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Introduction, Scope, and General Requirements of the BPE

1.1 Introduction

While the scope of the BPE Standard defines the physical and technical boundaries of what it covers, its introduction provides an overview of its intent. It also touches on the philosophical aspect of the Standard when content relevant to the needs of a user is not specifically addressed in the Standard. Meaning that, based on the relevant requirements and recommendations contained in the Standard, it is advisable to interpolate from those guidelines and requirements what would be appropriate for a particular situation not specifically covered in the Standard.

The BPE Standard, as explained in its introduction, applies to components in a processing system that come in contact with product, product intermediates, and raw material fluids. What is not mentioned, but is included by inference, is process fluids. And to be clear, what is also covered by the BPE Standard are utility services such as those that handle compendial waters and steam. Compendial waters as well as steam are those utilities that meet the requirements of the pharmacopoeias for utility fluid services. Fluid services include Water for Injection (WFI), purified water, and clean steam.

In the case of pharmaceutical manufacturing, a compendial is essentially a specification that complies with the US Pharmacopoeia (USP). There are three main pharmacopoeia organizations around the world: USP, European Pharmacopoeia (Ph. Eur.), and the Japanese Pharmacopoeia (JP). These organizations harmonize in creating drug formulary (specifications) as well as specifications for water used in the manufacture of drugs and drug products.

Bioprocessing Piping and Equipment Design: A Companion Guide for the ASME BPE Standard, First Edition. William M. (Bill) Huitt.

The BPE Standard is not a stand-alone standard, but instead works in association with the Boiler and Pressure Vessel Code (BPVC) Section VIII and the B31.3 Process Piping Code. From a pressure vessel standpoint, the primary requirements for any pressure vessel will default to Section VIII requirements. The high-purity (HP) BPE aspects and requirements of a pressure vessel will overlay those Section VIII requirements. That is to say, Section VIII provides the safety and integrity requirements of a pressure vessel, while BPE provides the HP cleanability requirements in addition to that.

The same holds true for BPE's association with the B31.3 Process Piping Code. B31.3 provides the safety and integrity requirements of a piping system while BPE provides the HP cleanability requirements in addition to that. The reader of the BPE Standard will find many references to Section VIII and B31.3 throughout the Standard. There are liaison members of the BPE Standard that are also members of the BPVC and B31.3. This indeed is essential in harmonizing these codes and standards as they change and evolve over the years. Liaison efforts between the various codes and standards help provide coordination and harmonization between such codes and standards. Section 7.4.3 goes into greater detail with regard to the ways in which BPE and B31.3 work together.

1.2 Scope of the ASME BPE Standard

The ASME BPE Standard (hereinafter referred to as "Standard," "BPE," or "BPE Standard" depending on context) is the pseudo accepted international standard for system design, component standardization, and equipment design for the bioprocessing and pharmaceutical industries as well as other industries that require clean-in-place (CIP) or steam (sanitize)-in-place protocols. Essentially this is any process or segment of a process in which living organisms are used to facilitate the manufacturer of a product. Whether the end product is related to pharmaceutical, food, biofuel, or any other end product whose manufacturing process at some point contains living organisms, it does not matter. The need to preserve the appropriate cleanliness of a process system and its ability to prevent cross-contamination, external contamination, and leachable contamination from wetted parts is essential.

While the Standard is specifically designated to apply only to new systems, it is acceptable to apply it to in-service or existing systems. During the period of time this book was being written, modification to the wording of the Standard was voted on and approved to make this fact abundantly clear in the Standard. This is discussed further in Chapter 4 of this book. Before applying the Standard to existing systems, it is recommended that the existing system's Fitness for Service (FFS) be assessed. Where applicable, this means wall thickness examinations, fatigue assessment, corrosion under insulation examination, and much more depending on the expanse of the system, its years in service, and its operating conditions while in service. All of this being of chief concern with regard to a system's integrity with respect to its intended continued service. Such analysis should be performed by personnel experienced in FFS analysis.

