable to original starting materials or agriculture commodities	Supply chain is not traceable and origin of manufacture of the component and its starting materials is unknown
Well-substantiated claims for product performance	Weak substantiation for performance claims	Performance claims lack substantiation
Component is produced by a simple product synthesis that is well established	Component is produced by a more recently developed synthesis that is somewhat well established	Component is produced by a complex synthesis that is relatively new
Comprehensive component production flow chart available	Component production flow chart lacks detail	No component production flow chart

Table 8.2 Supplier characteristics and factors for assessing risk

Low Risk	Medium Risk	High Risk
Strong technical dossier (e.g., SIDI™ Protocol)	Technical dossier with gaps in key basic information	No technical dossier
Mature company with many years experience producing target component	Experienced company with some experience producing target component	Start-up company with limited or no production experience with target component
Company manufactures in well-developed country with mature government regulatory system	Company manufactures in country with moderately robust government regulatory system	Company manufactures in country with a developing government regulatory system
Strong regulatory history with record of corrective actions	No regulatory history or minor regulatory citations	Significant regulatory citations and weak corrective action execution
Well-documented specifications for identity, strength, purity, composition, and limits on contaminants	Minor gaps identified in specifications	Major gaps identified in specifications
Comprehensive change control system	Documented change control system with minor gaps	Lack of and/or poorly documented change control system
Formal process capability studies on file	Some formal process capability on file, but no formal analysis of data	No process capability data
Low incidence of customer complaints with formal corrective actions program	Moderate incidence of customer complaints with no formal corrective actions program	High incidence of customer complaints or undocumented program with no formal corrective actions
Component is not known or suspected to be subject to EMA	Component has limited potential for EMA	Component is known or suspected to be subject to EMA
Direct purchasing/sourcing relationship with manufacturer of the component	Indirect purchasing/sourcing relationship with respected broker or distributor of the component	Indirect purchasing/sourcing relationship with broker/distributor with unknown or poor compliance/service history
Favorable audit results by third party	Minor deficiencies noted by third-party audit firm	Major deficiencies noted by third-party audit firm
Favorable direct audit results	Minor deficiencies noted by direct audit	Major deficiencies noted by direct audit
Strong technical services support personnel with comprehensive knowledge of component and process	Some technical services support, but lacking in experience and component and process knowledge	No technical service support personnel available

APPENDIX A: SUPPLIER/COMPONENT QUALIFICATION EXAMPLES

Disclaimer: *The following examples are for illustrative purposes only. Any similarities with actual circumstances are coincidental. The examples should not be used to designate a specific ingredient or country of origin in a high, medium, or low risk category. The examples are designed to provide a framework for understanding how to conduct your own analysis of the particular facts of your circumstances.*

A.1 Introduction

The examples contained herein are intended to provide guidance with respect to supplier/component risk classification, supplier/component requalification, and supplier disqualification, as well as to inform decision making pertaining to suppliers and components for use in dietary supplements.

The application of risk management principles allows the user of the component to fully understand the supplier and component attributes that need to be considered as part of the supplier qualification process. This facilitates proper engagement of suppliers for the purpose of mitigating risk and ensures the allocation of resources to those suppliers/components that bear the highest risk.

Decisions should be made without a conflict of interest and should be documented for compliance in accordance with applicable cGMP regulations.

These examples are not intended to be all-inclusive and should not be taken as legal advice. The supplier and user activities highlighted herein are illustrative and additional due diligence activities on the part of both parties may be appropriate, depending on the situation.

Where appropriate, companies should consult with regulatory, quality assurance, and legal resources within their own organizations to ensure that statutory and regulatory obligations have been met.

The examples have been placed into categories that include all of the major elements involved in supplier/component qualification. The examples are organized as follows:

- A.2 Pre-Commercial Supplier/Component Risk Assessments
- A.3 cGMP Audit Supplier/Component Risk Assessments
- A.4 Certificate of Analysis Confirmation
- A.5 Supplier Disqualification

In each of the examples, the supplier (i.e., A, B, C...) refers to a component supplier that has the potential to supply its component to a user. An overview of the due diligence activities is provided, but is not meant to be all-inclusive.

