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July 26, 2010

VIA HAND DELIVERY

Donald S. Clark
Office of the Secretary
U.S. Federal Trade Commission
601 Pennsylvania Avenue, N.W.
Washington, D.C. 20580

Re: Rx-360 Audit Programs - Request for Advisory Opinion

Dear Don:

On behalf of the Rx-360 International Pharmaceutical Supply Chain Consortium ("Rx-360" or the "Consortium"), we are writing to request an advisory opinion from the staff of the Federal Trade Commission ("FTC" or the "Commission") pursuant to Commission Rules of Practice 1.1-1.4. 16 C.F.R. §§ 1.1-1.4. Rx-360 plans to implement two separate supplier audit programs, specifically: (i) the sharing of supplier quality audits conducted by or on behalf of individual Rx-360 members ("Rx-360 Audit Sharing Program") and (ii) the performance of joint quality audits of pharmaceutical suppliers ("Rx-360 Joint Auditing Program").

As explained in further detail below, Rx-360 expects that each of these programs will further the Consortium's goal of enhancing the security of the pharmaceutical supply chain. Before Rx-360 implements these audit programs, it seeks an opinion from the FTC about whether either program would raise any antitrust concerns.

Rx-360 is a not-for-profit, international consortium created by members of the biotech and pharmaceutical industries, including both research-based and generic pharmaceutical manufacturers, and their suppliers. The mission of Rx-360 is to protect patient safety by enhancing the quality of the supply chain and authenticity of materials within the supply chain. Professional organizations, trade associations, and government regulators, such as the U.S. Food and Drug Administration ("FDA"), are invited to participate in the Consortium as observers.

Established 1849

NON-PUBLIC

Pharmaceutical Supply Chain Background

Millions of people around the world are treated every day with vital medicines discovered and developed by pharmaceutical and biotech companies. Ensuring the safety and quality of those medicines has become a top public health concern. Accordingly, management of the drug supply chain is of paramount importance. Globalization of distribution for both drug components – such as raw materials, active pharmaceutical ingredients ("APIs") and excipient ingredients – and finished products has introduced many complications that challenge the security of the supply chain. These complications can provide opportunities for the introduction of counterfeited, adulterated and contaminated materials, sometimes with tragic consequences. This issue is highlighted by the following highly publicized incidents:

- Adulterated glycerin with diethylene glycol (antifreeze) used to manufacture cough syrup led to 67 deaths in Panama and 103 deaths in Haiti (mostly children).[1]
- Adulterated heparin with hypersulfated chondroitin sulfate led to 81 deaths in the US and Europe.[2]
- Adulterated milk with melamine led to contaminated infant formula causing kidney stones and deaths of infants in China.[3] (Melamine contamination is a risk in pharmaceutical components as well.[4])
- Adulterated glycerin with diethylene glycol used to manufacture teething gel led to over 40 infant deaths in Nigeria.[5]

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[1] Walt Bogdanich, *From China to Panama, a Trail of Poisoned Medicine,* N.Y. TIMES, May 6, 2007, *available at* http://www.nytimes.com/2007/05/06/world/06poison.html.

[2] Walt Bogdanich, *The Drug Scare that Exposed a World of Hurt*, N.Y. TIMES, March 30, 2008, *available at* http://www.nytimes.com/2008/03/30/weekinreview/30bogdanich.html.

[3] Edward Wong, *China Says More Milk Products Show Signs of Being Tainted*, N.Y. TIMES, Sept. 18, 2008, *available at* http://www.nytimes.com/2008/09/19/world/asia/19milk.html.

[4] *See* FDA GUIDANCE FOR INDUSTRY ON PHARMACEUTICAL COMPONENTS AT RISK FOR MELAMINE CONTAMINATION (August 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM175984.pdf.

[5] Lydia Polgreen, *84 Children Are Killed By Medicine in Nigeria*, N.Y. TIMES, Feb. 6, 2009, *available at* http://www.nytimes.com/2009/02/07/world/africa/07nigeria.html?ref=world.

- The World Health Organization ("WHO") estimates that 10 percent of all medicines around the world are counterfeit. WHO also estimates that up to 25 percent of medicines sold in developing countries may be counterfeit. Some studies conclude that the percentage may be even higher.[6]

Naturally, such incidents have prompted loud and swift reactions from consumers, health authorities and policy makers.

The biotech and pharmaceutical industries require secure and reliable supply chains that deliver the appropriate ingredients and other materials of a suitable quality so that medicines can be trusted by health care practitioners and patients. The growth and globalization of the pharmaceutical supply chain presents an enormous challenge for manufacturers to monitor the quality of production at their supplier sites. A single drug manufacturer may source materials from hundreds, even thousands, of supplier sites around the world.

FDA regulations and guidance documents require pharmaceutical manufacturers to perform audits of their suppliers' sites in order to ensure that these suppliers meet the necessary standards for providing safe, high-quality materials.[7] Audits may be performed by a pharmaceutical manufacturer's in-house auditors or by third-party auditors hired by the pharmaceutical manufacturer.

Although the FDA also conducts inspections of both finished drug product manufacturers and certain other suppliers,[8] it has limited capacity to inspect all drug manufacturing activity worldwide. Indeed, the Government Accountability Office ("GAO") estimates that the FDA inspects only about 8 percent of foreign drug

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[6] World Health Organization, FACT SHEET NO. 275 ON SUBSTANDARD AND COUNTERFEIT MEDICINES (Nov. 2003), *available at* http://www.who.int/mediacentre/factsheets/2003/fs275/en/.

[7] *See, e.g.*, FDA GUIDANCE FOR INDUSTRY ON QUALITY SYSTEMS APPROACH TO PHARMACEUTICAL CGMP REGULATIONS, at p.16 ("The quality systems approach also calls for periodic auditing of suppliers based on risk assessment. During the audit, a manufacturer can observe the testing or examinations conducted by the supplier to help determine the reliability of the supplier's [Certificate of Analysis]. An audit should also include a systematic examination of the supplier's quality system to ensure that reliability is maintained.")

[8] FDA inspection of suppliers of inactive ingredients on a surveillance basis is discretionary. *See* FDA GUIDE TO INSPECTIONS OF BULK PHARMACEUTICAL CHEMICALS (July 1991), *available at* http://www.fda.gov/iceci/inspections/inspectionguides/ucm074902.htm.

manufacturing establishments each year. At this rate, it would take the agency more than 13 years to inspect all registered foreign drug facilities just once.[9]

While the FDA has inspection capabilities, these capabilities are limited. As such, primary responsibility for ensuring the quality and safety of pharmaceutical components rests with the finished product manufacturers themselves. Drug manufacturers follow a risk-based approach to auditing, meaning that sites generally are audited once every several years. Sites that are deemed a "low risk" may be audited less often.

For many suppliers, the problem is reversed. A supplier may receive a multitude of requests from finished product manufacturers to conduct audits, yet many of these audits are duplicative in nature. Suppliers spend significant effort and resources responding to audits of facilities that may have only recently been examined by other manufacturers. Thus, while some suppliers may find themselves the subject of a multitude of duplicative audit requests, other suppliers may find that they are seldom, if ever audited, for instance because they supply only small quantities of chemicals to any one pharmaceutical company.

Rx-360 Background

Rx-360 was formed in 2009 to address the challenges described above. Membership of Rx-360 is open to any entity whose "activities relate to the research, development, or manufacture of pharmaceutical or biotechnology products, including research-based pharmaceutical companies, generic pharmaceutical companies, biotechnology companies, as well as suppliers of ingredients and components of pharmaceutical or biotechnology products and suppliers of services to the pharmaceutical and biotechnology industries."[10] (A list of current Rx-360 members is attached hereto as Appendix A.)

Drinker Biddle & Reath LLP ("DBR") serves as Secretariat and Legal Counsel to Rx-360. In this capacity, DBR provides support for Rx-360's activities, provides antitrust and other legal advice to the Consortium, and monitors Rx-360 activities for legal compliance. (A copy of the Rx-360 Antitrust Policy and Guidelines is attached hereto as Appendix B.)

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[9] GAO, BETTER DATA MANAGEMENT AND MORE INSPECTIONS ARE NEEDED TO STRENGTHEN FDA'S FOREIGN DRUG INSPECTION PROGRAM (GAO-08-970), at 6 (2008), *available at* http://www.gao.gov/new.items/d08970.pdf.

[10] Rx-360 Bylaws, at § 4.01(A). To avoid possible conflicts of interest, auditors and consultants are excluded from Rx-360 membership. However, auditors are eligible to serve as Observers.

In accordance with its mission to protect patient safety by enhancing the quality of the supply chain and authenticity of materials within the supply chain, Rx-360 has identified the following concrete objectives:

- Share publicly-available information on proposed or new legislation and regulation that impacts the pharmaceutical supply chain.
- Share publicly-available information on counterfeits, cargo thefts and adulterated products in the pharmaceutical supply chain.
- Develop voluntary standards for the quality and authenticity of supplies and suppliers.
- Develop and implement audit standards and audit training and certification programs.
- Create or obtain the infrastructure necessary to share data regarding quality and authenticity of supplies and suppliers that could adversely impact patient health or welfare.
- Fund the further development of new technologies for securing the supply chain and detecting adulteration in the supply chain.

Pursuit of these objectives will involve the sharing of information already within the public domain. It will also involve sharing certain non-public information – subject to confidentiality obligations – pursuant to the terms of the Rx-360 Audit Sharing Program and the Rx-360 Joint Auditing Program. Thus, Rx-360 will become a clearinghouse of both public and non-public information concerning the global pharmaceutical supply chain, including information on suppliers to the industry.

The Proposed Rx-360 Audit Programs

To enhance the security of the pharmaceutical supply chain, Rx-360 seeks to implement two audit programs. The Rx-360 Audit Sharing Program will allow Rx-360 members to share supplier quality audits conducted by Rx-360 members or on their behalf. The Rx-360 Joint Auditing Program will allow Rx-360 members to conduct joint quality audits of pharmaceutical suppliers. Details about each of these proposed programs are provided below.

Rx-360 Audit Sharing Program

Under the Rx-360 Audit Sharing Program, existing audit reports will be redacted to protect trade secrets and confidential business information and to remove the audit

sponsor's name. The redacted reports will then be provided to the Rx-360 Secretariat who will coordinate the audit sharing process. The Rx-360 Secretariat will place the reports into a secure database that can be accessed only by permitted members. The database will contain only those audit reports that both the audit sponsor (i.e., the biotech or pharmaceutical company that commissioned the audit) and the auditee (i.e., the audited supplier) have agreed to share. The auditee would identify those Rx-360 members permitted to access each redacted audit report. The auditee is neither asked nor required to provide a reason for permitting access to some members while denying access to others, although the likely explanation is that some members are viewed as potential customers while other are viewed as potential competitors of the supplier.

The redacted audit reports may be used by those permitted access to help make decisions about which suppliers to select, similar to what many companies now accomplish through a vendor questionnaire.

The Rx-360 Audit Sharing Program is envisioned as a multi-step process. These steps are identified and described as follows:

1) Each audit sponsor and auditee interested in participating in the Rx-360 Audit Sharing Program will execute a confidentiality agreement with Rx-360. (A draft Confidentiality Agreement is attached hereto as Appendix C.)

2) Each auditee will choose those audit reports commissioned by individual Rx-360 members that it wishes to share with other Rx-360 members. The auditee will send a list of these reports to the Rx-360 Secretariat.

3) The Rx-360 Secretariat will inform the respective audit sponsor of each of the listed audits that the auditee is willing to share. Each audit sponsor will determine whether it wishes to share the audit report. If yes, then with respect to each audit report that will be shared:

   a. The auditee will redact competitively sensitive information from the audit report, in accordance with a Redaction Policy developed by Rx-360. (The Redaction Policy is attached hereto as Appendix D.) The auditee will then send the redacted report to the Rx-360 Secretariat. At the same time, the auditee will inform the Secretariat of which Rx-360 members will be permitted to access the redacted report.

4) The Rx-360 Secretariat will send the redacted report to the audit sponsor, who in turn will redact its company name and any competitively sensitive information from the audit report, in accordance with the Rx-360

Redaction Policy. The sponsor will then return the redacted report to the Rx-360 Secretariat.

5) The Rx-360 Secretariat will review the report to confirm that the report is appropriately redacted. Once the Secretariat determines that the report is appropriately redacted, the Secretariat will enter the audit report into the database and set access permissions so that only permitted members can view the report. The report will be blinded as to audit sponsor, and there will be no way for an Rx-360 member to identify which other members have been given access to the report. Audit reports will remain accessible to authorized members for up to 48 months from the date of the audit.

Rx-360 Joint Auditing Program

Under the Rx-360 Joint Auditing Program, one or more Rx-360 member(s) would be able to request that the Consortium sponsor the audit of a particular supplier. The Rx-360 Secretariat would internally identify all those members who wish to sponsor a joint audit. It is not necessary for multiple members to participate in an audit in order for an audit to be conducted under this program. The willingness of only a single member to support the costs of a joint audit is sufficient to start this process. A third-party auditing firm would be engaged to conduct the audit. Each member interested in auditing a particular supplier would not be given knowledge of the other companies that would be interested in auditing that supplier. Each Rx-360 member would independently utilize the audit findings. Further details about the proposed process are as follows:

1) Individual Rx-360 members submit requests to the Secretariat for particular audits to be conducted. The Secretariat then surveys the Rx-360 membership to determine whether other members wish to act as joint sponsors of the audit. The identity of the original requesting sponsor and subsequently identified sponsors would be known only to the Secretariat.