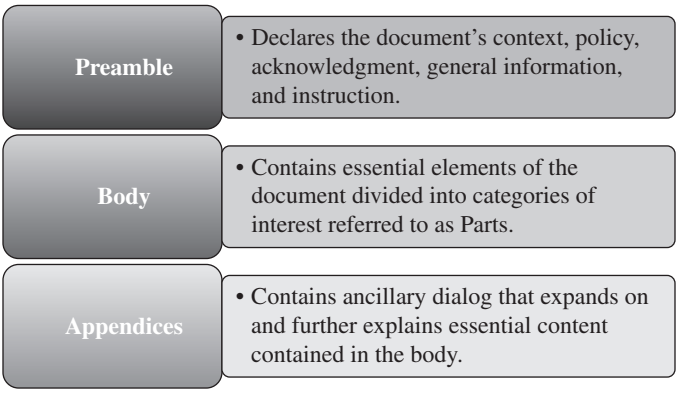

Figure 1.2.1 Main segments of the BPE standard

With regard to existing systems that have been abandoned in place, from a purity standpoint, it is suggested that while such systems may prove to be structurally sound, they may pose a contamination risk that is simply too problematic to undertake in attempting to remediate for hygienic use. If, on the other hand, after being thoroughly examined with consideration given to verifiable cleanability, an acceptable remediation plan established, and a proper protocol written, an existing system may be deemed acceptable for possible use in HP processing. Otherwise such systems should be dismantled, left as is, or simply not considered for the purpose of a HP process or utility service.

In referring to Figure 1.2.1, the BPE Standard consists of three main segments: Preamble, Body, and Appendices, which is typical of most ASME codes and standards. And, I might add, some of the terminology used here is not necessarily what ASME would use in describing the makeup and compilation of their codes and standards. It is instead my way of compartmentalizing and describing how these code and standard books are assembled. To continue, The Preamble portion of the book describes the document's context, points out ASME policy, acknowledges the membership, provides general information, gives a brief timeline history, and provides instruction. The Body of the Standard contains essential elements of the document divided into categories of interest referred to as Parts. This is where the requirements, recommendation, and guidance of the Standard reside. The Appendices is where ancillary dialog is added to expand on and further explain essential content contained in the body.

With regard to the Body of the Standard, the 2014 edition is currently divided into 10 sections referred to as Parts, as follows:

- **Part GR**—General Requirements: This section sets the tone and defines the scope and intent of the Standard. It defines terms that are specific to the bioprocessing industry and other terms that may have originated elsewhere and have been adopted by the BPE standard and given a definition that better relates to its intended use. It also provides a listing of documentation that is essential in

meeting Food and Drug Association (FDA) compliance requirements. These are documents that would serve other industries well in proving verifiable and traceable evidence of material and workmanship.