Following the due diligence overview is the supplier/component risk assessment that is determined by the user. Note that each example is unique and each element of due diligence may carry a different weight in a risk assessment based on intended use.

A.2 Pre-Commercial Supplier/Component Risk Assessments and Decision Impact

Example A.2.1 Low-Risk Component/Supplier

Due Diligence Overview: Supplier A sells chondroitin sulfate manufactured from the trachea of domestic cattle. Supplier A has a strong compliance program in place to monitor the health of cattle and provides documented evidence that ensures traceability and compliance to international regulations to minimize the potential for bovine spongiform encephalopathy contamination at the time of slaughter. The supplier has been in the chondroitin sulfate manufacturing business for over 15 years without regulatory enforcement actions and the facilities are located in a country with a mature government regulatory system and a low rate of consumer food/dietary supplement safety incidents.

The user makes a determination that the component is susceptible to EMA and, therefore, determines that an onsite audit is warranted. The audit confirms that Supplier A is in compliance with applicable cGMPs and has excellent traceability and the appropriate documentation and recordkeeping. The user fully tests the first 5 component batches received from Supplier A and the test results confirm that the COA is reliable.

Supplier/Component Risk Assessment and Decision: The user concludes that Supplier A and the component are low risk, and moves to reduced testing on incoming shipments to include identity testing only. The user establishes a COA reconfirmation frequency of once every 3 months based on the potential for EMA. A re-audit period is established by the user of once every 3 years and a provision is made to allow for the acceptance of an independent third-party audit.

Example A.2.2 Low-Risk Component/Supplier

Due Diligence Overview: Supplier B manufactures and markets a blue corn dietary ingredient to the food and dietary supplement industries. The corn starting material is purchased under contract from many different regions in the United States and Canada. Supplier B has a complex system of traceability and ensures that the starting material is batch-controlled to a geographic region or to each individual harvester. The component is susceptible to aflatoxin contamination if not properly harvested and stored. Supplier B has a comprehensive aflatoxin surveillance program and provides details of the program to component users as requested. Supplier B also provides a comprehensive COA to users upon request, and this COA includes aflatoxin testing results. Supplier B also provides an independent third-party audit report to component users upon request. The audit report reveals no critical observations and the supplier response is

determined to be acceptable. Supplier B has been in business for over 10 years and has no history of regulatory enforcement actions. The dietary supplement manufacturer fully tests the first 3 batches of the component received from Supplier B and the test results, including those for aflatoxin, confirm that the COA is reliable.

Supplier/Component Risk Assessment: The user concludes that Supplier B and the component are low risk, and approves reduced testing on incoming batches to include identity testing only. The user establishes an annual COA reconfirmation frequency, accepts the independent third-party audit report, and waives the direct audit of Supplier B. The user requests that an independent third-party audit be conducted annually.

Example A.2.3 Low-Risk Component/Supplier

Due Diligence Overview: Supplier C is located in the United States and sells potassium chloride to food and dietary supplement manufacturers. Supplier C has a comprehensive technical dossier that includes the manufacturing process and process capability data, demonstrating that the potassium chloride consistently meets the specifications defined in the Food Chemicals Codex. Supplier C has been in business supplying potassium chloride for over 10 years and has no history of regulatory enforcement action. Supplier C has been audited but is not able to share independent third-party audit reports due to confidentiality reasons.

Supplier/Component Risk Assessment: The user concludes that Supplier C and the component are low risk, and approves reduced testing on incoming batches to include identity testing only. The user establishes an annual COA reconfirmation frequency, and determines that the risk factors associated with this component are so low that an audit is not required.