2) The Rx-360 Secretariat or an individual designated by Rx-360 as responsible for coordinating the program ("Rx-360 Coordinator") would contact the supplier to request an audit on behalf of the requesting firms, specifying the names of the requesting firms to the supplier. As with audit requests of individual drug manufacturers, the supplier may either agree or not agree to be audited.[11] The supplier is also provided the opportunity to

[11] Strictly speaking, it is not mandatory under U.S. regulations for a drug product manufacturer to conduct an on-site audit of the manufacturing site of a supplier. Instead, all lots of all components (API, excipients, etc.) could be tested before use for compliance with the required specifications. To reduce the full testing of each lot of a component, manufacturers are permitted to establish the reliability of a supplier's analytical

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exclude any requesting company from acting as a joint sponsor. (Although a reason for exclusion will not be requested, the most likely reason is that a requesting party is viewed as a potential competitor.) If a requesting company is excluded, the Secretariat informs that company of this. If the supplier has agreed to be audited, then the supplier executes a confidentiality agreement with the Consortium. The terms of that agreement will require the supplier to maintain in confidence the identity of the audit sponsors. (A draft Confidentiality Agreement for this purpose is attached hereto as Appendix E.)

3) Rx-360 engages a third-party auditor to conduct the audit. The auditor will be selected based on objective minimum requirements that each auditor will be expected to satisfy. (A list of Minimum Requirements for Rx-360 Auditors is attached hereto as Appendix F.) The auditor selection process involves self-registration with Rx-360 by auditing service providers interested in conducting Rx-360 joint audits. The Auditor Qualifications Working Group, a committee comprised of Rx-360 members, will review the information provided by each auditor candidate to determine which providers meet Rx-360 minimum requirements. The Auditor Qualifications Working Group will also ask auditing service providers to submit bids for the cost of conducting one or more audits. Auditors will subsequently be chosen by the Auditor Qualifications Working Group based on a number of objective factors, including cost and past auditing experience. The Consortium anticipates soliciting bids for bundles of audits within a particular geographic region rather than separately soliciting bids for each individual audit to be conducted. Nevertheless, multiple auditing service providers will be utilized rather than relying on a single provider. Each audit service provider must execute an auditing services agreement with Rx-360. The services agreement will require, inter alia, that the auditor maintain the confidentiality of information learned in the course of performing services.

4) The auditor will send any questions it may have concerning the audit to the Rx-360 Secretariat. The Rx-360 Secretariat will forward those

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tests and manufacturing processes. Suppliers sometimes decline manufacturer on-site audit requests, for example because the quantity of product supplied is small and the costs of undergoing an audit is deemed to outweigh the risk of losing the business.

questions to the relevant sponsor(s), as appropriate, and coordinate the return of responses.

5) The auditor will send a pre-audit questionnaire to the supplier. (A Pre-Audit Questionnaire Template is attached hereto as Appendix G.) Based on the supplier's responses to that questionnaire, the auditor will develop an audit plan. After agreement with the supplier on the audit plan, the audit is conducted pursuant to Rx-360 audit guidelines. In its report, the auditor will categorize each of its observations as either "critical" or "other." The purpose of defining an observation as "critical" is to ensure that the observation receives priority attention by the audit sponsor(s) and the auditee. A "critical" observation is defined by Rx-360 as a deficiency or a combination of deficiencies that indicates a critical system failure which has produced, or leads to a significant risk of producing a product which is harmful to consumers or that may result in adverse impact to the safety, identity, strength or purity of a product.[12] A critical observation requires immediate corrective action by the supplier. The classification of an observation as critical requires the auditor to accurately and clearly define the consequences of the deficiency in terms of risk to patient safety or adverse impact to the safety, identify, strength or purity of the product. The classification of an observation as critical should be objectively verifiable based upon documentation, facts and observations established by the auditor.

6) The auditor orally reviews his/her findings with the supplier and then prepares a draft audit report for review by the audit sponsors. Critical observations must be immediately reported to the audit sponsors, even prior to issuance of the draft audit report. The auditor will send the draft audit report to the Secretariat, who in turn will forward a copy to each of the audit sponsors. (An Audit Report Template is attached hereto as Appendix H.) The Secretariat will compile comments received and forward them to the auditor. The auditor will seek clarification, as necessary, from the auditee.

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[12] This is very similar to the definition of a "critical" deficiency as defined by the European Medicines Agency (i.e., "A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal."). *See* EMA COMPILATION OF COMMUNITY PROCEDURES IN INSPECTIONS AND EXCHANGE OF INFORMATION (Rev 1) at p. 6, *available at* http://www.ema.europa.eu/Inspections/docs/CoCP/CoCP_GMPInspReport.doc.

7) To ensure fairness, the auditee is permitted to contest the accuracy of any observations, including the appropriateness of an observation being rated as critical. A decision of the majority of the joint sponsors (as conveyed via the Rx-360 Secretariat) will be followed for purposes of the final report to be maintained in the Rx-360 database and for purposes of any required Rx-360 follow-up concerning corrective and preventive actions ("CAPAs"). Nevertheless, each sponsor retains the right to independently decide whether an observation has been correctly categorized as "critical" or "other" for its own purposes. For example, a sponsor who believes that the objective evidence concerning a deficiency or combination of deficiencies supports the classification of an observation as "critical" may classify it as such for its own purposes, even if it is classified in the audit report as "other." [13] Rx-360 will not approve or disqualify any supplier based on the findings of a joint audit. Instead, each Rx-360 member that participates in a joint audit will independently utilize the audit findings.

8) The supplier will develop a plan for CAPAs to address observations identified in the audit report. These are agreed with the auditor and a majority of the joint sponsors (as conveyed via the Rx-360 Secretariat). Individual sponsors will be free to pursue directly with the supplier other corrective actions they deem necessary.

9) If the audit report identifies any critical observations, then the Rx-360 Secretariat will choose a "lead sponsor" to follow-up on implementation of associated CAPAs. In select cases, the auditor may be re-engaged to conduct this follow-up, but for cost efficiency purposes, members will be expected to perform these tasks in the ordinary course. The lead sponsor will ordinarily be the first Rx-360 member to have requested the supplier audit. The lead sponsor will report its findings concerning implementation to the Secretariat, who in turn will report them to each of the other sponsors. For other (i.e., non-critical) observations, the auditee will be able to self-report to the Rx-360 Secretariat regarding the status of CAPA implementation. The Rx-360 Secretariat will make this information available to the audit sponsors.

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[13] Furthermore, even though there is a definition of "critical" and a classification as "critical" requires objective evidence, there still may be room for reasonable disagreement over interpretation of that evidence. In particular, disagreement arises in the case of a combination of deficiencies that, in the auditor's opinion, do not each alone rise to the level of critical, but do in combination warrant a critical finding.

10) Other members of Rx-360 will be able to purchase access to the final audit report from Rx-360, provided the auditee agrees to allow access to such companies.

As discussed in Step (5), Rx-360 joint audits will be conducted pursuant to Rx-360 audit guidelines. The use of these guidelines, as well as the template pre-audit questionnaire and template audit report, serves to ensure a standard audit approach and, therefore, consistency in audits despite the use of multiple third party auditors. The guidelines will be based largely on existing government and public standards. Existing standards will be modified only to the extent gaps are identified between the existing standard and current regulatory expectations.

Rx-360 has established an Audit Standards Working Group to review existing standards and compare them with current regulatory expectations, and then to make recommended modifications where necessary. These working groups are open to Rx-360 finished product manufacturers, suppliers, and observers. The final standards or guidelines will be made available to the public for both use and comment. For example, as indicated below with respect to the planned Rx-360 Audit Guideline for APIs, Rx-360 plans to adopt the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") Good Manufacturing Practice ("GMP") Guide, with the addition of certain information from the European Union's EMEA/410/01 revision 2, relating to Bovine Spongiform Encephalopathy ("BSE") and Transmissible Spongiform Encephalopathies ("TSE").

Rx-360 will develop new audit guidelines only where existing documented standards are unavailable. For example, Rx-360 plans to adopt the following audit guidelines for use in the Rx-360 Joint Auditing Program:

- **Rx-360 Audit Guidelines for APIs and API Intermediates.** These guidelines will be based on the ICH Q7, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients,[14] and will contain added information pertaining to TSE/BSE. (A copy of the draft Audit Guidelines is attached hereto as Appendix I.)

- **Rx-360 Audit Guidelines for Basic Chemicals and Raw Materials.**[15] These audit guidelines will be based on the International Pharmaceutical

[14] ICH, GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS (2000), *available at* http://www.ich.org/cache/compo/363-272-1.html#Q7A.

[15] **Basic chemicals** are processing aids including materials driven off during manufacture, e.g. water, solvents; materials used for safety reasons, e.g. headspace gases; materials used in manufacturing area, but

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Excipients Quality Group ("IPEC")/Pharmaceutical Quality Group ("PQG") GMP Audit Guide for Pharmaceutical Excipients (2008).[16] Any revisions required as a result of the updated IPEC/PQG excipients guidelines will be made, once those guidelines are finalized.

- **Rx-360 Supply Chain Security Checklist**. This checklist will be based on a number of different documents including the C-TPAT best practices guide.[17] The Rx-360 Supply Chain Security Checklist will be able to be used along with the GMP audit guidelines, listed above, to conduct a concurrent security audit as well as a quality systems audit.

Other Rx-360 audit guidelines will be developed for excipients, primary packaging materials and for printed components.

Competition Considerations

We do not expect that either the Rx-360 Audit Sharing Program or the Rx-360 Joint Auditing Program will pose any material risk of anticompetitive effects. To the contrary, we believe that each program will ultimately benefit consumers by providing more certainty that the global supply chain for pharmaceuticals is safe and secure.

As an initial matter, it is important to clarify that participation in either of the proposed Rx-360 audit programs will be entirely voluntary. In addition, neither audit program is expected to have an effect on prices paid by consumers for pharmaceuticals. These programs are expected to produce benefits including the generation of more detailed audits which should result in greater confidence in the quality of materials used to manufacture pharmaceuticals. The Rx-360 audit programs are also expected to result in fewer duplicative audits for suppliers to host, thereby decreasing the threat that

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not in direct contact with product, e.g. disinfectants, detergents, lubricants. **Raw materials** are starting materials, e.g. chemicals used to manufacture API intermediates, and materials used in the transfer between processing steps, e.g. tubing, filters. Materials used for sterile applications are excluded from this definition.

[16] IPEC & PQG, GOOD MANUFACTURING PRACTICES AUDIT GUIDE FOR PHARMACEUTICAL EXCIPIENTS (2008), *available at* http://ipec-europe.org/UPLOADS/GMP_Audit_Guidelines__2008Final(1).pdf.

[17] CUSTOMS-TRADE PARTNERSHIP AGAINST TERRORISM (C-TPAT), U.S. CUSTOMS AND BORDER PROTECTION, U.S. DEP'T. OF HOMELAND SECURITY, SUPPLY CHAIN SECURITY BEST PRACTICES CATALOG (January 2006), *available at* http://www.cbp.gov/linkhandler/cgov/trade/cargo_security/ctpat/ctpat_members/ctpat_best_practices.ctt/ctpat_best_practices.pdf.

suppliers will be distracted from their primary business of providing key inputs to pharmaceuticals.

It is also important to note that these programs are not the only means by which audits will be conducted going forward. Instead, they are options for manufacturers to consider as part of their audit process. The Rx-360 audit programs are proposed as efficient options for both pharmaceutical manufacturers and their suppliers. The audit programs offer efficiencies to manufacturers because they will make more information available, thereby allowing manufacturers to make better-informed decisions about prospective and existing suppliers. The programs offer efficiencies to suppliers because they diminish the likelihood of redundant audits, which can be disruptive to a supplier's business.

The Rx-360 Audit Sharing Program is expected to allow pharmaceutical manufacturers to exchange objective information about suppliers, thereby facilitating their selection and evaluation of available suppliers. None of the information that will be shared relates to costs or prices. As a safeguard to ensure that there is no sharing of competitively sensitive information, the Rx-360 Secretariat will review audit reports before they are shared to affirm that any information regarding costs, product specifications, quantities, and any other information that may be considered competitively sensitive has been redacted from the report.

The Rx-360 Joint Auditing Program is expected to enable manufacturers and suppliers to achieve efficiencies by reducing costly, duplicative, and disruptive audits at common suppliers. This in turn will enable manufacturers to focus their auditing resources on (1) other suppliers that produce product-specific components, (2) new suppliers, and (3) suppliers that the manufacturer may not have previously been able to audit in the past to the desired frequency. In addition, each Rx-360 member that participates in a joint audit will independently utilize the audit findings.

The Rx-360 Joint Auditing Program should not raise any concerns that audit sponsors may engage in concerted refusal to deal with certain auditors. This is because the criteria for selecting an auditor are objective. Similarly, the procedures for selecting an auditor under the Rx-360 Joint Auditing Program are clear and objective. As such, there should be no threat of bias in selecting an auditor for an Rx-360 joint audit.[18]

In sum, neither the Rx-360 Audit Sharing Program nor the Rx-360 Joint Auditing Program is likely to facilitate any sort of anticompetitive practice or effect. The benefits

[18] The Rx-360 Joint Auditing Program would not change the existing status quo with respect to an auditee's ability to object to the use of a particular auditor.

to Rx-360 members and consumers are significant. Manufacturers and suppliers will benefit as a result of a more efficient process for monitoring the quality and integrity of the supply chain. Consumers will benefit as a result of a safe and secure supply chain.

We look forward to feedback from the FTC. Please do not hesitate to contact us if there is anything else we can provide that would be useful to your analysis.

