API GMP Warning Letter Update—Evolving Expectations and Basic Deficiencies

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INTRODUCTION

As if in conformance with Darwin’s Theory of Evolution, the active pharmaceutical ingredient (API) good manufacturing practice (GMP) continues its natural process of evolution. Although Darwin’s theory was postulated for living organisms, one can relate the same theories for growth and change to the ongoing process of GMP standards development. As science evolves in technical capability, so will the GMPs evolve as the principle way in which patient safety is ensured.

As with living organisms, API GMP principles do not develop in a vacuum and are not static in nature. GMPs are generally influenced by real-world experiences that highlight the need for such principles and standards. APIs are compounds or mixtures of compounds that are necessary for use in human and veterinary medicine. The API is the most important material in a medicine or drug product because it is responsible for the pharmacological activity of the medicine. The API makes the drug product effective and valuable for its intended use. It also has the most potential to impact the safety of the drug product. The API exists in a constantly changing world where constantly evolving conditions and factors can affect the API. New technology and resulting information has advanced the science of pharmaceutical development and control. The ongoing changes to API impurity requirements demonstrate evolving requirements as evidenced by a series of new guidance documents. Further, there is increased potential for extraneous contamination of the API and greater awareness of such contamination as a result of recent well-publicized events in the global marketplace.

While certain API GMP principles are continually evolving, there also are principles that remain fundamentally sound (i.e., they will remain essentially unchanged over the course of time). These are the basic tenets of current GMP that include such topics as procedures, training, documentation, and so on. They are the fundamental elements of process control that every pharmaceutical, device, and other regulated facility must implement. These are elements that are generally not negotiable in the eyes of the regulatory authorities—there must be a clear demonstration of these elements and associated systems to demonstrate compliant GMP manufacturing. The US Food and Drug Administration issues
483 observations to indicate deficiencies in basic GMP principles. FDA warning letters are issued for more severe violations of GMPs and other regulatory deviations that are notable as FDA policy and require immediate action by the recipient. Review of API GMP warning letters, issued between 2006 and early 2009, indicate that deficiencies include both evolving issues and basic GMP principles. In several cases, cited deficiencies were repeat offences which make them more critical as a GMP deviation.

This discussion reviews GMP violations cited in FDA warning letters. The following are discussed:

- **API GMP violations.** Details of recent specific FDA warning letters issued between 2006 and end of 2008 are provided.
- **Evolving requirements regarding safety—impurities, contaminants, and residues.** There are new and evolving requirements for APIs some of which are new applications of development work and quality by design (QbD) practices that may indeed go beyond the original intent of API GMP guidance.
- **Basic deficiencies.** These are deficiencies in fundamental GMP requirements.

It is important to note that some observations noted during the review of the warning letters may be filing issues and not GMP in nature; however, it is important enough to mention even if it is beyond the scope and intent of GMP as noted by International Conference on Harmonisation (ICH) Q7A, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (1). FDA recognizes ICH Q7A as the current guideline for defining minimum API manufacturing standards.

### API GMP VIOLATIONS—FDA WARNING LETTERS

The US FDA website (2) provides easy access to warning letters issued by FDA. Warning letters provide an indication of current GMP expectations of FDA. FDA issues 483 observations at the close of an inspection to identify deficiencies in basic GMP principles. The recipient then responds to the respective observations. FDA warning letters are issued for more severe violations of GMPs and other regulatory deviations that are notable as FDA policy and require immediate action by the recipient. Often deficiencies in the aforementioned responses may also be discussed in the warning letters. While warning letters should not be the only source used to examine current GMP thinking, they are useful to help determine current areas of focus and concern.

Review of the FDA website for warning letters from 2006-2008 shows that only limited numbers of letters have been issued to API manufacturers. Table I provides a listing of API GMP related warning letters as reported on the FDA website. One of the five 2008 inspections was actually performed after a major product safety issue (heparin) became known by FDA and the firm’s site was inspected to evaluate the conditions that existed at the facility.