Example A.2.4 Low-Risk Component/Supplier

Due Diligence Overview: Supplier D is located in the United States and sells methylsulfonylmethane to the US dietary supplement market. Supplier D has been in business manufacturing methylsulfonylmethane for over 10 years and is manufacturing this component to current compendial standards. Supplier D has comprehensive documentation, including an executed SIDI protocol dossier and comprehensive flow charts that document all processing steps and critical control points for quality. The manufacturing process is well established and the supplier has data to demonstrate that the process is operating in a state of control. These data include a process capability study. Supplier D has been audited by 2 independent third-party consultants, both of which are highly respected in the industry. Supplier D is willing to share the audit reports with potential customers after the execution of a confidentiality agreement. The independent third-party audit reports revealed only minor observations and the company response to the observations was deemed appropriate. The audit report also notes that Supplier D has a robust QMS with state-of-the-art facilities and laboratory capabilities.

Supplier/Component Risk Assessment: The user concludes that Supplier D and the component are low risk, and makes a determination that it will test the first 3 incoming component batches and, if acceptable, will proceed with reduced testing only. Reduced testing will include an identity test of this dietary ingredient. The user establishes an annual COA reconfirmation frequency. The user accepts the independent third-party audit report, waives any direct audit of Supplier D, and requests that the independent third-party audit be submitted every 2 years.

Example A.2.5 Medium-Risk Component/Supplier

Due Diligence Overview: Supplier E manufactures a dietary ingredient that uses corn starch as a carrier/excipient. The dietary ingredient is manufactured in the United States and the corn starch is purchased on the US commodity market and typically includes genetically modified corn. The user wishes to purchase this dietary ingredient; however, the finished product is intended to be labeled GMO-free. Supplier E and the user work together and determine that a custom formula can be created to address the specific requirements. A supply and quality agreement is developed that defines the needs/requirements for traceability of the corn starch with a reasonable degree of certainty. Supplier E, under the program, will have traceability of the starting corn material to document that the corn starch originated from identity-preserved corn. The user performs COA confirmation testing on 5 batches and the test results confirm that the COA is reliable. The user performs an onsite audit and determines Supplier E is in compliance with applicable cGMPs; however, several deficiencies are observed specific to the documentation and recordkeeping for the traceability on the corn starch.

Supplier/Component Risk Assessment: The user concludes that Supplier E and the component are medium risk and requires that Supplier E include a certificate of compliance for the corn starch sub-component with each shipment in addition to the COA. The user requires that Supplier E perform corrective actions specific to their documentation and recordkeeping practices and schedules a re-audit of the site for 1 month after the last committed corrective action is complete. The user establishes an annual COA reconfirmation frequency. Supplier E may be reassessed as low-risk once they have completed corrective actions specific to their documentation and recordkeeping.

Example A.2.6 Medium-Risk Component/Supplier

Due Diligence Overview: Supplier F is a manufacturer of a dietary ingredient that is a botanical extract standardized to specific marker compounds. The botanical is an aqueous/ethanolic extract that has been in use for over 50 years without any reports of adverse events. Supplier F has only been manufacturing this botanical extract for approximately 10 months. Supplier F has limited production experience with this component and has set specifications based on literature searches and a limited number of commercial production runs of the extraction process. Supplier F agrees to gain experience with respect to potential variation in starting material from season to season and develop an understanding of what

they must do to adjust the process to compensate for this variation. Supplier F also has a large portfolio of other products sold to the dietary supplement industry and has a good, solid reputation in the industry. Supplier F also has limited testing capabilities internally and it is known that this component can be susceptible to high microbial bio-burdens if not extracted, packaged, and stored properly. Supplier F does not have an independent third-party audit report available to share with its customers. The user performs a cGMP audit and finds no critical observations but several major and minor observations. Supplier F submits a corrective action plan that is approved by the user. The user tests the first 3 batches of the component received from Supplier F and the test results confirm that the COA is reliable.

Supplier/Component Risk Assessment: The user determines that Supplier F and the component are medium-risk and makes a determination that it will fully test an additional 3 batches of the component from Supplier F. The user will schedule a re-audit of Supplier F after the execution of its corrective action plan and determines that the frequency of COA reconfirmations will be 3 per year, based on the number of lots expected to be purchased annually. Supplier F may be reassessed as low-risk pending confirmation of completed corrective action plans.