Very truly yours,

Joanne C. Lewers

Peter A. Blenkinsop

Attachments

Appendix A

Rx-360 Members and Observers (As of July 22, 2010)

Members – Finished Product Manufacturers
Abbott Laboratories
Alcon Laboratories
Amgen
Amylin
AstraZeneca
Baxter
Biogen Idec
Boehringer Ingelheim
Bristol-Myers Squibb
Cephalon
Eli Lilly
GlaxoSmithKline
Hospira
Johnson & Johnson (Janssen)
Merck & Co., Inc.
Novartis
Pfizer
Sanofi-aventis
Takeda
Watson

Members - Suppliers
Archimica Group
BASF
Fagron
GE Healthcare
Hovione
Labochim
LifeConEx
Mallinckrodt Baker
Merck KGaA
Reliable Biopharmaceutical Corp.
Sigma Aldrich
TempTime
VWR
West Pharmaceutical Services

Observers – Auditors and Consultants
PSC Biotech Corp.
Regulatory Compliance Associates
RMC Pharmaceutical Solutions Inc.
Safis-Solutions
SQA Services Inc.
Weaver Group

Observers - Associations
Active Pharmaceutical Ingredients Committee (APIC)
Council for Responsible Nutrition
European Generic Medicines Association (EGA)
International Pharmaceutical Excipients Council of the Americas (IPEC-Americas)
Parenteral Drug Association (PDA)

Appendix B

Rx-360 ANTITRUST POLICY AND GUIDELINES

Antitrust Policy

The Rx-360 International Pharmaceutical Supply Chain Consortium (the "Rx-360 Consortium") operates in compliance with the antitrust and competition laws of all applicable countries, including the United States (both state and federal) and European Union. To that end, the Rx-360 Consortium has drafted the following competition guidelines (the "Guidelines") to serve as a general code of conduct for the Rx-360 Consortium as well as its constituent members. The Guidelines are based on the current understanding of the relevant antitrust and competition laws and are not intended to address any particular set of facts. As such, they are intended as a general overview and not specific antitrust advice on any issue.

Admonition

Each Rx-360 Consortium meeting will begin with a reading of the following admonition, unless replaced by an admonition reviewed and approved by antitrust counsel and the Board of Directors:

> *"The purpose of the Rx-360 Consortium is to develop and implement a global quality system to help members ensure product quality and authenticity through their supply chain in order to enhance patient safety. The Consortium includes companies that may be competitors as well as suppliers and customers. It is the intention of the Consortium to operate in strict compliance with antitrust laws. In particular, nothing discussed at this meeting is intended to result in an agreement on price, exclude suppliers from any market, or otherwise restrain competition. Those participating in this meeting are instructed to avoid discussion of competitively sensitive subjects, including costs, prices, sales, product marketing, and other confidential information. Members with questions regarding what is appropriate are directed to the Consortium's Antitrust Policy and Guidelines and are encouraged to raise questions with counsel or with the Chair."*

Antitrust Guidelines

The following Guidelines apply to the Rx-360 Consortium and its members.

1. The Rx-360 Consortium's purposes are to develop and implement enhanced global quality systems and processes to help members ensure product quality and authenticity through their supply chains in order to enhance patient safety. To this end, the Rx-360 Consortium may: (i) develop voluntary standards for the quality and authenticity of supplies and suppliers; (ii) develop and implement audit standards and auditor training and certification regarding the quality and authenticity of supplies and suppliers; (iii) jointly develop technologies to enhance the quality and authenticity of supplies; (iv) develop and implement a method for exchanging among members public information

regarding the quality and authenticity of supplies and suppliers and non-public information regarding the quality and authenticity of supplies and suppliers that could adversely impact patient health or welfare; and (v) adopt a seal for use by members that meet the Consortium's standards.

2. The Rx-360 Consortium's activities shall be limited to those developed in consultation with the Rx-360 Consortium's antitrust counsel and approved by the Board to enhance patient safety. The Rx-360 Consortium shall not engage in activities intended to restrain competition or to harm consumers. After consulting with antitrust counsel, the Board will consider notifying U.S. and European antitrust and competition authorities before implementing proposed activities.

3. Discussions or exchanges of information among Rx-360 Consortium members shall be consistent with these Guidelines and confined to the *bona fide* business of the Rx-360 Consortium. Under no circumstances shall the Rx-360 Consortium meetings be used as a means for competing companies to reach any understanding, expressed or implied, on price or which otherwise has the object or effect of restraining competition, or restricting the ability of members to exercise independent business judgment regarding matters affecting competition.

4. In no way shall any discussions or exchanges of information among Rx-360 Consortium members reveal any non-public information concerning a member's use of particular suppliers or vendors.

5. Each Rx-360 Consortium member agrees that it shall not, at any Rx-360 Consortium meeting or under the guise of proper Rx-360 Consortium business, whether seriously or in jest, in fact or appearance, agree on the price, output, cost or other terms of competition, or discuss or exchange competitively sensitive information. Competitively sensitive information includes, but is not limited to, the following:

   - individual company current or future prices; price changes; price differentials; markups; discounts; allowances; margins; or credit terms;
   - data that bear on current or future prices, including costs; production; capacity; inventories; and sales; industry pricing policies, pricing models, price levels, price changes, price differentials or profits;
   - bids on contracts for particular products, or procedures for responding to bid invitations;
   - individual company plans concerning the design, production, research and development, sales, distribution or marketing of particular products, including proposed territories or customers; and
   - matters relating to actual or potential individual suppliers that might have the effect of excluding them from any market or of influencing the business conduct of firms toward such suppliers or customers.

6. Each Rx-360 Consortium member agrees that it shall not engage in discussions of standard-setting when the object or effect of such standards is to limit the availability and

selection of products, limit competition, restrict entry into an industry, inhibit innovation, or inhibit the ability of competitors to compete, or otherwise restrict competition. Each Consortium member agrees that the implementation of such standards should not be compulsory nor used to artificially restrict competition.

7. Each Rx-360 Consortium member agrees that it shall not engage in discussions related to codes of ethics that might be administered in a way that could inhibit or restrict competition.

8. Each Rx-360 Consortium member agrees that it shall not engage in discussions related to group boycotts, the validity of patents, or on-going litigation.

9. Each Rx-360 Consortium member has the independent right and obligation to protest any activity that it believes threatens to violate the antitrust laws, and nothing contained herein shall limit said member from any necessary corrective action to prevent any perceived antitrust violation, including but not limited to disclosure of the alleged unlawful practice and/or disassociation from any such discussions or activities. Rx-360 Consortium members shall have an affirmative obligation to report, terminate and leave any meeting in which the aforementioned perceived violations are believed to have happened.

10. Rx-360 Consortium members shall have the unfettered right to seek the advice of their own independent antitrust counsel and/or the Rx-360 Consortium's antitrust counsel prior to, during or after engaging in any discussions or exchanges of information that may be inconsistent with these Guidelines, and they shall inform their own antitrust counsel and/or the Rx-360 Consortium's antitrust counsel immediately of any discussions or exchanges of information that are inconsistent with these Guidelines.

C

Appendix C

CONFIDENTIAL DISCLOSURE AGREEMENT CONCERNING AUDIT BY INDIVIDUAL RX-360 MEMBER

THIS CONFIDENTIAL DISCLOSURE AGREEMENT (the "Agreement"), is entered into as of **[INSERT EFFECTIVE DATE OF AGREEMENT]**, between the Rx-360 International Supply Chain Consortium ("Rx-360 Consortium"), a Pennsylvania non-profit corporation with offices at 1500 K Street, NW, Washington, DC 20005, and **[INSERT COMPLETE CORPORATE NAME OF OTHER PARTY]** ("Supplier"), a **[INSERT STATE OR JURISDICTION OF INCORPORATION/ORGANIZATION AND TYPE OF ENTITY (E.G., CORPORATION, LIMITED PARTNERSHIP, ETC)]** with offices at **[INSERT ADDRESS OF OTHER PARTY]**.

WHEREAS, Supplier has undergone one or more audits of its facilities by individual members of the Rx-360 Consortium, or such members' representatives and/or agents;

WHEREAS, the results of such audit(s) ("Audit Report(s)") and response(s) to the Audit Report(s) ("Audit Response(s)") contain Supplier confidential and proprietary information;

WHEREAS, the disclosure to third parties of any such Audit Report and/or Audit Response may be restricted by agreement between Supplier and the individual member of the Rx-360 Consortium on whose behalf such audit was undertaken (the "audit sponsor");

WHEREAS, one or more audit sponsors wish to disclose such Audit Report(s) and Audit Response(s) to other members of the Rx-360 Consortium and Supplier is willing to permit these disclosures as specified in the Annexes to this Agreement;

WHEREAS, in order to protect its confidential and proprietary information, Supplier desires to impose restrictions on the use and further dissemination of such Audit Report(s) and Audit Response(s), according to the terms and conditions set forth in this Agreement;

NOW, THEREFORE, in consideration of the mutual promises contained herein, the Parties, intending to be legally bound, agree as follows:

Agreement

1. **Definition of Confidential Information.** As used in this Agreement, the term "Confidential Information" means the Audit Reports and Audit Responses identified in the Annexes to this Agreement, and all the information contained therein.

2. **Obligation of Confidentiality and Non-Use.**

(a) The Rx-360 Consortium shall keep all Confidential Information confidential and shall use and share Confidential Information with its members only as permitted herein.

(b) Each Annex to this Agreement identifies an Audit Report and Audit Response that Supplier has agreed may be shared with the recipients identified in that Annex. The Rx-360 Consortium shall be entitled to share such Audit Reports and Audit Responses with such recipients.

(c) The Rx-360 Consortium agrees to require through written agreement each of its members that receives Confidential Information pursuant to this Agreement to abide by the same or substantially similar obligations of confidentiality to those applicable to the Rx-360 Consortium and contained herein. Such written agreements shall inure to the benefit of Supplier.

3. **Certain Exceptions to Obligations.** The obligations of confidentiality and non-use set forth in this Agreement shall not apply to any portion of the Confidential Information that:

(a) is or becomes available to the general public other than through the breach of the Rx-360 Consortium's obligations set forth in this Agreement;

(b) is obtained by the Rx-360 Consortium without restriction from a third party who had the legal right to disclose the same to the Rx-360 Consortium;

(c) was in the Rx-360 Consortium's possession and not subject to a duty of confidentiality prior to the effective date of this Agreement;

(d) is independently developed by the Rx-360 Consortium without use of or access to the Confidential Information; or

(e) is disclosed by the Rx-360 Consortium pursuant to a requirement of law or a valid request from a governmental authority, provided that the Rx-360 Consortium has complied with the provisions set forth in Section 5 hereof.

4. **Permitted Use.** Members of the Rx-360 Consortium shall use the Confidential Information solely for purposes of evaluating or monitoring the quality of production at Supplier's facilities, evaluating or monitoring the quality of products and services offered by Supplier, supporting an application to conduct clinical trials or to market goods or services that use Supplier's products as components or utilize Supplier's services, and/or other related or similar purposes.

5. **Permitted Disclosure Under Legal Process.** If the Rx-360 Consortium is requested or required by any formal or informal legal process (including, without limitation, an order of a court or administrative tribunal, subpoena, discovery request, or request for information by a governmental authority authorized by law to collect or receive such information) to disclose any Confidential Information, the Rx-360 Consortium will promptly notify Supplier. Supplier may seek an appropriate protective order and/or waive the Rx-360 Consortium's obligation to

comply with this Agreement. The Rx-360 Consortium will reasonably cooperate with Supplier's efforts to obtain any such order or other remedy. If no protective order is obtained and the Rx-360 Consortium has not received a waiver hereunder before two business days prior to the time the Rx-360 Consortium must disclose Confidential Information or else stand liable for contempt or suffer, or cause its members to suffer, other sanction or penalty, then the Rx-360 Consortium may disclose the requested Confidential Information. The Rx-360 Consortium will use commercially reasonable efforts to request that such disclosed Confidential Information be treated as confidential.

Notwithstanding the above agreement to promptly notify Supplier if the Rx-360 Consortium is requested or required by any formal or informal legal process to disclose any Confidential Information, no advance notification to Supplier will be required to be provided to the extent (i) disclosure is to a governmental authority authorized by law to collect or receive such information and relates to a regulatory filing by a member of the Rx-360 Consortium in support of an application to market goods or services, or relates to a governmental inspection of the Rx-360 Consortium or an Rx-360 Consortium member concerning such goods or services, or (ii) any delay in disclosure will cause the Rx-360 Consortium to stand liable for contempt or to suffer, or cause its members to suffer, other sanction or penalty. In such event, the Rx-360 Consortium will promptly notify Supplier that such disclosure has occurred.

6. **No Representations or Warranties as to Quality or Completeness of Audit Report.** The Rx-360 Consortium recognizes that Supplier makes no representation or warranty as to the quality or completeness of any Audit Report shared with the Rx-360 Consortium, except for any such representation or warranty that may be contained in a definitive written agreement executed and delivered after the date hereof by Supplier and the Rx-360 Consortium. Notwithstanding the preceding sentence, Supplier represents that it has no actual knowledge at the time of providing Confidential Information to the Rx-360 Consortium that such information is unreliable, inaccurate, or materially misleading.

7. **Return of Tangible Copies.** Upon the written request of Supplier, the Rx-360 Consortium shall promptly return all copies of tangible Confidential Information, except to the extent required to be retained by the Rx-360 Consortium under U.S. Food and Drug Administration or other government regulations, in which event such retained Confidential Information shall be destroyed or redacted at the end of the last-to-expire retention period. Notwithstanding anything herein to the contrary, the Rx-360 Consortium and each of its members to whom such Confidential Information is disclosed shall have the right to retain one copy of all such tangible Confidential Information for legal archiving purposes.

8. **Term of Agreement.** This Agreement and the obligations of confidentiality and non-use contained herein shall remain in effect for a period of ten (10) years from the date each item of Confidential Information is disclosed or made available to the Rx-360 Consortium.

9. **Availability of Specific Remedies.** The Rx-360 Consortium recognizes and acknowledges the competitive value and confidential nature of the Confidential Information and the irreparable damage that could result to Supplier if such

information is disclosed to any third party in violation of this Agreement. It is understood that Supplier may institute appropriate proceedings to enforce its rights hereunder. The Rx-360 Consortium acknowledges and agrees that money damages would not be a sufficient remedy for any violation of the terms of this Agreement and, accordingly, Supplier may, in addition to any monetary damages, seek specific performance and injunctive relief as remedies for any violation. These remedies shall not be deemed to be exclusive remedies for a violation of the terms of this Agreement but shall be in addition to all other remedies available to Supplier at law or in equity.