One should also understand that some warning letters may cross over from API to pharmaceutical products. When a reference is made to Part 211, the subject is normally referring to drug product, because 211 are not the governing regulations for API. Jurisdiction over API comes directly from the Food, Drug, and Cosmetics (FD&C) Act itself. GMP problems with the API are translatable to problems with the final product.

While the number of cited issues appears to be relatively equal from inspection to inspection, the observations themselves vary significantly in importance and product quality impact, as shown in the following examples.

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Number of cited issues in warning letter</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>USA</td>
<td>14</td>
</tr>
<tr>
<td>2006</td>
<td>China</td>
<td>1</td>
</tr>
<tr>
<td>2006</td>
<td>USA</td>
<td>7</td>
</tr>
<tr>
<td>2006</td>
<td>India</td>
<td>2</td>
</tr>
<tr>
<td>2007</td>
<td>China</td>
<td>5</td>
</tr>
<tr>
<td>2007</td>
<td>China</td>
<td>4</td>
</tr>
<tr>
<td>2007</td>
<td>Japan</td>
<td>3</td>
</tr>
<tr>
<td>2008</td>
<td>India</td>
<td>6</td>
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<tr>
<td>2008</td>
<td>China</td>
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<tr>
<td>2008</td>
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<tr>
<td>2008</td>
<td>China</td>
<td>2</td>
</tr>
<tr>
<td>2008</td>
<td>USA</td>
<td>6</td>
</tr>
</tbody>
</table>
Wyoming, USA 2006
This warning letter (3) issued to a company in Wyoming, USA involved a facility with both API and finished product manufacturing. FDA cited the following:

- “There is a failure to ensure that automatic, mechanical, or electrical equipment or other types of equipment will perform a function satisfactorily. Examples cited included various aspects of the reverse osmosis water system.
- “There is a failure to follow procedures. Examples again involved the reverse osmosis system.
- “The written program designed to assure proper performance of automatic, mechanical, or electronic equipment is not adequate. Redacted examples were provided.
- “There is a failure to assure that the air filtration system, including prefilters, is working correctly when used on air supplies to the production areas for both finished dosage forms and APIs.
- “Written procedures for cleaning and maintaining equipment used in the manufacture, processing, packing, or holding of a drug product are inadequate.
- “There is a failure to investigate a batch that did not meet specifications.
- “There is a failure to date and sign the Master Production and Control records.
- “Failure of the Master Production and Control Records for each batch of Morphine Sulfate Concentrate Oral Solution to include: A statement of the theoretical yield and a specimen of a copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling as required by 21 CFR 211.186(b)[7] and [8].
- “Adequate washing facilities, including hot and cold water, soap or detergent and clean toilet facilities easily accessible to all working areas are not provided.
- “Failure to have written procedures for complaints to include review to determine whether the complaint.”

Minnesota, USA 2006
This warning letter (4) is for an API repackaging facility located in Minnesota, USA. FDA cited the following:

- “Failure to demonstrate the adequacy of the retest
dating assigned to the 155 APIs that are repackaged by your firm for use by compounding pharmacies. Examples provided included Acyclovir HCl, Amitriptyline HCl, Cyclosporine A, Dexamethasone Sodium Phosphate, and Gentamicin Sulfate.
- “Failure to show on the COQ that you issue with the repackaged APIs the name, address, and telephone number of the laboratory that performed the analysis. Furthermore, you fail to reference on the COQs the name and address of the original manufacturer and the original batch certificate, which you fail to attach to the new certificate of analysis.
- “Failure to validate the authenticity of supplier’s COAs on a periodic basis in lieu of full compendia testing of APIs that you package.
- “Failure to conduct audits of contract laboratories that perform testing of incoming APIs.
- “Failure to maintain written procedures that describe the responsibilities and procedures applicable to the quality control unit.
- “Failure to retain reserve samples of each batch of each API that you repackage.
- “Failure to document that the pre and post-filters on the air-handling units in your repackaging suites are changed according to the frequency specified in your SOP.”