Example A.2.7 Medium-Risk Component/Supplier

Due Diligence Overview: Supplier G is a manufacturer and marketer of a Ceylon cinnamon component to the food and dietary supplement industries. The cinnamon is produced in a country with a developing government regulatory system and the supplier has appropriate documentation to document the geographic origin of the component. Supplier G has been in business manufacturing this unique flavor for sale worldwide for over 10 years and has no known regulatory enforcement actions. The user intends to use this component as a flavoring agent and intends to make a claim that its product contains natural Ceylon cinnamon flavor. This Ceylon cinnamon (*Cinnamomum verum*) component is significantly more expensive than the more commonly available Chinese cinnamon (*Cinnamomum aromaticum*). The naturally occurring coumarin level in Ceylon cinnamon is much lower than that found in Chinese cinnamon. Supplier G does not have an independent third-party audit available and the user has limited resources to perform a cGMP audit in another country. Supplier G submits a COA to the user for review and the user determines that the COA does not contain enough information to confirm the cinnamon flavor as authentic Ceylonese cinnamon. The user has concerns with respect to EMA and requests that a test for coumarin levels be added on the COA. Supplier G agrees to this COA amendment and the user tests the first 3 batches. The test results confirm that the COA is reliable and that the starting cinnamon used to manufacture the flavor is authentic Ceylon cinnamon.

Supplier/Component Risk Assessment: The user concludes that Supplier G and the component are medium risk and makes a determination that it will perform

full COA testing on first 5 batches including authenticity testing (for presence of coumarin) received from Supplier G. The user determines that the frequency of COA reconfirmations will be set at 2 per year. Supplier G may be reassessed as low-risk if the user were to choose to audit the supplier and confirm supply chain traceability.

Example A.2.8 Medium-Risk Component/Supplier

Due Diligence Overview: Supplier H is a manufacturer/marketer of a botanical dietary ingredient. The botanical dietary ingredient is manufactured in China from both wild crafted and farmed sources in the Asia/Pacific region. The manufacturer has been producing this component for 4 years. The component is standardized to a unique marker compound, but there is no compendial specification established for this component. Supplier H has been audited by a reputable independent third-party organization and is willing to share the audit report with prospective customers. The audit report reveals several major observations as well as numerous minor observations. The audit report also reveals that Supplier H has a QMS that has several elements that are sophisticated, but others that are less developed. Some of the less developed QMS include document control, change control, and method verification. Testing on commercial batches of material supplied by Supplier H has shown that the product meets all pre-established specifications. Supplier H does not have a complete technical dossier, such as the SIDI protocol dossier; however, their specifications are well established and supported by a significant amount of historical data.

Supplier/Component Risk Assessment: The user concludes that Supplier H and the component are medium risk and establishes COA reliability based on testing of the first 5 batches of the botanical dietary ingredient. The user will apply reduced testing on the dietary ingredient; however, the assay for marker compounds will be applied to each receipt in addition to the required identity testing. The user accepts the independent third-party audit and requires that Supplier H submit quarterly updates to the corrective action plans established in response to the third-party audit. The user requires that the independent third-party audit be performed the following year and that a report be submitted to include corrective action verification from the previous audit. The user also requests that Supplier H submit a SIDI protocol dossier for the component.

Example A.2.9 High-Risk Component/Supplier

Due Diligence Overview: Supplier I is a recently formed US subsidiary of a Chinese company that imports a dietary ingredient into the United States. The component is a concentrated extract of nutmeg. Due diligence reveals that the US subsidiary is simply a single salesperson in a rented office space with no appreciable assets. The user has been working with Supplier I to address gaps in their COA. Supplier I's COA does not report values for the presence of safrole, a naturally occurring compound present in nutmeg that has known toxicity and is prohibited from direct addition or from use in human food under US FDA

regulations. Supplier I refuses to test for safrole on behalf of the user and is also unable to provide substantiation to the user that the component is a grandfathered dietary ingredient under the Dietary Supplement Health and Education Act of 1994 or has appropriate regulatory status for use in dietary supplements. Thus, a determination of legal dietary ingredient status cannot be made.