10. **Entire Agreement; Amendment.** This Agreement constitutes the entire agreement between the Rx-360 Consortium and Supplier and supersedes and replaces all prior discussions, agreements and rights relating to the subject matter hereof. No variation or modification of any of the terms of this Agreement or any waiver of the terms of provisions hereof shall be valid unless in writing and signed by an authorized representative of each party.

11. **Severability or Partial Invalidity.** The invalidity or unenforceability of any provisions of this Agreement shall not affect the validity or enforceability of any other provision of this Agreement, which shall remain in full force and effect.

12. **Waiver.** Delay or failure by Supplier to exercise any right or remedy hereunder shall not impair such right or remedy or be construed or deemed to be a waiver of any other provision of this Agreement or a waiver of any subsequent breach of the same provision. Any single or partial exercise of any right or remedy shall not preclude any other or further exercise thereof or the exercise of any other right or remedy.

13. **Counterparts.** This Agreement may be executed in counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the Rx-360 Consortium and Supplier have caused this agreement to be executed by their respective duly authorized representatives as of the date first above written.

The Rx-360 Consortium	**[FULL NAME OF OTHER PARTY]**
By:_____	By:_____
Name:	Name:
Title:	Title:

Annex A: Audit Report XYZ

Audit Report XYZ may be shared with:

[List of all then current Rx-360 Members minus companies identified by Supplier as excluded from receiving the audit results.]

FOR USE IF ADDITIONAL AUDIT REPORTS WISH TO BE SHARED AFTER EXECUTING THE ORIGINAL CONFIDENTIAL DISCLOSURE AGREEMENT.

ADDENDUM TO CONTRACT
ADDENDUM NO. 1

ADDENDUM made this __th day of _____ 201_ by and between the Rx-360 International Supply Chain Consortium ("Rx-360 Consortium"), a Pennsylvania non-profit corporation with offices at 1500 K Street, NW, Washington, DC 20005, and **[INSERT COMPLETE CORPORATE NAME OF OTHER PARTY]** ("Supplier"), a **[INSERT STATE OR JURISDICTION OF INCORPORATION/ORGANIZATION AND TYPE OF ENTITY (E.G., CORPORATION, LIMITED PARTNERSHIP, ETC)]** with offices at **[INSERT ADDRESS OF OTHER PARTY]**.

WHEREAS, the parties wish to incorporate additional appendices into the Confidential Disclosure Agreement Concerning Audit by Individual Rx-360 Member, dated _____ ("Confidential Disclosure Agreement");

NOW THEREFORE, in consideration of the promises and mutual covenants contained therein, the parties agree to add the attached appendices to the Confidential Disclosure Agreement.

IN WITNESS WHEREOF, the Rx-360 Consortium and Supplier have caused this agreement to be executed by their respective duly authorized representatives as of the date first above written.

The Rx-360 Consortium	**[FULL NAME OF OTHER PARTY]**
By:_____	By:_____
Name:	Name:
Title:	Title:

D

Appendix D

Rx-360 Audit Sharing Redaction Policy

I. Right to Redact Information

Both the supplier who is the subject of an audit report and the company who sponsored the audit will be provided the opportunity to redact information from the audit report and related materials prior to sharing with third parties. The supplier and sponsoring company may redact any information that they feel is competitively sensitive. While any information may be redacted, it should be done so as to not materially alter the findings of the audit. If a sponsoring company finds that the redacted information materially alters the conclusions that one may draw from the remaining text, the sponsoring company should decline to share the redacted audit report with the Rx-360 Consortium.

II. Information That Must Be Redacted

The following information should be redacted from all audit reports, supplier responses to audit reports, and any other materials prior to sharing with other members of the Rx-360 Consortium:

- Any information that identifies the company that sponsored the audit, such as the sponsoring company's name or address.
- Any information that identifies individuals employed by the sponsoring company, such as their names.
- Brand names of any of the sponsoring company's products.

III. Responsibility for Redaction

Responsibility for redaction of the above information lies with the audited supplier and audit sponsoring company.[1]

IV. Redaction Method

Redaction may be performed on paper (i.e., by obscuring or covering the information) or electronically. If redaction is conducted electronically, care should be taken to prevent accidental disclosure in the form of hidden metadata.

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[1] For purposes of antitrust compliance, the Secretariat of the Rx-360 Consortium will review all audit reports and related materials prior to sharing them with other Rx-360 members to provide a second check against accidental disclosure. The Consortium disclaims any assumption of liability to the sponsor or audited supplier for the failure to redact information that the sponsor or audited supplier later deems commercially sensitive.

E

Appendix E

AUDIT AND CONFIDENTIALITY AGREEMENT

THIS AUDIT AND CONFIDENTIALITY AGREEMENT (the "Agreement"), is entered into as of **[INSERT EFFECTIVE DATE OF AGREEMENT]**, between the Rx-360 International Supply Chain Consortium ("the Rx-360 Consortium"), a Pennsylvania non-profit corporation with offices at 1500 K Street, NW, Washington, DC 20005, and **[INSERT COMPLETE CORPORATE NAME OF OTHER PARTY]** ("Supplier"), a **[INSERT STATE OR JURISDICTION OF INCORPORATION/ORGANIZATION AND TYPE OF ENTITY (E.G., CORPORATION, LIMITED PARTNERSHIP, ETC)]**, with offices at **[INSERT ADDRESS OF OTHER PARTY]**.

Background

Supplier may disclose or make available to the Rx-360 Consortium certain of its confidential and proprietary information in connection with an audit of Supplier's operations located at [**address**] (the "Facility") to be conducted by members, representatives and/or agents of the Rx-360 Consortium ("Rx-360 Authorized Representatives") concerning **[INSERT BRIEF DESCRIPTION OF THE PURPOSE OF THE DISCLOSURE – E.G., THE NAME OF THE PROJECT]** (the "Purpose"). The results of the audit shall be included in a report prepared by such Rx-360 Authorized Representatives (the "Audit Report"). In order to protect this information, Supplier desires to impose restrictions on its use and further dissemination according to the terms and conditions set forth in this Agreement. Accordingly, the parties, intending to be legally bound, agree as follows:

Agreement

1. **Definition of Confidential Information.** As used in this Agreement, the term "Confidential Information" means information that Supplier desires to maintain as confidential and that is provided or made available to the Rx-360 Consortium, including without limitation, technical data and drawings, quantitative and qualitative formula information, and scientific, clinical, regulatory, marketing, financial and commercial information, data or results. Confidential Information includes, without limitation, the portion of any analyses, studies and other documents prepared by or for the benefit of the Rx-360 Consortium, including the Audit Report (collectively, "Rx-360 Consortium Documents") that incorporate Confidential Information therein. Confidential Information shall not include information obtained or acquired orally or by visual observation of Supplier's facilities or processes unless designated as confidential by Supplier pursuant to Section 2 below.

2. **Identification of Confidential Information.** All written disclosures of Confidential Information considered confidential by Supplier shall bear the notation "Confidential Information of [SUPPLIER'S NAME]." Supplier shall confirm in writing to the Rx-360 Consortium all non-written disclosures of Confidential Information as being confidential within 30 days following the non-written disclosure. The written confirmation shall identify the particular Confidential

Information, state that it is considered confidential, and shall identify the person(s) who received such non-written disclosures.

3. **Obligation of Confidentiality and Non-Use.**

(a) The Rx-360 Consortium shall keep all Confidential Information confidential and shall use and disclose Confidential Information only as permitted herein.

(b) The Rx-360 Consortium shall identify any individuals or entities entitled to receive Confidential Information on its behalf as Rx-360 Authorized Representatives. Rx-360 Authorized Representatives shall be bound in writing by the Rx-360 Consortium to abide by the same or substantially similar obligations of confidentiality to those applicable to the Rx-360 Consortium and contained herein. Such written agreements shall inure to the benefit of Supplier.

(c) The Rx-360 Consortium shall be entitled to share the Audit Report and any responses by Supplier to the Audit Report ("Audit Responses") with those members of the Rx-360 Consortium authorized to receive and review such Audit Report and Audit Responses as identified in Annex A (the "Permitted Recipients").

(d) Following the preparation of the Audit Report, the Rx-360 Consortium may request that Supplier consent to written requests by the Rx-360 Consortium to add additional third parties to the list of Permitted Recipients. Supplier shall not unreasonably withhold or delay its consent to any such requests.

(e) The Rx-360 Consortium agrees to require through written agreement each of its members that receives Confidential Information pursuant to this Agreement to abide by the same or substantially similar obligations of confidentiality to those applicable to the Rx-360 Consortium and contained herein. Such written agreements shall inure to the benefit of Supplier.

4. **Certain Exceptions to Obligations.** The obligations of confidentiality and non-use set forth in this Agreement shall not apply to any portion of the Confidential Information that:

(a) is or becomes available to the general public other than through breach of the Rx-360 Consortium's obligations set forth in this Agreement;

(b) is obtained by the Rx-360 Consortium without restriction from a third party who had the legal right to disclose the same to the Rx-360 Consortium;

(c) was in the Rx-360 Consortium's possession and not subject to a duty of confidentiality prior to the effective date of this Agreement;

(d) is independently developed by the Rx-360 Consortium without use of or access to the Confidential Information;

(e) is disclosed to a governmental authority authorized by law to collect or receive such information and relates to a regulatory filing by a member of the Rx-360 Consortium in support of an application to conduct clinical trials or to market

goods or services, or relates to a governmental inspection of the Rx-360 Consortium or an Rx-360 Consortium member concerning such goods or services, provided that Supplier is promptly notified (i) of any negative feedback from such governmental authority concerning any audit findings, and (ii) if, following a governmental inspection, a copy of the audit report is taken off-site by the inspector; or

(f) is disclosed by the Rx-360 Consortium pursuant to a requirement of law or a valid request from a governmental authority, provided that the Rx-360 Consortium has complied with the provisions set forth in Section 6 hereof.

5. **Permitted Use.** Members of the Rx-360 Consortium shall use the Confidential Information solely for purposes of evaluating or monitoring the quality of production at the Facility, evaluating or monitoring the quality of products and services offered by Supplier, supporting an application to conduct clinical trials or to market goods or services that use Supplier's products as components or utilize Supplier's services, and/or other related or similar purposes.

6. **Permitted Disclosure Under Legal Process.** If the Rx-360 Consortium is requested or required by any formal or informal legal process (including, without limitation, an order of a court or administrative tribunal, subpoena, discovery request, or request for information by a governmental authority authorized by law to collect or receive such information) to disclose any Confidential Information, the Rx-360 Consortium will promptly notify Supplier, except as specified in Section 4(e). Supplier may seek an appropriate protective order and/or waive the Rx-360 Consortium's obligation to comply with this Agreement. The Rx-360 Consortium will reasonably cooperate with Supplier's efforts to obtain any such order or other remedy. If no protective order is obtained and the Rx-360 Consortium has not received a waiver hereunder before two business days prior to the time the Rx-360 Consortium must disclose Confidential Information or else stand liable for contempt or suffer, or cause its members to suffer, other sanction or penalty, then the Rx-360 Consortium may disclose the requested Confidential Information. The Rx-360 Consortium will use commercially reasonable efforts to request that such disclosed Confidential Information be treated as confidential.

Notwithstanding the above agreement to promptly notify Supplier if the Rx-360 Consortium is requested or required by any formal or informal legal process to disclose any Confidential Information, no advance notification to Supplier will be required to be provided to the extent any delay in disclosure will cause the Rx-360 Consortium to stand liable for contempt or to suffer, or cause its members to suffer, other sanction or penalty. In such event, the Rx-360 Consortium will promptly notify Supplier that such disclosure has occurred, except as specified in Section 4(e).

7. **Ownership of Confidential Information.** All Confidential Information other than the Rx-360 Consortium Documents shall remain the property of Supplier and nothing herein shall be construed as giving the Rx-360 Consortium any right, title or interest in or to such Confidential Information. With respect to any portion thereof that is or becomes covered by any patent, the Rx-360 Consortium's rights with respect thereto shall be subject to all rights of the patent owner and/or licensee.

8. **Return of Tangible Copies.** Upon the written request of Supplier, the Rx-360 Consortium shall (a) promptly return all copies of tangible Confidential Information, other than the Rx-360 Consortium Documents, and (b) redact or destroy all portions of the Rx-360 Consortium Documents that contain Confidential Information, except to the extent required to be retained by the Rx-360 Consortium under U.S. Food and Drug Administration or other government regulations, in which event such retained Rx-360 Consortium Documents shall be destroyed or redacted at the end of the last-to-expire retention period. In the event Supplier requests the Rx-360 Consortium to redact or destroy Confidential Information contained in any portions of the Rx-360 Consortium Documents pursuant to (b), such request shall explain why redaction or destruction is necessary to protect Supplier's interests. The Rx-360 Consortium is permitted to disclose to any of its members the fact of such request under (b). Notwithstanding anything herein to the contrary, the Rx-360 Consortium and each of its members to whom such Confidential Information is disclosed shall have the right to retain one copy of all such tangible Confidential Information for legal archiving purposes.

9. **Representations and Warranties.** Each party hereto represents and warrants that the signatory below is duly authorized to bind it to the obligations hereunder and that this Agreement does not conflict with any other law or contract to which such party is bound.

10. **Term of Agreement.** This Agreement and the obligations of confidentiality and non-use contained herein shall remain in effect for a period of ten (10) years from the date each item of Confidential Information is disclosed or made available to the Rx-360 Consortium.