Deficiencies in previous responses to the FDA 483 observation were also discussed.

India 2006
This warning letter (5) appears to be the result of an inspection of a facility in India that covered both drug products and APIs. FDA cited the following:

- “Written production and process control procedures were not always followed and documented at the time of performance.
- “Control records do not include complete and accurate information relating to the production and control of each batch.”

Of particular apprehension noted in this warning letter is that “two previous inspections also noted failure to maintain complete and accurate records.” Poor recordkeeping practices which are detected following repeat inspections are always of concern. Such
observations may indicate poor management support for GMP and may raise questions about the reliability of any records kept by the firm.

**Kunshan City, China 2007**

This warning letter (6) makes reference to a recent audit as well as to previous observations cited during a previous inspection performed five years earlier at a Kunshan City, China facility. Some of the deficiencies noted five years ago were still apparent. FDA cited the company for the following infractions:

- “Batch production records do not include complete information relating to the production and control of each API batch.
- “Method validation documentation did not include appropriate data to verify that the analytical method produced accurate and reliable results.
- “Production equipment was not adequately cleaned and was not maintained in a good state of repair.
- “Laboratory equipment calibration was not adequately documented.
- “The FDA discovered that the firm has continued to ship materials from an unacceptable site to the USA even though the Investigator was told that product from that plant was intended for non-USA markets.”

This warning letter references observations that have been previously identified. What is difficult to evaluate is whether the deficiencies themselves were considered objectionable (as they should be), or the fact that they were not corrected since the previous inspection performed five years earlier.

**Japan 2007**

This warning letter (7) is date stamped Jan 1, 2008; however, the WL number is from 2007. The inspection was performed at a facility in Japan that occurred July 31 to August 2, 2007. FDA cited the following:

- “The analyst worksheets were deficient in that the following was observed
- There was no reference to the analytical test methods used
- There was no reference to the [ ]or instruments used
- There was no reference to the manufacturer’s standards and/or the lot number used
- There were unidentified post-it notes with the sample and standard weights and no reconciliability of the batches being tested
- There were weights reported without indicating the gross, tare, or net weight.

This was a repeat observation from the previous inspection of the site performed in 2005.

- “Failure of your investigations of out-of-specification (OOS) results to determine if corrections or preventative actions are needed.
- “Failure to have a validated and secure computerized system. Additionally, there were no written protocols to assign levels of responsibilities for the system.”

FDA noted in their letter that the firm also refused to provide copies of records requested by the FDA investigator and analyst for their later review. Refusing to provide copies of GMP documents to regulators during an inspection is never well received by such authorities. This warning letter makes this concern perfectly clear.

**India 2008**

This warning letter (8) to a company in India addresses problems in a facility that manufactures API and finished products. FDA cited the following:

- “Beta-lactam containment control program. Failure to adequately establish separate or defined areas for the manufacture and processing of non-penicillin beta-lactam products to prevent contamination or mixups. Multiple examples of this deficiency were cited. Deficiencies in the response to the FDA 483 response were also cited. Your containment control and monitoring programs are inadequate to prevent cross contamination of non-penicillin pharmaceutical products (APIs and finished dosage forms) with possible residues of penicillin, cephalosporin, or penem compounds. Examples cited included surface monitoring of each drug type, documentation, and contingency procedures. The response to the FDA 483 was also deficient.
- “Production records. Batch production and control records do not include complete information relating to the production and control of each
batch produced. Examples included lack of weight of excipients, second person verification, lack of information on media fills, lack of information on integrity tests, etc.

- “Failure investigations. Your procedures do not provide for a thorough review of explained discrepancies or failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed. An example failure investigation was discussed. Deficiencies in the response to the FDA 483 were also discussed.