Supplier/Component Risk Assessment: The user concludes that Supplier I and the component are high-risk and that risk mitigation is not possible at the current time because Supplier I is not forthcoming with documentation to establish legal dietary ingredient status and contaminant testing due diligence. All activities pertaining to the qualification of Supplier I are terminated and an alternate supplier is sought.

Example A.2.10 High-Risk Component/Supplier

Due Diligence Overview: Supplier J purchases commonly consumed berries from Chinese suppliers in the spot market. The berries are processed in a country with a developing government regulatory system as dehydrated fruit and then shipped to various customers domestically and internationally. The dehydrated berries have been subject to FDA automatic detention procedures specific to the presence of pesticides and sulfiting agents. The user intends to develop a standardized extract from the berries and develop this into a finished dosage form dietary supplement for sale in the United States. The user receives small samples of the berries for extraction trials and submits these to an independent third-party laboratory for contaminant testing. Test results show the presence of several pesticide residues for which there are no established US Environmental Protection Agency tolerances. The test results also show the presence of sulfiting agents at 200 ppm.

Supplier/Component Risk Assessment: The user concludes that Supplier J and the component are high risk and that risk mitigation is not possible because further processing of the dehydrated berries into an extract will not address the issue of the violative pesticide residues. All activities pertaining to the qualification of Supplier J are discontinued and an alternate supplier is sought.

Example A.2.11 High-Risk Component/Supplier

Due Diligence Overview: Supplier K has submitted a bid to a user for a specific line of dietary ingredients that have been established in the marketplace for many years. Supplier K is relatively new to the dietary ingredient market and is selling these components significantly below market costs. Supplier K is only willing to share limited information to the user concerning the component and is unwilling to engage in an audit or the completion of the SIDI protocol dossier for the specific components proposed.

Supplier/Component Risk Assessment: The dietary supplement manufacturer concludes that Supplier K and the component are high risk. Supplier K is not

approvable because it is not willing to engage the user in the necessary due diligence activities required to establish that the supplier is qualified.

Example A.2.12 High-Risk Component/Supplier

Due Diligence Overview: Supplier L is a manufacturer of chondroitin sulfate sodium. The manufacturing facilities are located in a country with a developing government regulatory system and the starting materials are sourced from throughout the Asia/Pacific region; however, there is no traceability because most of these starting materials come from small farms. Supplier L has been producing this material for over 10 years and has developed some technical documentation but has not completed a full SIDI protocol dossier for this component. Supplier L has not been audited by a potential user, nor have they been audited by any independent third-party auditing organization. The user requests that 3 batches of the component be submitted to them for testing against all established specifications. The user receives the test results and determines that the component meets all applicable compendial requirements and established specifications; however, they have not received full commercial quantities.

Supplier/Component Risk Assessment: The user concludes that Supplier L and the component are high-risk due to the component's susceptibility to EMA, a lack of facility-specific audit information, and incomplete technical documentation (a comprehensive SIDI protocol dossier). The user decides to proceed with the qualification of this supplier and implement specific risk mitigation measures to ensure compliance. The user performs a full QMS audit and makes the determination that each receipt of the component will be subjected to full testing for all established specifications for a minimum of 1 year or 20 individual batches, whichever is greater. The user will closely monitor Supplier L to ensure that any audit corrective actions are promptly completed, commensurate with a formal risk assessment. The user assists Supplier L in the development of a comprehensive SIDI protocol dossier. The audit corrective action plan includes ensuring full traceability of all starting materials used by Supplier L as well as statements from the supplier's government that the bovine trachea is suitable for use in human food and not at risk for bovine spongiform encephalopathy contamination.