- **Part SD**—Systems Design: Part SD creates a forum for lessons learned in the bioprocessing industry and also establishes standardized methodologies for achieving cleanable process systems. It provides discussion on how to design cleanability and sterility into a system and covers specific design issues with regard to instrumentation, hose assemblies, filtration, and other equipment. In addition to hydrostatic testing, this section also touches on testing fundamentals for spray balls, drainability, cleanability, and sterility. This section is one place in which the BPE Standard steps beyond the main focus of the B31.3 format. For instance, B31.3 is written and developed around the cornerstone of safety and system integrity, and the BPE, while also integrating safety and integrity, is focused mainly on providing acceptable criteria for system design. Since its inception, the SD subcommittee (SC) has taken on the task of researching accepted industry design practices that are currently being used in the bioprocessing industry. This, in an effort to validate, and, where necessary, rectify those largely unsubstantiated design practices and criteria while developing new and beneficial design criteria for adoption into the BPE Standard.
- **Part DT**—Dimensions and Tolerances for Process Components: Part DT has created standard dimensions for HP fittings. Prior to the availability of the BPE Standard and Part DT, there were no industry standard dimensions on fittings and valves and no common set of manufacturing tolerances. This meant that components from one manufacturer to the next were not necessarily interchangeable. This was a situation that had long presented a nightmare for many designers, forcing a situation in which all fittings had to be purchased from the same manufacturer to ensure compatibility. By working with the fitting manufacturers, they were able to create a standardized set of fittings. In addition they added a much needed option for the sulfur content of ASTM A270 stainless steel to support the use of autogenous orbital welding. This will be discussed in depth in Chapter 4 of this book.
- **Part MJ**—Materials Joining: For both metallic and nonmetallic material Part MJ touches on all aspects of the welding and bonding of pressure vessels, tanks, tubing, and fittings. It provides guidance on acceptable requirements related to material selection, inspection, examination, and testing. It also discusses joining processes and procedures, weld joint design and preparation, weld acceptance criteria, procedure and performance qualification, and documentation requirements. Several tables list weld acceptance criteria, and detailed graphics illustrate acceptable and unacceptable welds.
- **Part SF**—Process Contact Surface Finishes: A crucial element in the ability to attain and maintain a clean system is in the quality of the finish on the product contact surface. Whether in the bioprocessing industry or other sectors in which at least a segment of the processing scheme involves bioprocessing (such as biofuel production), the cleanability of the product contact surface is crucial. In addition to Part SF providing the methods by which surface finishes are classified, it also spells out the acceptance criteria for compliance.

- **Part SG**—Sealing Components: This part covers equipment seals and provides a classification scheme that describes the required integrity of a seal under specific service conditions. Seals are segregated into two groups: static and dynamic. The static seal is the type that would be used in a hygienic clamp union. A dynamic seal is the type that would be used to seal two surfaces, one of which is a nonstatic surface such as a rotating ball in a ball valve.
- **Part PM**—Polymeric and Other Nonmetallic Materials: Added to the Standard in 2002, this section covers criteria related to polymers in the form of thermoplastics, thermosetting resins, and elastomers as well as other nonmetallic forms. It touches on design considerations, joining methods, interior product contact surfaces, and materials of construction.
- **Part CR**—Certification: This part was first included in the 2009 publication of the standard and gives users a way to ensure that the tubing and fittings they purchase are compliant with ASME BPE Standard requirements. This is achieved through a well-defined and implemented certification program for compliance with the BPE Standard by those manufactures, fabricators, and service providers that qualify. The certification process is a multifaceted program based on an in-depth quality management system (QMS) program that is defined in Part CR. Specifically, the program requires that the applicant for certification create a QMS manual, as defined in the BPE Standard, which is expected to mirror the quality program actually being used in their production process. Among many other requirements, the manual should reflect a company's organizational hierarchy, inspection protocols, materials handling procedures (from receiving through manufacturing and shipping), procedure for segregation of materials, inspection personnel qualifications, reject resolution, and documentation needs.
- **Part MM**—Metallic Materials: This section was first published in the 2009 issue of the BPE Standard. Its incorporation into the standard was driven by the growing importance of alternative materials of construction beyond Type 316L stainless steel. The main objective of this section is to help system designers and facility owners improve system quality and sustainability and to improve compatibility with fluids that are too aggressive for Type 316L stainless steel. Adding Part MM allows the standard to elaborate and expand its information on metallic materials in a centralized and comprehensive way. This section offers a definitive but ever-changing listing of acceptable materials in their various forms and provides further information on pitting resistance equivalent number (PREN) rankings, corrosion test references for alloys, discussion points on superaustenitics, duplex stainless steels, nickel alloys, ferrite content restrictions, and much more.
- **Part PI**—Process Instrumentation: First included in the 2012 publication of the BPE Standard, this much needed section of the Standard establishes standard requirements for instrumentation as it applies to bioprocessing and other HP process requirements. It touches on minimum requirements for such instrument items as transmitters, analyzers, controllers, recorders, transducers, final control elements, signal converting or conditioning devices, and computing devices. It also discusses electrical devices such as annunciators, switches, and pushbuttons.