- “Quality Control Unit. The quality control unit (QCU) failed to ensure that its organizational structure, procedures, processes, resources, and activities are adequate to ensure that APIs and drug products, sterile and non-sterile, meet their intended specifications for quality and purity (21 CFR 211.22). This same issue also applies to APIs produced at this site. Examples included improper QCU signoffs and failure to evaluate cleaning and sanitizing.

- “Aseptic operations. Procedures designed to prevent microbiological contamination of drug products and APIs purported to be sterile are not adequately written and followed to include adequate validation of the aseptic process [21 CFR 211.113(b)]. Examples provided included inadequate media fills, poor aseptic practices, and sanitization records.

- “The controls to prevent contamination or mix-ups in defined (critical and supporting clean) areas are deficient regarding operations related to aseptic processing of drug products [21 CFR 211.42 (C)(10)]. Examples described included various aspects of smoke studies in parenteral operations, lack of viewing stations, and other issues.”

FDA recommended disapproval of any new applications or supplements from this facility until the above problems are corrected. Further, shipments of product are subject to refusal of admission. Third-party supervision may be implemented in this facility.

**Changzhou, China 2008**

This warning letter (9) issued to a company in Changzhou, China is directly related to a drug product problem potentially associated with the API used to produce the drug product. FDA cited the following:

- “There is no assurance that processing steps used to manufacture heparin sodium, USP are capable of effectively removing impurities.
- “You fail to have adequate systems for evaluating the suppliers of heparin crude materials, and the crude materials themselves, to ensure that these materials are acceptable for use.
- “The test methods performed for heparin sodium USP have not been verified to ensure suitability under actual conditions of use.
- “Equipment used to manufacture heparin sodium USP is unsuitable for its intended use.”

How many of the cited observations in this warning letter would have occurred if the inspection was performed prior to the public health problem becoming obvious will never be known. However, the issues raised are indeed the subject of concern in Q7A if a sound impurity profile does not exist. What is particularly challenging in this instance is whether the unknown compounds could have been identified under normal conditions.

**Pucheng, China 2008**

This warning letter (10) addresses current good manufacturing practice (CGMP) audit deficiencies and response deficiencies at a company in Pucheng, China. FDA cited the following:

- “Your firm has not adequately addressed whether the final batch production test records, and the in-process test records, contain true and accurate information. For example:
  - Your firm’s response does not clarify which personnel actually perform the identification test for Chlortetracycline Hydrochloride and therefore leaves open the authenticity of the data appearing on prior and future final documents for the Chlortetracycline Hydrochloride.
  - Your firm’s response regarding changes made to the identification test for Chlortetracycline Hydrochloride standard preparation does not address the accuracy of the amount weighed by the analysts, which was questioned by the FDA investigators. You do not explain how changing
the methodology to a more precise measurement (+0.01 mg) will address the analyst’s performance of the weighing. For example, we cannot tell whether a precise balance is referenced in the revised SOP. The submitted revised Standard Operational Procedure (SOP) # is in Chinese. Without an English translation, we cannot evaluate whether it adequately addresses our concerns.

• “The quality unit failed to assure that its organizational structure, procedures, processes, and activities are adequate to ensure that APIs will meet their intended specifications for quality and purity. There should be an effective system for managing quality that involves the active participation of management. The quality unit should be independent and properly execute its quality assurance (QA) and quality control (QC) responsibilities. The quality unit should be involved in all quality-related matters including, but not limited to, reviews and audits. The responsibilities of the quality unit should be documented in writing and should encompass the organizational structure, procedure, processes and resources, as well as activities to ensure that APIs will meet their intended specifications to identify, strength, quality, and purity.

• Your SOP # describes the analyst as the person performing the test and recording the data and the reviewer as the person reviewing the accuracy of the data. However, when the FDA investigators were auditing the testing of Chlortetracycline Hydrochloride, one employee stated that at times the reviewer performs the test and the analyst performs the review. Another employee stated that she was both the analyst and reviewer. In contrast to what is stated in the SOP, there appears to be no distinction between the Quality Assurance and Quality Control personnel.