A.3 cGMP Audit Supplier/Component Risk Assessment

Example A.3.1

A user performs a routine due diligence audit on Supplier A of a key component it has been purchasing for 3 years. Yearly audits have been conducted on Supplier A with only minor observations noted in all previous audits. Supplier A was previously classified as a low-risk supplier. The current audit reveals several major observations that relate to the change and use of analytical methods that have not been established as suitable for their intended use. The test methods that were changed since the previous audit include methods for assay and identity.

Supplier Risk Assessment: The user makes a determination that Supplier A should be reclassified as high risk and immediately initiates full testing for all established specifications on each component batch received. The user works with Supplier A to verify the assay and identity test methods. The user will move to reduced testing once the 2 methods have been verified and once the user has a high degree of assurance that the COA submitted by Supplier A with each batch is reliable.

A.4 Certificate of Analysis Confirmation

Example A.4.1

A user purchases calcium carbonate from Supplier A located in China and has qualified the supplier by performing COA confirmation testing and a cGMP audit, and also has an approved quality agreement with Supplier A. During the course of finished product testing, the user determines that the finished product is just outside the specification for lead. The lead specification is established at NMT 250 ppb. The user tests the calcium carbonate and obtains a result of 260 ppb. Supplier A's COA shows the lead value at 235 ppb. The user contacts Supplier A and requests a full investigation. Supplier A prepares a comprehensive written report and informs the user that they have recently changed sources of starting material (limestone) and qualified the source. This qualification included testing for lead and other heavy metals to ensure that the finished component would meet all pre-established specifications. Supplier A also concludes that its COA was accurate and reflected the actual level of lead. Supplier A also informs the user that they believe the discrepancy between the 2 values is likely due to measurement uncertainty for the trace analysis. Supplier A concludes that in order to ensure that lead requirements would consistently be met, they will have to return to their previous supplier of limestone. Supplier A adjusts their internal specification to 225 ppb to account for measurement uncertainty and recommends that the user maintain their specification at 250 ppb.

Supplier/Component Risk Assessment: The user agrees to all of the recommendations made by Supplier A and approves their comprehensive report. The user adjusts Supplier A's risk profile to medium-risk and recommends that the next 5 consecutive batches be subjected to lead testing as a prerequisite to release. The 5 batches are tested and all 5 meet the 250 ppb specification for lead. Supplier A's risk classification is then adjusted back to low-risk and the incident is closed.

A.5 Supplier Disqualification

Example A.5.1 Supplier Disqualification – Multiple-Sourced Component

Due Diligence Overview: Supplier A has been an approved, qualified supplier of a component to a user for approximately 3 years. The user performs an audit of Supplier A and discovers, during a confirmation of COAs submitted to them, that some of the data have been falsified. The user informs Supplier A that this is a critical observation and requests an explanation in writing.

Supplier Disposition: The user receives a letter of explanation from Supplier A, reviews this letter, and determines that the QMS of Supplier A has failed and that this issue cannot be reconciled in the short term. The user determines that they have multiple sources of the same material and immediately proceeds to disqualify Supplier A for future purchases of the component in question. The user also proceeds to conduct an investigation on any components in process or already incorporated into finished products. This disqualification includes returning all material that has been received and is unused at its site. The user also considers disqualifying this supplier for all components if they supply multiple components.

Example A.5.2 Supplier Disqualification – Single-Sourced Component

Due Diligence Overview: Supplier B has been an approved, qualified supplier of a component to a user for approximately 3 years. The user performs an audit of Supplier B and discovers, during a confirmation of COAs submitted to them, that some of the data have been falsified. The user informs Supplier B that this is a critical observation and requests an explanation in writing.

Supplier Disposition: The user receives a letter of explanation from Supplier B. The user is single-sourced for this component and determines that the qualification of a new supplier will take 4–6 months. The user reviews the letter of explanation and determines that the QMS of Supplier B has failed and that its only course of action is to mitigate the risk from Supplier B by fully testing each component batch received. The user also performs full testing on all components in stock and immediately begins the process for qualifying a new supplier with the intent to disqualify Supplier B as soon as a new supplier is approved.