As mentioned, the sum of the aforementioned parts make up what is referred to as the body of the BPE Standard. Following are what could be considered extensions of the Standard in the form of a mandatory appendices and a nonmandatory appendices.

- Mandatory Appendices: It is editorial policy to be concise, to the point, and without elaboration in the body of any standard or code when stating a requirement or recommendation. Such documents are written and published under the accreditation guidelines of American National Standards Institute (ANSI), which do not permit, under those rules, educational-type dialog within the body of an accredited standard or code. However, there are instances in which it is felt that further explanation and guidance on various compliance statements within a standard or code are needed. Unable to properly make such elaborations within the body of a standard or code such guidance is provided in the mandatory appendices. The mandatory appendices in the BPE Standard are therefore an extension of the body of the Standard and allows for elaboration, clarification of subject matter, and guidance on *required* elements contained in the Standard itself—content that would otherwise not be permitted. Content of the mandatory appendices shall be complied with the same as that found in the body of the Standard unless otherwise amended by specification.
- Nonmandatory Appendices: Much like the mandatory appendices, the nonmandatory appendices are an extension of the Standard itself. Wherein, guidance and extended information on various topics pertaining to the Standard can be provided. Information contained in the nonmandatory appendices are, as the name suggests, not mandatory. It can be treated as information for guidance only or it can be adopted as needed in requiring compliance for particular activities. In the event that it is adopted, it then becomes mandatory.

The Preamble of the Standard along with its Foreword, Statement of Policy, Committee Roster, Summary of Changes, the Body, and the Appendices constitute all of the elements necessary in an industry standard. Like all other codes and standards, the BPE will also continue to add, modify, and remove content as it keeps pace with industry and technologies in finding new and better ways to improve how we design and build safer and more productive pharmaceutical manufacturing facilities.

1.3 Intent of the BPE Standard

While the actual content of the Standard is clear and concise in stating the requirements necessary in creating a piping system conducive to FDA regulations and cleanability, there are nuances and interpretations that can allow the designer to expand on what is written. These nuances and interpretations are similar to performing interpolation between data points. For example, if you are given what the pressure rating value of a mechanical joint is at 300°F and its pressure rating value at 400°F, you can determine the pressure rating value for that same joint at

360°F through interpolation. Understanding and applying the logical intent of a standard such as the BPE are much the same way. This can be referred to simply as applying the "philosophical intent" of the Standard.

The same logic used in what is written in the Standard can be expanded into areas that may be of a proprietary nature to a company and not covered specifically in the Standard. Such needs can be addressed in a manner that follows the philosophical intent of the Standard. Such interpolations of the Standard will be touched on as we move through this book.

1.4 ASME B31.3 Chapter X

At a 2005 meeting of the ASME B31.3 Process Piping Code committee, a presentation was made to its section committee pointing out the need to adopt a chapter on Ultrahigh-purity (UHP) piping. UHP is a term used to define a level of cleanness more associated with the semiconductor industry than any other industry. The initial vanguard in this effort to develop a new chapter in the piping code consisted mainly of personnel from the semiconductor industry, thus the use of the term UHP in describing the chapter.

Members of the ASME BPE Standard, who are also members of the B31.3 committee, learned of the work being done on this new chapter in B31.3, referred to as Chapter X, and saw an opportunity to better integrate the BPE Standard with the piping code it most closely relates to. Two members of the fledgling B31.3 Chapter X UHP piping section were subsequently invited to the October 2007 BPE meeting held in Philadelphia. The visiting gentlemen were introduced and gave a presentation to the BPE Standards Committee with regard to the new B31.3 Chapter X.

At the time BPE members became involved in the development of Chapter X, it was titled UHP Piping and the chapter prefixes were "U." It was pointed out that if the new chapter were to include more than just content on the semiconductor industry, it would have to change its title since the term "UHP" pertained almost singularly to the semiconductor industry. It was then agreed to title it simply "Chapter X High Purity Piping."