• Your responses indicate that the Quality Assurance personnel and Quality Control personnel received CGMP training, and that the training was completed on or about October 14, 2007. Two exam papers were submitted to illustrate the training. These exam papers are in Chinese. Without an English translation, we cannot evaluate whether they adequately address our concerns.”

Several points addressing deficiencies in previous responses to the agency were mentioned.

Pennsylvania, USA 2008
This warning letter (11) addresses drug products, bulk drug substances, and drug components. Further, it comments on deficient responses to the FDA 483. It is difficult to determine if this warning letter truly applies to API as inferred in the text of the letter. However, just to be sure, it has been included in the review. The following are items cited:

• “Production and process controls. You failed to assure that there are written production and process controls designed to assure that the drug products have the identify, strength, quality, and purity they purport or are represented to possess. Several examples were provided.

• “Failure investigations. Failures are not fully investigated and documented, nor extended to other batches as appropriate. Examples were again provided.

• “Laboratory controls. Laboratory controls do not include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure components and products conform to appropriate standards of identify, strength, quality, and purity. Examples relating to stability of drug components were provided.

• “Building and Facilities. Written procedures for the use of cleaning and sanitizing agents designed to prevent contamination of your facility are incomplete. An example related to decontamination is provided.

• “Maintenance of equipment. Written procedures are not followed for the maintenance of equipment used in manufacture, processing, and packing or holding. Multiple examples of procedures not performed without justification were provided.

• “Containers and closures. You failed to assure that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of bulk drug substances and sterile solutions used in products.”

The deficiencies in this letter were indicative of the
quality control unit inability to assure identity, strength, quality, and purity of drug product and drug substance.

**Evolving Requirements—Impurities, Contaminants, and Residues**

All impurity requirements are potentially safety related issues that are both regulatory filing and CGMP expectations. Several observations in the warning letters presented in this paper cited problems with impurities, contaminants, and residues. Impurities and contamination have always been of concern to FDA and other regulators. An impurity is defined in ICH Q7A as any component present in the intermediate or API that is not the desired entity. General requirements for impurities are clearly stated in ICH Q7A. API specifications should include control of impurities (e.g., organic impurities, inorganic impurities, and residual solvents). An impurity profile describing the identified and unidentified impurities present in a typical batch should be established for each API. The impurity profile should include the identity or qualitative designation such as retention time, range of impurity observed, and impurity classification (e.g., organic, inorganic, solvent). The impurity profile should be periodically compared to the regulatory submission or historical data to detect changes due to incoming materials, process changes, and so on. Other guidances covering filing issues have been issued such as: Guidance on specifications for chemical substances in APIs including decision trees. These are provided in ICH Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (12).

Several more recent documents discuss impurity requirements and demonstrate the evolution of regulatory requirements for impurities, many of which may not really be GMP related but driven by regulatory filing expectations. ICH Q3A (R2), Impurities in New Drug Substances (13) provides a classification and definitions of impurities; this classification is presented in Table II. This concept, in the context of the paper, is more appropriately called an adulterant. Also excluded are polymorphic forms and enantiomeric impurities; both these issues are addressed in ICH Q6A. FDA has issued a guidance on pharmaceutical solid polymorphism CMC information in ANDAs (14). ICH Q3A (R2) provides guidelines for the reporting threshold, identification threshold, and qualification threshold of impurities, all related to the maximum daily dose of the API; a decision tree is also provided. ICH Q3C (R3) Impurities: Guidelines for Residual Solvents (15) discusses requirements for organic volatile chemicals used in API manufacturing. The document provides a solvent classification based on risk assessment, methods to determine exposure limits, recommended limits, and associated information.

The next development in the evolution of impurity requirements was the FDA issuance of draft guidance Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (16). This document provides specific recommendations regarding the safety qualification of impurities with known or suspected genotoxic or carcinogenic potential. Compounds known to induce genetic mutations or related effects may, at very low levels, be of significant concern. The identification limits prescribed in ICH Q3A (R2) may thus not be sensitive enough for genotoxic or carcinogenic impurities.