11. **Availability of Specific Remedies.** The Rx-360 Consortium recognizes and acknowledges the competitive value and confidential nature of the Confidential Information and the irreparable damage that could result to Supplier if such information is disclosed to any third party in violation of this Agreement. It is understood that Supplier may institute appropriate proceedings to enforce its rights hereunder. The Rx-360 Consortium acknowledges and agrees that money damages would not be a sufficient remedy for any violation of the terms of this Agreement and, accordingly, Supplier may, in addition to any monetary damages, seek specific performance and injunctive relief as remedies for any violation. These remedies shall not be deemed to be exclusive remedies for a violation of the terms of this Agreement but shall be in addition to all other remedies available to Supplier at law or in equity.

12. **Entire Agreement; Amendment.** This Agreement constitutes the entire agreement between the Rx-360 Consortium and Supplier and supersedes and replaces all prior discussions, agreements and rights relating to the subject matter hereof. No variation or modification of any of the terms of this Agreement or any waiver of the terms of provisions hereof shall be valid unless in writing and signed by an authorized representative of each party.

13. **Severability or Partial Invalidity.** The invalidity or unenforceability of any provisions of this Agreement shall not affect the validity or enforceability of any other provision of this Agreement, which shall remain in full force and effect.

14. **Waiver.** Delay or failure by Supplier to exercise any right or remedy hereunder shall not impair such right or remedy or be construed or deemed to be a waiver of any other provision of this Agreement or a waiver of any subsequent breach of the same provision. Any single or partial exercise of any right or remedy shall not preclude any other or further exercise thereof or the exercise of any other right or remedy.

15. **Counterparts.** This Agreement may be executed in counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

IN WITNESS WHEREOF, Rx-360 Consortium and Supplier have caused this agreement to be executed by their respective duly authorized representatives as of the date first above written.

The Rx-360 Consortium	**[FULL NAME OF OTHER PARTY]**
By:_____	By:_____
Name:	Name:
Title:	Title:

Annex A: Permitted Recipients

[List of all then-current Rx-360 Members minus companies identified by Supplier as excluded from receiving the audit results.]

F

Appendix F

Minimum Requirements for Rx-360 Auditors

Note: Listed below are minimum requirements for Rx-360 auditors. For providers of auditing services, each auditor used in an Rx-360 audit must meet these requirements.

EDUCATION	Need a Bachelor's Degree in a science from an accredited university (a minimum of three years), or demonstrated relevant work experience that provides equivalent knowledge.
PROFESSIONAL EXPERIENCE	A minimum of five years of GMP operational pharmaceutical experience. Operational experience includes those skills and competencies gained while working within a pharmaceutical GMP environment.
REGULATORY KNOWLEDGE	Must be knowledgeable about pertinent regulatory and best-practices requirements (*e.g.* ICH Q7 for APIs, CFRs for USA, IPEC guidelines for excipients).
AUDITOR TRAINING	A quality systems approach that includes training and refresher training of auditors is expected for auditors associated with a provider of auditing services. *Note:* Good communication and interpersonal skills are a "must" and are included in this category.
AUDIT EXPERIENCE	Need involvement in at least five audits of the relevant supplier/audit type, including leadership of at least one relevant audit. [See also the maintenance requirement (*i.e.*, at least three audits of the relevant supplier/audit type in the last 12 months)]. *Note:* Professional experience may impact the amount of audit experience required.
AUDITOR ACCREDITATION/ CERTIFICATION	Auditors must be accredited/certified by one of the programs [to be identified by the Working Group].
MAINTENANCE OF QUALIFICATION	The auditor must be up-to-date on Good Manufacturing Practices (GMPs) and currently performing audits (at least three audits of the relevant supplier/audit type in the last 12 months).
RECORDS OF QUALIFICATION	A formal recordkeeping system must be maintained of auditors' qualifications. The system should include information concerning each auditor's areas of expertise.
LANGUAGE	The auditor must be able to communicate with Rx-360 in written and spoken English. In addition, the auditor should be able to communicate effectively (e.g., via planned use of interpreters internal to auditee or contracted as necessary) and demonstrate sensitivity to or experience with the local culture.

G

Appendix G

FORM 5

Pre-Audit Questionnaire Template

Supplier:

Address:

Material(s) Supplied:

Questionnaire Issued by:

Questionnaire Issued to:

Date of Issue:

Completion of the following signature blocks signifies the approver has read, understands, and agrees with the content of this document.

Name	Role	Signature	Date
Questionnaire filled by:			
Questionnaire approved by: (If applicable)			

As part of the Rx-360 supplier qualification process, please provide the relevant information as requested in the following supplier questionnaire.

If some information has been already provided please indicated this in the relevant section and provide details regarding to whom this information was provided.

Thank you very much for your time.

A. COMPANY BACKGROUND AND ORGANISATION

1. Please describe company ownership.
2. In what type of location / surrounding activity is the manufacturing site? (e.g. industrial park, remote countryside etc.)
3. Please provide a site plan.
4. How is site security managed?
5. Please list other materials supplied, from this site, to the following member companies of Rx-360: [----------]
6. Is any part of manufacture, packaging, analysis etc. sub- contracted? (Please provide brief details).
7. Is your company the manufacturer, reseller or appointed agent for the material in question?

- If reseller or agent, please give contact details for the manufacturer, also give details of any processing carried out by your company (e.g. packaging, testing, re-labeling etc.)

8. Please list the type of activities/ products produced on site (or if available a product list).
9. Does your company operate on more than one site? If so, please provide details of other sites (please highlight those where the product in question could be manufactured).
10. Does an agent act on your behalf? If so, what is the preferred route of communication?
11. What percentage of the site's / company's business is with the pharmaceutical industry?
12. Please provide an organizational chart describing senior management / key functions (and deputization etc. during absence of key individuals).
13. Number of staff

Total:	
QA/QC:	
Technical Support:	
Production:	
Engineering:	
Regulatory:	

14. Is there a formal staff training program (with appropriate refresher courses) and with records kept, how is effectiveness measured?
    - For induction?
    - Job specific / GMP / Safety issues?
    - With appropriate refresher courses?

15. Are there any parts of your plant, systems and documentation that you would not be willing to let Rx-360 audit? If so, please give reason. Can process details of the relevant synthesis be shared with Rx-360?
16. In what language are key documents such as SOPs and batch records completed?
    - If not in English, are translations into English readily available?

B. PRODUCTION

Please provide a full equipment list for vessels, isolation and drying equipment. Equipment detailing capacities and materials of construction, together with support services such as heat transfer, scrubbers, condensers, distillation capabilities etc.

1. Does your company have any specialist techniques (e.g. hydrogenation, bromination, cryogenics etc.)?
2. Do you consider your manufacturing facilities to be in compliance with the current requirements of pharmaceutical Good Manufacturing Practice (cGMP)?
3. What is your definition of a batch or lot?
4. What is your batch numbering system and how does it identify a specific batch?
5. Are any particular sensitisers, cephalosporins, hormones or penicillins handled on site?
6. Are any of the following materials used in the manufacturing processes for the product to be supplied – benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, 1,1,1-trichloroethane?
    - If so, which ones?
7. Is the plant used for the material in question dedicated? If not, what other materials could be / are produced in that area / equipment?

8. Are documented cleaning procedures in place?
9. Are these validated?
10. Who is responsible for releasing plant for use?
11. Is an individual production document used and retrievable for each batch?
12. If so, how do batch records provide traceability of input materials, in-process testing and equipment used?
13. Are any materials of animal origin? If yes, please specify, including any controls on the nature and source of animal based materials.
14. Are any materials known to be genetically modified? If yes, please specify,
15. Does the site have a process water treatment system? Please describe the plant and delivery system.
16. What solvents are used in the synthesis / purification of the material (s) supplied to the Rx-360 members named above (part A, question 5), and to what level (%, ppm) are they controlled?
17. Are solvents, mother liquors etc., recycled/ reused or recovered - how is this controlled?
18. Are manufacturing procedures well defined? How are deviations from these monitored /controlled?
19. Are critical process parameters and measuring devices defined? How is calibration of control instruments managed?
20. Is an automated plant used, with computer controls? If so, is this plc or sequence control?
21. Are manufacturing processes routinely validated?
22. How is the issue of blank batch records controlled?
23. At what stage in manufacture are special steps taken to protect the product from contamination?
24. Is any environmental monitoring conducted in production / finishing area?
25. When it leaves the production area is material packaged in intermediate or the final dispatch container?
26. If intermediate where is it repackaged?
27. What is the procedure for the issue and control of labels?
28. Please provide brief details of facilities available for dealing with liquid and solid wastes and potential releases to atmosphere?

C. WAREHOUSING, STORAGE AND TRANSPORT.

1. How and where are input materials and finished products sampled?
2. Who takes the samples?
3. How many samples are taken?
4. Are storage facilities environmentally controlled or monitored for temperature and humidity?
5. How are approved, quarantined and rejected materials distinguished?
6. Is there a separated area for the storage of rejected materials?
7. How is stock rotation assured?
8. How do you control infestation e.g. birds, vermin, insects?
9. What is your normal packaging (materials / quantities)?
10. What control do you have over the delivery mechanism of materials to your customers?

D. QUALITY

1. Who is the senior quality contact for issues relating to the supply to Rx-360?
2. Is any of the site ISO 9000 certified? If so, what is the scope and who was the certifying body.
3. Do you have a quality i) policy / ii)manual? If so, please provide a i) copy / ii) index
4. Are there any Total Quality Management or Continuous Improvement initiatives in operation?
5. Please describe the reporting relationship of Quality to other functions (if not shown in organogram).

6. Please provide an organogram of the quality department and a brief description of responsibilities (including cover in the event of absence of key staff).
7. Who has responsibility for releasing raw materials, packaging materials, intermediates, finished goods and what is the routine procedure for these activities (e.g. ID test and C of A review, full analysis to in house spec. review of batch documents etc.)?
8. If water is used in the process, what quality is it considered to be and what chemical and microbiological testing is conducted? At what frequency?
9. Please provide a copy of your specification for the material(s) in question.
    - With whom should the agreement of a purchasing specification be discussed?
10. Is finished product released against a pharmacopoeial monograph?
    - if yes - are the methods of the monograph employed for release?
    - if no - are the analytical methods validated?
11. Please indicate your recommended retest and/or expiry period for the materials [need to specify which ones].
    - Do you have supporting stability data available that covers your recommendations for retest / expiry period?
    - How would deterioration of the product manifest itself?
12. Is an approved supplier list maintained? (by whom?)
13. Do you conduct supplier audits?
14. Please provide an analytical laboratory instrument list.
15. What is the procedure for validation, maintenance and calibration of these instruments?
16. Do you have a procedure to control the review and retesting of samples, which generate out of specification or atypical data?
17. Are certificates of analysis available for the material supplied?
    - Do these relate to analysis of specified batch or a statistical assessment?
18. How are changes to the site, process, analysis or input materials controlled?
    - What is the mechanism for agreeing with customers?
19. Do you have an internal audit program?
    - What is the frequency and who conducts the audits?
    - Is progress against recommendations monitored?
20. Is there a formal system for rejection / complaint investigations?
21. For how long are production and analytical records kept?
22. Are samples of product and input materials retained?
    - If so for how long?
23. Please briefly describe any on-going stability program that is operated.
24. Do you conduct periodic (campaign / annual) product reviews which looks for trends in analytical data and yields and summarizes batch failures, deviations and process changes?
    - Are the results of the review made available to customers?

E. REGULATORY

1. Please provide relevant manufacturing license numbers / issued by:
2. Has the site been inspected by the FDA?
    - If yes, please describe the reason, date, and summary of outcome (copies of correspondence are available under "freedom of information" but it would be more convenient if you could provide this).
3. Has the site been inspected by any other regulatory authority? - If so please provide brief details.
4. Are any DMFs (US or European) filed with FDA / submitted to any major authority?
5. Do you hold a Ph. Eur. Certificate of suitability for the material in question?
6. Has there been any enforcement or improvement action taken by environmental or health and safety regulators over the last three years?

- If so, please provide brief details.

F. SAFETY, HEALTH AND ENVIRONMENT (S,H & E)

1. Is any of the site ISO 14000 certified?
   - If so, what is the scope and who was the certifying body.
2. Is (are) there policy statement(s) for S, H and E in place? - Please provide copies.
3. Is there a S, H & E department?
   - If so, please provide details.
4. Are records/ investigations kept / trended for accidents and incidents?
   - What is the site performance for lost time accidents, fires / explosions over the last 2 years?
5. Do you have the capability to assess reaction hazards e.g. by calorimetry?
6. Do you perform HAZOPS and other risk studies on new / modified processes and plant?
7. What fire fighting facilities are available?
   - on-site / from the local authority.
8. Please describe fire protection / detection systems in place.
9. Have all points of emission been identified and routinely monitored?
   - Internally and/or by local authority?
10. Have there been any reported excursions from permitted limits?
11. Are internal S, H & E inspections performed?
12. What medical facilities are available on site/ in the local area.
13. Please describe any geographical hazards in the area (e.g. earthquake/ typhoon/ hurricane).
    - and measures in place to cope with these.

G. ENGINEERING

1. Is there a plant inventory based on a structured numbering system?
2. Is there a planned preventative maintenance program (manual or computerized) in place?
   - Does this include statutory inspections such as boilers, lifting equipment, relief valves etc.?
3. Do you have pre-planned shut downs for major maintenance work?
   - If so, when do these usually take place?
4. Are drawings held in a drawing register, including a list of modifications?
5. Is there a well documented system for recording plant as built and modified (including process control software changes)?
6. What functions do contract engineers perform and how are these internally managed?
7. What is the procedure for the handover of engineering projects upon completion?
8. To what codes of practice is plant designed?
9. Are electric cables, starters, switchboards labeled, and reference drawings available?