After another 5 years of writing, rewriting, balloting, and more balloting, Chapter X was finally approved and then published in the 2012 issue of ASME B31.3. This effort accomplished a number of things but two in particular. First, it influenced and impacted the safety aspect of the BPE with regard to piping and equipment in industries which heretofore operated to a large extent under their guidance. Safety, based on integrity of design, is the hallmark of B31 codes. And to be integrated into that process is to inherit that philosophy and methodology.

Secondly, references made from the BPE Standard to B31.3 prior to the addition of Chapter X did not harmonize as they should. The addition of Chapter X provided improved continuity between BPE and B31.3 that did not previously exist. The content of Chapter X helped B31.3 interface better with both the BPE and the SEMI International Standards and in so doing melded the essentials of design for HP and UHP piping with that of the safety and integrity requirements of B31.3.

1.5 Terms and Definitions

Many, if not the majority of words and terminology, have variations in their meaning. Codes, standards, and legal documents have to generally be very explicit in what it is they mean when using certain terms. In declaring something to be a requirement in codes and standards, there has to be specific meaning in the term or terms that are used. This is to prevent the intended meaning from becoming lost or misconstrued due to possible nuances in the term's general use and definition. In other words there can be no variation in what is meant when making statements that direct the user of a code or standard to do something or in describing a requirement. The essence of each word takes on a heightened degree of import when safety, integrity, and even personal health are at stake, as is the case when writing content for industry codes and standards.

A "term of art" therefore describes a term that has been adopted or contrived with a very specific definition that has been applied to a term for a special or particular meaning in context with, or more appropriate for its intended application. The generally accepted definition for a term that already exists may need to be nuanced in order to more accurately define its specific purpose in a code or standard. Codes, standards, and legal documents frequently have to provide such specific definitions for some terminology in order to make a term's meaning explicitly accurate as to its intent within the context the term is used in these types of documents.

In cases in which a code or standard is being referenced in material specifications, a design basis, or in a procedural document, it is advisable to understand the definitions of the terminology defined within those codes or standards. Terms that are intended to apply in a particular manner, in the context of the code or standard, are specifically defined in that document to avoid having their intent misconstrued or misinterpreted.

As an example we will consider the term "hygienic," defined in the Merriam–Webster dictionary as follows:

Hygienic
a: of or relating to hygiene
b: having or showing good hygiene
c: of, relating to, or conducive to health or hygiene

Such definitions, as previously listed, while describing the general use of the term, do not convey the explicit description for which the term is used in the BPE Standard. The BPE Standard has therefore adopted the term (making it a "term of art") for use under a definition that better fits its specific use and application within the Standard; a definition that more directly and explicitly relates to its intended use in the Standard as follows:

Hygienic: of or pertaining to equipment and piping systems that by design, materials of construction, and operation provide for the maintenance of cleanliness so that products produced by these systems will not adversely affect human or animal health.

And there are, of course, terms particular to an industry or to a standard that are contrived, created, or simply find their way into the vernacular of an industry. Over time such terminology becomes adopted to define certain aspects related specifically to an industry or content within a standard. Some of these terms are adopted by an accredited standard and legitimized in the process. With regard to the BPE Standard and the bioprocessing industry that it serves, there are such terminology as:

Autogenous weld: A weld made by fusion of the base material without the addition of filler.

Closed head: For orbital GTAW, a welding head that encapsulates the entire circumference of the tube/pipe during welding and that contains the shielding gas.

Compression set: Permanent deformation of rubber after subscription in compression for a period of time, as typically determined by ASTM D395.

Dead leg: An area of entrapment in a vessel or piping run that could lead to contamination of the product.

Clean-in-place (CIP): Internally cleaning a piece of equipment without relocation or disassembly. The equipment is cleaned but not necessarily sterilized. The cleaning is normally done by acid, caustic, or a combination of both, with WFI rinse.

Open head: For orbital GTAW, a welding head that is open to the atmosphere external to the tube/pipe being welded and that does not enclose the shielding gas, which is still provided through the torch.