**Categories of Impurities**

Impurities may be categorized into four groups: Identified, Unidentified, Potential, and Extraneous (see Table III). Identified and unidentified impurities are addressed and characterized based on guidance in ICH Q3A (R2). The requirement to address potential impurities (i.e., impurities that theoretically can arise during manufacture or storage, which may or may not actually appear in the new drug substance) is stated in ICH Q3A (R2) and in the FDA Compliance Program Guidance Manual for API Process Inspection (17). An extraneous impurity is defined in ICH Q3A (R2) as an impurity arising from any source extraneous to the manufacturing process. Per ICH Q3A (R2), extraneous impurities are more appropriately addressed as GMP issues. Such impurities can always potentially exist. However, they are generally either ignored or monitored until scientific evidence or GMP reviews would indicate a need to establish greater controls and procedures to manage their presence in the API.

While the warning letters issued from 2006-2008 have no surprises from a regulatory perspective, there are some signals in the China 2008 warning letter of
Impurities and the processes for detecting and monitoring them have generally been defined during the review and approval process used to approve API for use in drug products for the US. Establishing identification and limits for both known and unknown impurities are usually determined during the regulatory filing process and also by the USP requirements established for the API. Thereafter, manufacturing performance within established limits is based on GMP compliance, and performance against standards is monitored for shifts and trends.

There is an increased emphasis on extraneous impurity problems based on several well-publicized events in the recent past. The most recent of these was cited in the Changzhou, China 2008 warning letter involving contamination of API heparin sodium. The Changzhou warning letter was issued covering deviations associated with impurities that occurred from sources yet unknown and by compounds that were not detectable by then existing testing procedures. The United States Pharmacopeia (USP) has recently revised the heparin sodium and heparin calcium monographs (18). These revisions include new methodologies for identification, new potency assay, and new tests for impurities. Several other global occurrences of extraneous contamination have been reported in addition to the heparin incident in the China warning letter. USP has also recently revised the glycerin monograph in response to ethylene glycol contamination reported worldwide (19, 20, 21). Other incidents (not cited in the warning letters presented in this article) involving extraneous impurities include the 2006 Swiss Viracept contamination case caused by improper equipment cleaning (22), China methotrexate and cytarabine contamination with vincristine sulfate in 2007 (23), and the cholestyramine resin contamination with pesticide degradation and intermediates in 1988 (24). The cholestyramine resin incident was significant in furthering the importance of cleaning validation. These examples demonstrate that API manufacturers must be vigilant in upgrading their analytical methods when new technology emerges. Further, they must focus on high-risk GMP concerns with potential for cross contamination. Finally, there must be good control of the material supply chain including incoming raw materials, third-party manufacturers, and post manufacturing distribution.

**BASIC CGMP DEFICIENCIES**

The review presented in this paper of warning letters was performed to determine if there are any focus points that need to be examined as an indicator of a possible evolutionary or changing GMP process. Some of these inspections found repetitive conditions at the firms and may have been the primary reason for the issuance of the Warning Letter. However, when some rather simple concepts cannot be appropriately applied by a firm, there is an urgent need to get the attention of the company’s management, hence the warning letter and subsequent actions (see India 2008).

The inspections conducted that resulted in the issuance of a warning letter generally reflected the basic and fundamental concepts of Q7A. The primary items identified in the above warning letters included methods and documentation, facility and equipment, and quality unit responsibilities. Other lesser identified areas included personnel and procedures, product quality, and miscellaneous items. Failure to follow procedures and documentation problems are often cited in FDA review presentations as among the most frequent violations of

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**TABLE II: ICH Q3A (R2) classification of API impurities.**