H. TECHNICAL SUPPORT

1. How much business is contract manufacture versus commodity supply?
2. How many chemists are employed to introduce new technology and undertake process development/ improvement?
3. How is technology received to the site? Is there a written procedure?

- If so, please provide a copy.

4. Are Development Laboratory activities performed to GLP standards?

I. COMPUTER SYSTEMS

1. Are control systems validated?
2. Have your software suppliers been audited?
3. Is a change history maintained?

H

Appendix H

FORM 7

RX-360 AUDIT REPORT TEMPLATE

Company audited	
Name	**Location & Contact Details**

Products/Materials/Services within scope of audit	**I. Dates of Audit**
Class of product	
I. ☐ *API* ☐ *Excipient* **II.** ☐ *Finished product* ☐ *Packaging material* **III.** ☐ Other (please state)	

Audit Reference	**Standards used (as applicable)**
XXXX-XXX	☐ *Rx-360 Audit Guideline for APIs* ☐ *Rx-360 Audit Guideline for Excipients* ☐ *Rx-360 Audit Guideline for Basic Chemicals and Raw Materials* ☐ *Rx-360 Supply Chain Security Checklist*

Auditors (Name and signature)			
Report issued by & date:		Lead auditor	
Report reviewed by & date:		Audit assistant	

Distribution	
Supplier Contact Name and email address	
Rx-360 Coordinator* Name and email address	
*Rx-360 Coordinator will also distribute to Sponsor companies as agreed by Supplier	

This Page Will Not Be Maintained in the Rx-360 Database. Each Sponsor Should Separately Complete and Maintain this Page.

Supplier Status Summary Statement from Audit Sponsor
[Each Sponsor Company enters its own status summary here]
Sponsor Company representative's name, signature and date

Purpose of the Audit:

Summary:

[Please provide a detailed comment for any **CRITICAL** observations including the potential risk (impact)]

"The response was reviewed by [Insert Reviewers] and was determined to be [acceptable or unacceptable]." [Include any other additional information as required, such as "No further response was necessary regarding the corrective and preventative actions planned."]

Add an overall summary paragraph for the audit.

NOTE: Summaries for each system/subsystem are provided with the observations towards the end of this report.

Strengths:

Observations:

All observations are considered as "OTHER" if nothing else is stated. Any observations made, e.g. "a missing equipment log", for one type of equipment should be interpreted to include all similar equipment, and therefore we assume that a corrective action will cover the entire audited area.

The audit resulted in total of X observations of which X were classified as Critical. The individual observations and supplier's response details are available in the Audit Observation List (see attachment)

Personnel present	
IV. Company, Name and Position	**V. Contact details – Telephone and E-mail**

VI. General information concerning the company		
Owner structure:		
Number of production sites within the company:		
Details of the most important:		
Percentage of the business with the pharmaceutical industry:		
Detail of other activities:		
Number of employees:	▪ For the total site: ▪ In production: ▪ In QA/QC:	

VII. Quality status of the company		
Registration files e.g. DMFs, Certificate of Suitability (CEP) etc.		
Audits and certificates from the authorities: (Examples, dates & results)		
Third party certification: (Examples & dates)		
Safety Statements in place: (Dates for the last signed copies)	STATEMENT:	DATE:
	▪ Residual Solvents	
	▪ TSE	
	▪ GMO	

	▪ Avian Influenza	
	▪ Allergens, e.g. Latex	
	COMMENTS:	
Previous audits: (Dates, & Reference number)		

VIII. Follow-up to Last Rx-360 Audit Observations:

IX. Major Changes Since Last Rx-360 Audit:

X. Key Audit Highlights:

Future Rx-360 Audit Considerations	
System	Sub System / Description

Attachments

Attachment Number	Document Title/Description	Page(s)
1	Audit Plan	
2	Closing Letter to Supplier	
3	Section Summaries / Observations	
4	Supplier Response	
5	Rx-360 Audit Checklists (Completed)	
6	Auditor CVs	

Attachment 1: Audit Plan

Attach Filled-Out Audit Plan Here

Attachment 2: Closing Letter to Supplier:

Date

Xxxx xxxxxx
Regional Quality Manager
Xxxxxxx
address
city, state, zip

Subject: Audit Observations

Dear Mx. xxxx:

I would like to thank you and your colleagues for hosting me during the audit of XXXX's facility located in XXXXXX on [audit date].

⇨ The audit focused on the quality, facilities and equipment, materials, and packaging systems supporting the repacking operations, and warehousing and distribution of XXXX."
⇨
⇨ Enclosed is a list of observations that were discussed at the closeout meeting on [date]. I respectfully request a written response detailing the corrective and preventative actions planned, responsible individual and the proposed implementation schedule, by [15 calendar days, unless otherwise required].

If you have any questions or concerns regarding the observations and recommendations, please do not hesitate to contact me at name@XXXXX.com or [phone number], as I am confident that we can work together to address the items listed.

Regards,

Lead Auditor
Title

cc: XXXX-xxx

Attachment 3: Section Summaries / Observations:

All observations are considered as "OTHER" if nothing else is stated. Any observations made, e.g. "a missing equipment log", for one type of equipment should be interpreted to include all similar equipment, and therefore we assume that a corrective action will cover the entire audited area.

Order by Criticality: Critical observations first, Others second

Quality Management

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Personnel

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Facilities & Equipment

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Materials Management

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Production Controls

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Packaging and Labeling Controls

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Storage and Distribution

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Documentation and Records

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Laboratory System

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments

Observation/s

Validation

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Change Control System

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Rejection and Re-use of Materials

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Complaints and Recalls

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Contract Services (Including Manufacturing, Labs, Calibration)

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Agents, Brokers, Traders, Distributors, Repackagers, Relabellers

XXX Subsystem
Summary comments
Observation/s

XXX Subsystem
Summary comments
Observation/s

Attachment 4: Supplier Response:

Attach Accepted Supplier Response Here

Attachment 5: Rx-360 Audit Checklists (Completed)

Attach Completed Rx-360 Audit Checklists Here

Attachment 6: Auditor CVs

Attach Auditor CVs Here

Appendix I

	Document Name: Rx-360 Audit Guide for Active Pharmaceutical Ingredients and API Intermediates_v1.0
	Document Number: 2460627
	Revision Date:
	Effective Date:

ACTIVE PHARMACEUTICAL INGREDIENTS (API) AND API INTERMEDIATES AUDIT STANDARDS

INTRODUCTION

The agreed Rx-360 audit standards for Active Pharmaceutical Ingredients (APIs) and API Intermediates are based upon two existing standards/guidance documents:-

ICH Q7 – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, dated 10 November 2000. (http://www.ich.org/LOB/media/MEDIA433.pdf)

EMEA/410/01 Revision 2 – October 2003 – Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. (http://www.ema.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf)

SCOPE

The standards do not include details of sterility assurance and are therefore only partially applicable to sterile Active Pharmaceutical Ingredients.

GLOSSARY

The glossary is included in ICHQ7.

AUDIT GUIDELINES

Quality audit guidelines are attached which may be used as a tool to perform audits.

February 2010

Rx-360 API and API Intermediates Quality Audit Guideline

Note-the section numbers the same as the sections in ICH Q7.

2. Quality Management					
2.1 Principles					
#	**Section #**	**Section Title**	**Description and Guidance** **ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients**	**Objective Evidence**	**Outcome***
1	2.10	Quality Management: Principles	Quality should be the responsibility of all persons involved in manufacturing.		
2	2.11	Quality Management: Principles	Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.		
3	2.12	Quality Management: Principles	The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.		
4	2.13	Quality Management: Principles	There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.		

*Outcome, √ Acceptable, D Deficiency Noted, NC Not Confirmed, NA Not Applicable

5	2.14	Quality Management: Principles	The persons authorized to release intermediates and APIs should be specified		
6	2.15	Quality Management: Principles	All quality related activities should be recorded at the time they are performed.		
7	2.16	Quality Management: Principles	Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.		
8	2.17	Quality Management: Principles	No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation)		
9	2.18	Quality Management: Principles	Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).		
10	2.20	Quality Management: Responsibility of the Quality Unit	The quality unit(s) should be involved in all quality-related matters.		
11	2.21	Quality Management: Responsibility of the Quality Unit	The quality unit(s) should review and approve all appropriate quality-related documents.		

12	2.22	Quality Management: Responsibility of the Quality Unit	The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to: 1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company; 2. Establishing a system to release or reject raw materials, intermediates, packaging and labeling materials; 3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution; 4. Making sure that critical deviations are investigated and resolved; 5. Approving all specifications and master production instructions; 6. Approving all procedures impacting the quality of intermediates or APIs; 7. Making sure that internal audits (self-inspections) are performed; 8. Approving intermediate and API contract manufacturers; 9. Approving changes that potentially impact intermediate or API quality; 10. Reviewing and approving validation protocols and reports; 11. Making sure that quality related complaints are investigated and resolved; 12. Making sure that effective systems are used for maintaining and calibrating critical equipment; 13. Making sure that materials are appropriately tested and the results are reported; 14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and 15. Performing product quality reviews (as defined in Section 2.5).		

13			Determine if the SOPs include all steps to be followed in the processing, testing, labeling, and distribution of biological drug products. Verify the most current version of approved SOPs is readily available for use by key personnel in the areas where the procedures are performed.		
14	2.3	Quality Management: Responsibility for Production Activities	The responsibility for production activities should be described in writing, and should include but not necessarily be limited to: 1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures; 2. Producing APIs and, when appropriate, intermediates according to preapproved instructions; 3. Reviewing all production batch records and ensuring that . these are completed and signed; 4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded; 5. Making sure that production facilities are clean and when appropriate disinfected; 6. Making sure that the necessary calibrations are performed and records kept; 7. Making sure that the premises and equipment are maintained and records kept; 8. Making sure that validation protocols and reports are reviewed and approved; 9. Evaluating proposed changes in product, process or equipment; and 10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.		
15	2.40	Quality Management: Internal Audits	In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.		

16	2.41	Quality Management: Internal Audits	Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.		
17	2.50	Quality Management: Product Quality Review	Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least: • A review of critical in-process control and critical API test results; • A review of all batches that failed to meet established specification(s); • A review of all critical deviations or non-conformances and related investigations; • A review of any changes carried out to the processes or analytical methods; • A review of results of the stability monitoring program; • A review of all quality-related returns, complaints and recalls; and • A review of adequacy of corrective actions.		
18	2.51	Quality Management: Product Quality Review	The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.		
3. Personnel					
19	3.10	Personnel: Qualifications	There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.		
20	3.11	Personnel: Qualifications	The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.		

21	3.12	Personnel: Qualifications	Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.		
22	3.20	Personnel: Hygiene	Personnel should practice good sanitation and health habits.		
23	3.21	Personnel: Hygiene	Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.		
24	3.22	Personnel: Hygiene	Personnel should avoid direct contact with intermediates or APIs.		
25	3.23	Personnel: Hygiene	Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.		
26	3.24	Personnel: Hygiene	Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.		
27	3.30	Personnel: Consultants	Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.		
28	3.31	Personnel: Consultants	Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.		

4. Buildings and Facilities					
29	4.10	Buildings and Facilities: Design and Construction	Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.		
30	4.11	Buildings and Facilities: Design and Construction	Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.		
31	4.12	Buildings and Facilities: Design and Construction	Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.		
32	4.13	Buildings and Facilities: Design and Construction	The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.		
33	4.14	Buildings and Facilities: Design and Construction	There should be defined areas or other control systems for the following activities: • Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection; • Quarantine before release or rejection of intermediates and APIs; • Sampling of intermediates and APIs; • Holding rejected materials before further disposition (e.g., return, reprocessing or destruction); • Storage of released materials; • Production operations; • Packaging and labeling operations; and • Laboratory operations.		

34	4.15	Buildings and Facilities: Design and Construction	Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.		
35	4.16	Buildings and Facilities: Design and Construction	Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.		
36	4.20	Buildings and Facilities: Utilities	All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.		
37	4.21	Buildings and Facilities: Utilities	Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.		
38	4.22	Buildings and Facilities: Utilities	If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.		
39	4.23	Buildings and Facilities: Utilities	Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.		
40	4.24	Buildings and Facilities: Utilities	Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.		

41	4.30	Buildings and Facilities: Water	Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.		
42	4.31	Buildings and Facilities: Water	Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.		
43	4.32	Buildings and Facilities: Water	If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.		
44	4.33	Buildings and Facilities: Water	Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.		
45	4.34	Buildings and Facilities: Water	Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.		
46	4.40	Buidlings and Facilities: Containment	Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.		
47	4.41	Buidlings and Facilities: Containment	Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.		
48	4.42	Buidlings and Facilities: Containment	Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.		
49	4.43	Buidlings and Facilities: Containment	Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.		
50	4.50	Buildings and Facilities: Lighting	Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.		

51	4.60	Buildings and Facilities: Sewage and Refuse	Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.		
52	4.70	Buildings and Facilities: Sanitation and Maintenance	Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.		
53	4.71	Buildings and Facilities: Sanitation and Maintenance	Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.		
54	4.72	Buildings and Facilities: Sanitation and Maintenance	When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.		
5 Process Equipment					
55	5.10	Process Equipment: Design and Construction	Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.		
56	5.11	Process Equipment: Design and Construction	Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.		
57	5.12	Process Equipment: Design and Construction	Production equipment should only be used within its qualified operating range.		
58	5.13	Process Equipment: Design and Construction	Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.		

59	5.14	Process Equipment: Design and Construction	Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.		
60	5.15	Process Equipment: Design and Construction	Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.		
61	5.16	Process Equipment: Design and Construction	A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).		
62	5.20	Process Equipment: Equipment Maintenance and Cleaning	Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.		