Example A.5.3 Supplier Disqualification – Microbial Contamination

Due Diligence Overview: A user tests its finished dosage form products for microbial levels on a routine basis. During a routine test, a presumptive positive result for *Salmonella* is found on a batch of finished product. The user conducts an investigation and determines that a component obtained from Supplier C is the source of the contamination. Supplier C is contacted and provides a written report to the user in which they stand behind the results on their COA that showed *Salmonella* to be negative. The user rejects and destroys the product and immediately determines that all future receipts of this material from Supplier

C shall be tested for microbial levels and confirms that Supplier C only supplies this one component. Testing on 3 additional batches received after the incident also shows positive results for *Salmonella*. Supplier C performs an investigation that includes a more comprehensive sampling plan and also confirms that samples are positive for *Salmonella*. The user has multiple sources of this component.

Supplier Disposition: The user disqualifies this supplier for this specific component until such a time that Supplier C is able to determine the root cause and develop a corrective action plan to address the deficiency.

Example A.5.4 Supplier Disqualification – Unauthorized Change Control

Due Diligence Overview: Supplier D is a manufacturer of a dietary ingredient provided to a user in the United States. The user performs periodic COA confirmation testing on the component received from Supplier D and an out-of-specification result is obtained for lead. The investigation with the supplier reveals that Supplier D changed sources of starting material and was using historical values instead of testing each batch for lead. Had the supplier been testing each batch, they would have realized the impact of the change on their finished component. This is the third change control event that Supplier D has initiated without prior notification to the user in the past year. The previous events were discovered through reviews of specifications, COAs, and SIDI protocol dossiers.

Supplier Disposition: The user determines that 3 change control events taking place without notice in a single year is cause for disqualification of Supplier D. The user moves to an alternate source of the component and informs Supplier D that they will no longer be approved for the purchase of this or any other component.

Example A.5.5 Supplier Disqualification – Certificate of Analysis Data Integrity

Due Diligence Overview: Supplier E is a manufacturer of a pomegranate powder that is supplied to both the dietary supplement and food industries. A user performs COA pre-commercial testing and determines that the component is suitable for its intended use in dietary supplements. There are 3 marker compounds that are assigned specification values to support claims made in labeling. The compounds include total punicalagins A and B at >5% and ellagic acid <15%. These compounds are also indicative of high-quality, pure dehydrated pomegranate. The user tests the first 3 batches of the material received and the results are well within pre-established specifications. The user elects not to perform a cGMP audit and documents rationale for this risk-based decision. The values for total punicalagins and ellagic acid are listed as discrete values on the COA. The user communicates to Supplier E that it will be accepting material based on the COA. The next batch of material received by the user is accompanied by an incomplete COA with test results reported as “Complies to

Standard" for both the punicalagin and the ellagic acid assays, rather than quantitative values. This raises questions for the user who then determines to test the component. The results from an independent third-party laboratory show 4.8% for the total punicalagins A and B and 15.2% for ellagic acid. The user requests an explanation from Supplier E but is offered no explanation for the discrepant results. The user rejects the component and performs testing on the next 3 batches received; all 3 show the same level of consistency with the total punicalagins and ellagic acid values failing to meet specification limits. Supplier E continues to offer no rational explanation for the sudden change in values.

Supplier Disposition: The user has determined that Supplier E is classified as high-risk based on 3 change control events taking place without notice, disqualifies Supplier E, and moves component purchasing to an alternate supplier. The user informs Supplier E that they are no longer an approved supplier for this or any other component. The user made this determination because the supplier was unable to identify a root cause of the failure to meet specifications.

APPENDIX B: SUPPLIER AND COMPONENT RISK ASSESSMENT GRID

		Supplier and Its Systems (Degree of Risk)		
		Low	Medium	High
Component (Degree of Risk)	High			
	Medium			
	Low			

Key

Black, no/limited opportunity for risk mitigation.