<table>
<thead>
<tr>
<th>Type of Impurity</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic impurities — Process and drug related</td>
<td>Starting materials, By-products, Intermediates, Degradation products, Reagents, ligands, and catalysts</td>
</tr>
<tr>
<td>Inorganic impurities</td>
<td>Reagents, ligands, and catalysts, Inorganic salts, Other materials (e.g., filter aids, charcoal)</td>
</tr>
<tr>
<td>Residual solvents</td>
<td>Processing</td>
</tr>
<tr>
<td>Extraneous contaminants</td>
<td>Processing and environment</td>
</tr>
<tr>
<td>Enantiomeric impurities</td>
<td>Process</td>
</tr>
<tr>
<td>Polymorphic forms</td>
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</table>
GMP requirements. Warning letters often included comments on deficiencies in responses to FDA 483 observations, as well as instances of recurring observations. Compliance with procedures, proper documentation, validated processes and methods, qualified equipment, and other supporting activities are the bases for successful manufacturing.

Key elements of GMPs cited in the 2006-2008 API warning letters discussed previously included the following:

• Proper documentation practices and records should exist and be in writing. All records should be complete, recorded at the time of performing the activities, and accurate. This includes all GMP related records such as production, control, labeling, and warehouse/storage/distribution records.
• Analytical methods must be validated and properly documented.
• Even methods that don’t require validation such as official USP compendia procedures need to have full and proper verification and documentation of the appropriateness of the applied method for the product being manufactured and controlled.
• Processing equipment should be maintained in a good state of repair and cleaning procedures and records properly recorded.
• All calibration procedures need to be scientifically sound, using appropriate standards, in writing and properly documented.
• Prevention of contamination or cross contamination is a key element of GMP. This concept cannot be ignored.
• Stability programs need to be in compliance with the established written program. Deviations need to be properly documented, explained and justified if appropriate. Deviation from the established program is normally unacceptable.
• The quality control unit’s responsibilities must be in conformance with Q7A API GMP and properly implemented and documented.

**TABLE III: Categories of impurities.**

<table>
<thead>
<tr>
<th>Identified impurities</th>
<th>Unidentified impurities</th>
<th>Potential impurities</th>
<th>Extraneous impurities</th>
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</thead>
</table>

**CONCLUSIONS**

Review of FDA warning letters provides valuable insight as to new areas of focus or evolving expectations of GMP by investigators. Warning letters for API manufacturers during 2006-2008 highlight several key areas. Most observations addressed basic GMP principles such as documentation, batch records, compliance with procedures, training, and related areas. In many instances, warning letters were issued in part due to the inadequacy of responses to FDA 483 observations. Impurities were another area of concern. Typical API impurities such as identified and unidentified impurities are addressed during development and are part of the regulatory submission. New considerations and evolving requirements have been noted. These are addressed in ICH Q3A (R2) and ICH Q3C (R3). FDA has also issued a draft guidance on genotoxic and carcinogenic impurities in December 2008. These documents demonstrate a potential evolution in GMP requirements.

Another evolving concern is extraneous impurities that are not part of the manufacturing process. Recent examples of these include heparin contamination, ethylene glycol contamination of glycerin, Viracept contamination, and other examples. The issues became obvious only after medical problems were noted in patients in the field. Extensive work was performed to address the adverse medical observations. So in retrospect, citations were issued based upon the new information that was not available under normal production and control procedures commonly used during the
approved manufacturing processes. These newly identified problems have real potential to push for what we have defined as an evolutionary change in API GMP. Manufacturers should upgrade analytical methods in cases of obsolete technology to help detect potential contamination. Manufacturers should also have good control of supply chains including sources of incoming raw materials, third party manufacturers, and subsequent distribution channels to continually prevent extraneous impurities.

REFERENCES
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24. FDA, Guide to Inspections of Validation of Cleaning Processes, July 1993. GXP

ARTICLE ACRONYM LISTING
API Active Pharmaceutical Ingredient
FD&C Food, Drugs, and Cosmetics Act
GMP Good Manufacturing Practice
QbD Quality by Design
SOP Standard Operating Procedures
USP United States Pharmacopeia

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