63	5.21	Process Equipment: Equipment Maintenance and Cleaning	Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include: • Assignment of responsibility for cleaning of equipment; • Cleaning schedules, including, where appropriate, sanitizing schedules; • A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment; • When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning; • Instructions for the removal or obliteration of previous batch identification; • Instructions for the protection of clean equipment from contamination prior to use; • Inspection of equipment for cleanliness immediately before use, if practical; and • Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.		
64	5.22	Process Equipment: Equipment Maintenance and Cleaning	Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.		
65	5.23	Process Equipment: Equipment Maintenance and Cleaning	Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).		
66	5.24	Process Equipment: Equipment Maintenance and Cleaning	Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.		

67	5.25	Process Equipment: Equipment Maintenance and Cleaning	Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.		
68	5.26	Process Equipment: Equipment Maintenance and Cleaning	Equipment should be identified as to its contents and its cleanliness status by appropriate means.		
69	5.30	Process Equipment: Calibration	Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.		
70	5.31	Process Equipment: Calibration	Equipment calibrations should be performed using standards traceable to certified standards, if existing.		
71	5.32	Process Equipment: Calibration	Records of these calibrations should be maintained.		
72	5.33	Process Equipment: Calibration	The current calibration status of critical equipment should be known and verifiable.		
73	5.34	Process Equipment: Calibration	Instruments that do not meet calibration criteria should not be used.		
74	5.35	Process Equipment: Calibration	Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.		
75	5.40	Process Equipment: Computerized Equipment	GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.		

76	5.41	Process Equipment: Computerized Equipment	Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.		
77	5.42	Process Equipment: Computerized Equipment	Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.		
78	5.43	Process Equipment: Computerized Equipment	Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.		
79	5.44	Process Equipment: Computerized Equipment	Written procedures should be available for the operation and maintenance of computerized systems.		
80	5.45	Process Equipment: Computerized Equipment	Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.		
81	5.46	Process Equipment: Computerized Equipment	Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.		
82	5.47	Process Equipment: Computerized Equipment	Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.		
83	5.48	Process Equipment: Computerized Equipment	If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.		

84	5.49	Process Equipment: Computerized Equipment	Data can be recorded by a second means in addition to the computer system.		
6. Documentation & Records					
85	6.10	Documentation and Records: Documentation System and Specifications	All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.		
86	6.11	Documentation and Records: Documentation System and Specifications	The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.		
87	6.12	Documentation and Records: Documentation System and Specifications	A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.		
88	6.13	Documentation and Records: Documentation System and Specifications	All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.		
89	6.14	Documentation and Records: Documentation System and Specifications	When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.		
90	6.15	Documentation and Records: Documentation System and Specifications	During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.		

91	6.16	Documentation and Records: Documentation System and Specifications	Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.		
92	6.17	Documentation and Records: Documentation System and Specifications	Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.		
93	6.18	Documentation and Records: Documentation System and Specifications	If electronic signatures are used on documents, they should be authenticated and secure.		
94	6.20	Documentation and Records: Equipment Cleaning and Use Record	Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.		
95	6.21	Documentation and Records: Equipment Cleaning and Use Record	If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.		

96	6.30	Documentation and Records: Records of Raw Materials, Intermediates, API Labeling and Packaging Materials	Records should be maintained including: • The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt; • The results of any test or examination performed and the conclusions derived from this; • Records tracing the use of materials; • Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications; and • The final decision regarding rejected raw materials, intermediates or API labeling and packaging materials.		
97	6.31	Documentation and Records: Records of Raw Materials, Intermediates, API Labeling and Packaging Materials	Master (approved) labels should be maintained for comparison to issued labels.		
98	6.40	Documentation and Records: Master Production Records	To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).		

99	6.41	Documentation and Records: Master Production Records	Master production instructions should include: • The name of the intermediate or API being manufactured and an identifying document reference code, if applicable; • A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics; • An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified; • The production location and major production equipment to be used; • Detailed production instructions, including the: o sequences to be followed, o ranges of process parameters to be used, o sampling instructions and in-process controls with their acceptance criteria, where appropriate, o time limits for completion of individual processing steps and/or the total process, where appropriate; and o expected yield ranges at appropriate phases of processing or time; • Where appropriate, special notations and precautions to be followed, or cross references to these; and • The instructions for storage of the intermediate or API to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.		
100	6.50	Documentation and Records: Batch Production Records	Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.		

101	6.51	Documentation and Records: Batch Production Records	These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.		
102	6.52	Documentation and Records: Batch Production Records	Documentation of completion of each significant step in the batch production records (batch production and control records) should include: • Dates and, when appropriate, times; • Identity of major equipment (e.g., reactors, driers, mills, etc.) used; • Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing; • Actual results recorded for critical process parameters; • Any sampling performed; • Signatures of the persons performing and directly supervising or checking each critical step in the operation; • In-process and laboratory test results; • Actual yield at appropriate phases or times; • Description of packaging and label for intermediate or API; • Representative label of API or intermediate if made commercially available; • Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and • Results of release testing.		
103	6.53	Documentation and Records: Batch Production Records	Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.		

104	6.60	Documentation and Records: Laboratory Control Records	Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows: • A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing; • A statement of or reference to each test method used; • A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions; • A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested; • A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors; • A statement of the test results and how they compare with established acceptance criteria; • The signature of the person who performed each test and the date(s) the tests were performed; and • The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.		
105	6.61	Documentation and Records: Laboratory Control Records	Complete records should also be maintained for: • Any modifications to an established analytical method; • Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices; • All stability testing performed on APIs; and • Out-of-specification (OOS) investigations.		
106	6.70	Documentation and Records: Batch Production Records Review	Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.		

107	6.71	Documentation and Records: Batch Production Records Review	Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).		
108	6.72	Documentation and Records: Batch Production Records Review	All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.		
109	6.73	Documentation and Records: Batch Production Records Review	The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.		
7. Materials Management					
110	7.10	Materials Management: General Controls	There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.		
111	7.11	Materials Management: General Controls	Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.		
112	7.12	Materials Management: General Controls	Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).		
113	7.13	Materials Management: General Controls	If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.		
114	7.14	Materials Management: General Controls	Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.		

115	7.20	Materials Management: Receipt and Quarantine	Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.		
116	7.21	Materials Management: Receipt and Quarantine	Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.		
117	7.22	Materials Management: Receipt and Quarantine	If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following: • certificate of cleaning • testing for trace impurities • audit of the supplier.		
118	7.23	Materials Management: Receipt and Quarantine	Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.		
119	7.24	Materials Management: Receipt and Quarantine	Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.		
120	7.30	Materials Management: Sampling and Testing of Incoming Production Materials	At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.		

121	7.31	Materials Management: Sampling and Testing of Incoming Production Materials	Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.		
122	7.32	Materials Management: Sampling and Testing of Incoming Production Materials	Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.		
123	7.33	Materials Management: Sampling and Testing of Incoming Production Materials	Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.		
124	7.34	Materials Management: Sampling and Testing of Incoming Production Materials	Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.		
125	7.35	Materials Management: Sampling and Testing of Incoming Production Materials	Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.		

126	7.40	Materials Management: Storage	Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.		
127	7.41	Materials Management: Storage	Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.		
128	7.42	Materials Management: Storage	Materials should be stored under conditions and for a period that have no adverse affect on their quality, and should normally be controlled so that the oldest stock is used first.		
129	7.43	Materials Management: Storage	Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.		
130	7.44	Materials Management: Storage	Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.		
131	7.50	Materials Management: Re-evaluation	Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).		
8. Production and In-Process Controls					
132	8.10	Production and In-process Controls: Production Operations	Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.		
133	8.11	Production and In-process Controls: Production Operations	If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available: • Material name and/or item code; • Receiving or control number; • Weight or measure of material in the new container; and • Re-evaluation or retest date if appropriate.		
134	8.12	Production and In-process Controls: Production Operations	Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.		

135	8.13	Production and In-process Controls: Production Operations	Other critical activities should be witnessed or subjected to an equivalent control.		
136	8.14	Production and In-process Controls: Production Operations	Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.		
137	8.15	Production and In-process Controls: Production Operations	Any deviation should be documented and explained. Any critical deviation should be investigated.		
138	8.16	Production and In-process Controls: Production Operations	The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.		
139	8.17	Production and In-process Controls: Production Operations	Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.		
140	8.20	Production and In-process Controls: Production Operations	Specific time limits in the master production instructions should be met to ensure the quality of intermediates and API's. Deviations should be documented and evaluated.		
141	8.21	Production and In-process Controls: Production Operations	Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.		

142	8.30	Production and In-process Controls: Production Operations	Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the developmental stage or from historical data.		
143	8.31	Production and In-process Controls: Production Operations	Review the acceptance criteria and type and extent of the testing of the intermediate or API. Early processing steps may require less stringent controls verses later steps, which will need to be tighter. (e.g. isolation and purification steps).		
144	8.32	Production and In-process Controls: Production Operations	Critical in-process controls (and critical process monitoring), including control points and methods, should be stated in writing and approved by the quality units.		
145	8.33	Production and In-process Controls: Production Operations	In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.		
146	8.34	Production and In-process Controls: Production Operations	Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.		
147	8.35	Production and In-process Controls: Production Operations	In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.		
148	8.36	Production and In-process Controls: Production Operations	Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.		
149	8.40	Production and In-process Controls: Production Operations	Blending is only defined for those materials that are combined within the same specification to produce a homogeneous intermediate or API.		

150	8.41	Production and In-process Controls: Production Operations	Out-of-specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.		
151	8.42	Production and In-process Controls: Production Operations	Refer to the Q7 standard for acceptable blending operations.		
152	8.43	Production and In-process Controls: Production Operations	Blending processes should be adequately controlled and documented, and the blended batch should be tested for conformance to established specifications, where appropriate.		
153	8.44	Production and In-process Controls: Production Operations	The batch record for the blending process should allow traceability back to the individual batches that make up the blend.		
154	8.45	Production and In-process Controls: Production Operations	Where physical attributes of the API are critical, blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes that may be affected by the blending process.		
155	8.46	Production and In-process Controls: Production Operations	If the blending could adversely affect stability, stability testing of the final blended batches should be performed.		
156	8.47	Production and In-process Controls: Production Operations	The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailing or batch in the blend.		
157	8.50	Production and In-process Controls: Production Operations	Refer to Q7 standard for examples of contamination control.		

158	8.51	Production and In-process Controls: Production Operations	Production operations should be conducted in a manner that prevents contamination of intermediates or APIs by other materials.		
159	8.52	Production and In-process Controls: Production Operations	Precautions should be taken when APIs are handled after purification.		
9 Packaging and Identification Labeling of APIs and Intermediates					
160	9.10	Packaging and Identification Labeling of APIs and Intermediates	There should be written procedures describing the receipt, identification, quarantine, sampling, examination, and/or testing, release, and handling of packaging and labeling materials.		
161	9.11	Packaging and Identification Labeling of APIs and Intermediates	Packaging and labeling materials should conform to established specification. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.		
162	9.12	Packaging and Identification Labeling of APIs and Intermediates	Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.		
163	9.20	Packaging and Identification Labeling of APIs and Intermediates	Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.		
164	9.21	Packaging and Identification Labeling of APIs and Intermediates	Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.		

165	9.22	Packaging and Identification Labeling of APIs and Intermediates	If containers are reused, they should be cleaned in accordance with documented procedures, and all previous labels should be removed or defaced.		
166	9.30	Packaging and Identification Labeling of APIs and Intermediates	Access to the label storage areas should be limited to authorize personnel.		
167	9.31	Packaging and Identification Labeling of APIs and Intermediates	Procedures should be established to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of container labeled and the number of labels issued. Discrepancies should be investigated and the quality unit(s) should approve the investigation.		
168	9.32	Packaging and Identification Labeling of APIs and Intermediates	All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.		
169	9.33	Packaging and Identification Labeling of APIs and Intermediates	Obsolete and out-dated labels should be destroyed.		
170	9.34	Packaging and Identification Labeling of APIs and Intermediates	Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.		
171	9.35	Packaging and Identification Labeling of APIs and Intermediates	Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.		

172	9.36	Packaging and Identification Labeling of APIs and Intermediates	A printed label representative of those used should be included in the batch production record.		
173	9.40	Packaging and Identification Labeling of APIs and Intermediates	There should be documented procedures designed to ensure that correct packaging materials and labels are used.		
174	9.41	Packaging and Identification Labeling of APIs and Intermediates	Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates and APIs.		
175	9.42	Packaging and Identification Labeling of APIs and Intermediates	Labels used on containers of intermediates or APIs should indicate the name or identifying code, batch number, and storage conditions when such information is critical to ensure the quality of intermediate or API.		
176	9.43	Packaging and Identification Labeling of APIs and Intermediates	For Intermediates or APIs that will be transferred outside the control of the manufacturer's material management system, see the Q7 standard.		
177	9.44	Packaging and Identification Labeling of APIs and Intermediates	Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.		
178	9.45	Packaging and Identification Labeling of APIs and Intermediates	Packaged and labeled intermediates or APIs should be examined to ensure that container and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.		
179	9.46	Packaging and Identification Labeling of APIs and Intermediates	Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.		

10. Storage and Distribution					
180	10.10	Warehousing Procedures	Facilities should be available for the storage of all materials under appropriate conditions. Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.		
181	10.11	Warehousing Procedures	Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been made.		
182	10.20	Distribution Procedures	APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.		
183	10.21	Distribution Procedures	APIs and intermediates should be transported in a manner that does not adversely affect their quality.		
184	10.22	Distribution Procedures	Special transport or storage conditions for an API or intermediate should be stated on the label.		
185	10.23	Distribution Procedures	The manufacturer should ensure that the contract acceptor for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.		
186	10.24	Distribution Procedures	A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.		
11. Laboratory Controls					
187	11.10	Laboratory Controls: General Controls	The independent quality unit(s) should have at its disposal adequate laboratory facilities.		
188	11.11	Laboratory Controls: General Controls	There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.		

189	11.12	Laboratory Controls: General Controls	All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).		
190	11.13	Laboratory Controls: General Controls	Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met		
191	11.14	Laboratory Controls: General Controls	Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.		
192	11.15	Laboratory Controls: General Controls	Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.		
193	11.16	Laboratory Controls: General Controls	Reagents and standard solutions should be prepared and labeled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.		