Dark gray, some opportunities for risk mitigation to a lower risk level.

Light gray, good opportunities for risk mitigation to a lower risk level.

White, very low risk component and supplier combination.

GLOSSARY

Adulteration	The presence of undeclared chemical, biological, physical, and or radiological substance(s) that should not be contained within the component for legal or other reasons.
Batch	A specific quantity of a component and/or dietary supplement that is uniform; that is intended to meet specifications for identity, purity, strength, and composition; and that is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. May also be interchangeable with “lot.”
Certificate of analysis (COA)	A document relating specifically to the results of testing a representative sample drawn from the batch of material to be delivered.
Change control	The processes and procedures to manage changes being made to a product, process, schedule, or budget, including the submission, analysis, decision making, approval, implementation, and post-implementation of the change. Change control is typically an element of agreements between the manufacturer and supplier (discussed in the SIDI protocol).
Corrective action	A solution meant to reduce or eliminate an identified problem.
Critical-to-quality (CTQ) specification	A specification related to a component that if not met would likely result in the finished dietary supplement being adulterated or misbranded if the component is used.
Detectability	The ability to discover or determine the existence, presence, or fact of a hazard.
Dietary supplement component	Defined as both dietary ingredients and other ingredients. Any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Components include dietary ingredients and other ingredients (e.g., excipients, preservatives, and colorants) that may be included in a dietary supplement. For the purposes of this document, component does not include packaging material.
Economically motivated adulteration (EMA)	The fraudulent, intentional substitution, or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its

	production (i.e., for economic gain).
Misbranding	A food, including a dietary supplement, shall be deemed to be misbranded if the label, brand, tag, or notice under which it is sold is false or misleading in any particular as to the kind, grade, quality or composition. Misbranding of food is defined in §403 of the Federal Food, Drug, and Cosmetic Act (FDCA).
Out-of-specification	A term that indicates that a unit does not meet a given requirement or specification.
Pre-commercial	Qualification activities that occur prior to commercial purchase of a component.
Probability	The likelihood of the occurrence of an event, action, or item.
Quality management system (QMS)	A formalized system that documents the structure, responsibilities, and procedures required to achieve effective quality management.
Risk management	Using managerial resources to integrate risk identification, risk assessment, risk prioritization, development of risk handling strategies, and mitigation of risk to acceptable levels.
Severity	A measure of the possible consequences of a hazard.
SIDI™ Protocol	SIDI™ Protocol is an outline representing the type and scope of information that an ingredient supplier typically needs to provide to a manufacturer. The primary goal of the protocol is to provide standards for voluntary use in the exchange of relevant and required information between ingredient suppliers and finished product manufacturers that will simplify this exchange and enable the reallocation of resources for both parties.
Specification	The quality parameters to which the component or component intermediate must conform and that serve as a basis for quality evaluation.
Supplier	A manufacturer or distributor who directly provides the component to the user.
User	A party who utilizes a component in the manufacture of a dietary supplement or another component.

ABBREVIATIONS LIST

API	Active Pharmaceutical Ingredients
ANSI	American National Standards Institute
COA	Certificate of Analysis
CTQ	Critical-to-Quality
EIP	Excipient Information Protocol
EMA	Economically Motivated Adulteration
FDA	US Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
FOIA	Freedom of Information Act
FTC	Federal Trade Commission
cGMP	Current Good Manufacturing Practices
GRAS	Generally Recognized as Safe
ICH	International Conference on Harmonization
IFAC	International Food Additives Council
IPEA	International Pharmaceutical Excipients Auditing Inc.
IPEC	International Pharmaceutical Excipients Council
ISO	International Organization for Standardization
NPA	Natural Products Association
NSF	NSF International
QMS	Quality Management System
SIDI	Standardized Information on Dietary Ingredients (in SIDI™ Protocol)
SQF	Safe Quality Food Institute
USP	US Pharmacopeial Convention