194	11.17	Laboratory Controls: General Controls	Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.		
195	11.18	Laboratory Controls: General Controls	Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.		
196	11.19	Laboratory Controls: General Controls	Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.		
197	11.20	Laboratory Controls: Testing of Intermediates and API's	For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.		
198	11.21	Laboratory Controls: Testing of Intermediates and API's	An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.		

199	11.22	Laboratory Controls: Testing of Intermediates and API's	The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.		
200	11.23	Laboratory Controls: Testing of Intermediates and API's	Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.		
201	11.3	Laboratory Controls: Validation of Analytical Procedures	See Section 12		
202	11.40	Laboratory Controls: Certificates of Analysis	Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.		
203	11.41	Laboratory Controls: Certificates of Analysis	Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.		
204	11.42	Laboratory Controls: Certificates of Analysis	The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).		
205	11.43	Laboratory Controls: Certificates of Analysis	Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.		

206	11.44	Laboratory Controls: Certificates of Analysis	If new Certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.		
207	11.50	Laboratory Controls: Stability Monitoring of API's	A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.		
208	11.51	Laboratory Controls: Stability Monitoring of API's	The test procedures used in stability testing should be validated and be stability indicating.		
209	11.52	Laboratory Controls: Stability Monitoring of API's	Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.		
210	11.53	Laboratory Controls: Stability Monitoring of API's	Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.		
211	11.54	Laboratory Controls: Stability Monitoring of API's	Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.		
212	11.55	Laboratory Controls: Stability Monitoring of API's	For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.		

213	11.56	Laboratory Controls: Stability Monitoring of API's	Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.		
214	11.60	Laboratory Controls: Expiry and Retest Dating	When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).		
215	11.61	Laboratory Controls: Expiry and Retest Dating	An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.		
216	11.62	Laboratory Controls: Expiry and Retest Dating	Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale.		
217	11.63	Laboratory Controls: Expiry and Retest Dating	A representative sample should be taken for the purpose of performing a retest.		
218	11.70	Laboratory Controls: Reserve/ Retention Samples	The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.		
219	11.71	Laboratory Controls: Reserve/ Retention Samples	Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.		
220	11.72	Laboratory Controls: Reserve/ Retention Samples	The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.		
12. Validation					

221	12.10	Validation: Validation Policy	The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, inprocess control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.		
222	12.11	Validation: Validation Policy	The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include: • Defining the API in terms of its critical product attributes; • Identifying process parameters that could affect the critical quality attributes of the API; • Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.		
223	12.12	Validation: Validation Policy	Validation should extend to those operations determined to be critical to the quality and purity of the API.		
224	12.20	Validation: Validation Documentation	A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.		
225	12.21	Validation: Validation Documentation	The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.		
226	12.22	Validation: Validation Documentation	A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.		
227	12.23	Validation: Validation Documentation	Any variations from the validation protocol should be documented with appropriate justification.		

228	12.30	Validation: Qualification	Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined: • Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose. • Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements. • Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges. • Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.		
229	12.40	Validation: Approaches to Process Validation	Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.		
230	12.41	Validation: Approaches to Process Validation	There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.		
231	12.42	Validation: Approaches to Process Validation	Prospective validation should normally be performed for all API processes as defined in 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.		
232	12.43	Validation: Approaches to Process Validation	Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.		

233	12.44	Validation: Approaches to Process Validation	An exception can be made for retrospective validation for well established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where: (1) Critical quality attributes and critical process parameters have been identified; (2) Appropriate in-process acceptance criteria and controls have been established; (3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and (4) Impurity profiles have been established for the existing API.		
234	12.45	Validation: Approaches to Process Validation	Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.		
235	12.50	Validation: Process Validation Program	The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally, data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.		
236	12.51	Validation: Process Validation Program	Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.		

237	12.52	Validation: Process Validation Program	Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.		
238	12.60	Validation: Periodic Review of Validated Systems	Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.		
239	12.70	Validation: Cleaning Validation	Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.		
240	12.71	Validation: Cleaning Validation	Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.		
241	12.72	Validation: Cleaning Validation	The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.		

242	12.73	Validation: Cleaning Validation	Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).		
243	12.74	Validation: Cleaning Validation	Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.		
244	12.75	Validation: Cleaning Validation	Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).		
245	12.76	Validation: Cleaning Validation	Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.		
246	12.80	Validation: Validation of Analytical Methods	Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.		

247	12.81	Validation: Validation of Analytical Methods	Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.		
248	12.82	Validation: Validation of Analytical Methods	Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.		
249	12.83	Validation: Validation of Analytical Methods	Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.		
13. Change Control					
250	13.10	Change Control	A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.		
251	13.11	Change Control	Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.		
252	13.12	Change Control	Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality unit(s).		
253	13.13	Change Control	The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.		
254	13.14	Change Control	When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.		

255	13.15	Change Control	After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.		
256	13.16	Change Control	The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.		
257	13.17	Change Control	Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API		
14. Rejection and re-use of materials					
258	14.10	Rejection	Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. The final disposition of the material will be recorded.		
259	14.20	Reprocessing	See Q7 standard for explanation of introducing an intermediate or API back into the process.		
260	14.21	Reprocessing	Continuation of a process step after an in-process control test has whown that the step is incomlete is considered to be part of the normal process. This is not considered to be reprocessing.		
261	14.22	Reprocessing	Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and over-reacted materials.		
262	14.30	Reworking	Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.		
263	14.31	Reworking	Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process.		
264	14.32	Reworking	Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process.		

265	14.40	Recovery of Materials and Solvents	Recovery of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.		
266	14.41	Recovery of Materials and Solvents	All recovery procedures must be controlled and monitored to ensure that solvents meet appropriate standards before reuse or commingling with other approved materials.		
267	14.42	Recovery of Materials and Solvents	Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.		
268	14.43	Recovery of Materials and Solvents	The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.		
269	14.50	Returns	Returned intermediates and APIs should be identified as such and quarantined.		
270	14.51	Returns	If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of the containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked or destroyed, as appropriate.		
271	14.52	Returns	Records for returned intermediates or APIs should be maintained.		
15 Complaints and Recalls					
272	15.10	Complaints and Recalls	All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.		

273	15.11	Complaints and Recalls	Complaint records should include: • Name and address of complainant; • Name (and, where appropriate, title) and phone number of person submitting the complaint; • Complaint nature (including name and batch number of the API); • Date complaint is received; • Action initially taken (including dates and identity of person taking the action); • Any follow-up action taken; • Response provided to the originator of complaint (including date response sent); and • Final decision on intermediate or API batch or lot.		
274	15.12	Complaints and Recalls	Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.		
275	15.13	Complaints and Recalls	There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.		
276	15.14	Complaints and Recalls	The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.		
277	15.15	Complaints and Recalls	In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.		
16. Contract Manufacturers					
278	16.10	Contract Manufacturers	All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.		
279	16.11	Contract Manufacturers	Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.		

280	16.12	Contract Manufacturers	There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.		
281	16.13	Contract Manufacturers	The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.		
282	16.14	Contract Manufacturers	Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.		
283	16.15	Contract Manufacturers	Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.		
284	16.16	Contract Manufacturers	Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.		
17. Agents, Brokers, Traders, Distributors, Repackers, and Relabellers					
285	17.10	Applicability	This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.		
286	17.11	Applicability	All agents, brokers, traders, distributors, Repackers, and relabelers should comply with GMP as defined in the guidance.		
287	17.20	Traceability of distributed APIs & Intermediates	Refer to the standard for a list of documents that should be retained and available by the outside source.		
288	17.30	Quality Management	Outside sources should have an effective quality system as defined in section 2 of the standard.		
289	17.40	Repackaging, Relabeling, and holding of APIs & Intermediates	Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of API or intermediate identity or purity.		

290	17.41	Repackaging, Relabeling, and holding of APIs & Intermediates	Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.		
291	17.50	Stability	Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.		
292	17.60	Transfer of Information	Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.		
293	17.61	Transfer of Information	The agent, broker, trader, distributor, repacker, or relabeller who suppliers the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.		
294	17.62	Transfer of Information	The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)		
295	17.63	Transfer of Information	The specific guidance for Certificates of Analysis included in Section 11.4 should be met.		
296	17.70	Handling of Complaints & Recalls	Agents, brokers, traders, distributors, repackers, or relabellers should maintain records of complaints and recallls, as specified in Section 15, for all complaints and recalls that come to their attention.		
297	17.71	Handling of Complaints & Recalls	If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabellers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.		

298	17.72	Handling of Complaints & Recalls	Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).		
299	17.80	Handling of Returns	Returns should be handled as specified in Section 14.52. The agents, brokers, traders, distributors, repackers or relabellers should maintain documentation of returned APIs and intermediates.		
18. Specific Guidance for APIs Manufactured by Cell Culture/Fermentation					
300	18.10	General	Guidance		
301	18.11	General	Guidance		
302	18.12	General	Guidance		
303	18.13	General	Guidance		
304	18.14	General	Guidance		
305	18.15	General	Guidance		
306	18.16	General	Guidance		
307	18.17	General	Guidance		
308	18.20	Cell Maintenance and Record Keeping	Access to cell banks should be limited to authorized personnel.		
309	18.21	Cell Maintenance and Record Keeping	Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.		
310	18.22	Cell Maintenance and Record Keeping	Records of the use of the vials from the cell banks and storage conditions should be maintained.		
311	18.23	Cell Maintenance and Record Keeping	Where appropriate, cell banks should be periodically monitored to determine suitability for use.		

312	18.24	Cell Maintenance and Record Keeping	N/A		
313	18.30	Cell Culture/ Fermentation	Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.		
314	18.31	Cell Culture/ Fermentation	Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.		
315	18.32	Cell Culture/ Fermentation	Personnel should be appropriately gowned and take special precautions handling the cultures.		
316	18.33	Cell Culture/ Fermentation	Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.		
317	18.34	Cell Culture/ Fermentation	Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.		
318	18.35	Cell Culture/ Fermentation	Culture media should be sterilized before use when appropriate to protect the quality of the API.		

319	18.36	Cell Culture/ Fermentation	There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.		
320	18.37	Cell Culture/ Fermentation	Records of contamination events should be maintained.		
321	18.38	Cell Culture/ Fermentation	Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.		
322	18.40	Harvesting, Isolation, and Purification	Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.		
323	18.41	Harvesting, Isolation, and Purification	Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.		
324	18.42	Harvesting, Isolation, and Purification	All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.		
325	18.43	Harvesting, Isolation, and Purification	If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.		
326	18.44	Harvesting, Isolation, and Purification	Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.		

327	18.50	Viral Removal/ Inactivation Steps	See the ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.		
328	18.51	Viral Removal/ Inactivation Steps	Viral removal and viral inactivation steps are critical processing steps fro some processes and should be performed within their validated parameters.		
329	18.52	Viral Removal/ Inactivation Steps	Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.		
330	18.53	Viral Removal/ Inactivation Steps	The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.		
19. APIs for Use in Clinical Trials					
321	19.10	API's for Use in Clinical Trials: General	Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.		
322	19.11	API's for Use in Clinical Trials: General	The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from preclinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.		
323	19.20	API's for Use in Clinical Trials: Quality	Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.		
324	19.21	API's for Use in Clinical Trials: Quality	A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.		

325	19.22	API's for Use in Clinical Trials: Quality	Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.		
326	19.23	API's for Use in Clinical Trials: Quality	Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.		
327	19.24	API's for Use in Clinical Trials: Quality	Process and quality problems should be evaluated.		
328	19.25	API's for Use in Clinical Trials: Quality	Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.		
329	19.30	API's for Use in Clinical Trials: Equipment and Facilities	During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.		
330	19.31	API's for Use in Clinical Trials: Equipment and Facilities	Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.		
331	19.40	API's for Use in Clinical Trials: Control of Raw Materials	Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.		
332	19.41	API's for Use in Clinical Trials: Control of Raw Materials	In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.		
333	19.50	API's for Use in Clinical Trials: Production	The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.		
334	19.51	API's for Use in Clinical Trials: Production	Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.		

335	19.60	API's for Use in Clinical Trials: Validation	Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.		
336	19.61	API's for Use in Clinical Trials: Validation	Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.		
337	19.70	API's for Use in Clinical Trials: Changes	Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.		
338	19.80	API's for Use in Clinical Trials: Laboratory Controls	While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.		
339	19.81	API's for Use in Clinical Trials: Laboratory Controls	A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.		
340	19.82	API's for Use in Clinical Trials: Laboratory Controls	Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.		
341	19.90	API's for Use in Clinical Trials: Documentation	A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.		
342	19.91	API's for Use in Clinical Trials: Documentation	The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.		
343	19.92	API's for Use in Clinical Trials: Documentation	A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.		

Additional Audit Guideline

Control of Transmissible Spongiform Encephalopathy Agents (TSE). Note – detailed guidance on minimising the risk of TSE is found in EMEA/410/1.					
344	N/A	TSE	A system should be in place to investigate the supply chain so that any use of animal derived materials can be identified and appropriate controls established. *(Note the supply chain materails to be considered include starting materials, reagents, solvents, enzymes, catalysts, processing aids such as charcoal, media components and cell banks. Materials which have the potential to come into direct contact with product contact processing or packaging equipment e.g lubricants and cleaning agents should be included in the assessment).*		
345	N/A	TSE	The potential for contamination of products with animal derived materials should be subject to a documented assessment. The assessment should include whether or not animal derived materials are used at any stage during the production of the material or product, including supplied materials.		
346	N/A	TSE	The supplier should have procurement controls in place that specify the grade of material to be supplied and any permitted use of animal derived materials or should confirm that no animal derived materials are used. Routine receipt procedures must confirm that the correct grade is received.		
347	N/A	TSE	Where certification by external bodies exists, it should be available and maintained. Any change in certification status must be immediately communicated to customers, including the provision of new or rev ised certificates. There must be a process in place that reconfirms the animal derived declaration status of supply, on a periodic basis.		