Passivation: Removal of exogenous iron or iron from the surface of stainless steels and higher alloys by means of a chemical dissolution, most typically by a treatment with an acid solution that will remove the surface contamination and enhance the formation of the passive layer.

Rouge: A general term used to describe a variety of discolorations in HP stainless steel biopharmaceutical systems. It is composed of metallic (primarily iron) oxides and/or hydroxides.

Under CFR Title 21 of the FDA, there also exists definitions for terminology used in context with FDA regulations, such as:

Active ingredient: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

Components: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

In-process material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

Such terms as those listed previously and their definitions can be found in the ASME BPE Standard or under CFR Title 21 of the FDA. And there are other "terms of art" in which a word or phrase in a published work, such as this book, has a meaning that may be more specific or slightly different from that which might otherwise be inferred by definition from another source—a meaning specifically defined in order to be made more explicit in its use. In such cases those terms or phrases are defined as to their intended meaning for the context in which they are used. The definitions that follow are for such terms used in this book and are defined here to more appropriately relate to their specific use herein, as follows:

Biopharmaceutical: Pharmaceutical products manufactured using bioprocessing.
Bioprocessing: Any chemical process in which living cells are utilized.
End user: A company or named person or persons designated as having overall ownership and/or responsibility for the manufacture of an end product or raw material.
Piping and tubing: These two terms are synonymous within the context of this discussion.
Piping system: All pipe/tube, fittings, inline components, equipment, instrumentation, insulation, and supports that make up a processing system.
Process solution (aka process): Any chemical or other additive solution that is combined with other chemicals or solutions to become an integral part of a finished product.
Process contact surface: Any surface (component, equipment, instrument, single-use component) that comes in direct contact with a process solution including the surfaces of ancillary systems handling fluids that come in contact with the process system on a secondary basis such as CIP.
Product solution (aka product): The final solution that makes up a finished product even though additional steps in the finishing process may still be required (e.g., encapsulation, crystallization, etc.).
Product contact surface: Any surface (component, equipment, instrument, single-use component) that comes in direct contact with a product solution.
Wetted (aka wetted surface): The surface of any part of a single component or equipment item that comes in contact with the product or process at any time during operation of a system.

Allow me to explain also the capitalization used in this book with regard to the terms "standard" and "code." Where either the term "standard" or "code" refers to a specific standard or code as in "BPE Standard" or "B31.3 Code" those terms will be capitalized. Or when making an implied reference to a specific standard or code, such as when Standard is in reference to BPE or when Code is in reference

to B31.3, the terms will be capitalized. When making a general statement about standards or codes, the terms will not be capitalized.

1.6 Quality Assurance

Ground rules first. The term "components," as used in CFR Title 21, refers to (chemical) ingredients used in the manufacture of an in-process material, drug product, food, or cosmetic product. It does not refer to fitting components such as tubing, tees, or elbows. So in referring to documentation requirements related to "components" such as those stated in CFR Title 21 Section 211.180 subparagraph (b) as follows:

> (b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date…

It does not pertain to tubing and fittings. The question then arises as to if the FDA does not state a requirement for documentation and traceability for process system material that comes in contact with process or product fluids, then why the need for all of the documentation requirements found in the BPE?

The reason for requiring documentation and traceability for such process or product contact material is a statement made under CFR Title 21 Part 211 Section 211.65 subsection (a), which reads:

> (a) Equipment shall be constructed so that surfaces that contact components (i.e., chemical ingredients or process fluid), in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

Within the hidden implication of the previous statement that reads, *…surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive…* lies the need to prove to the on-site FDA inspector the fact that, "*…surfaces that contact components, in-process materials, or drug products…"* are indeed not, *"…reactive, additive, or absorptive…"* Though such a latent requirement as the need for documented proof and traceability for components and equipment that come in contact with a process is not explicitly stated, but is instead implied, does not diminish the impact of the statement. In clarifying such regulatory compliance requirements, Standards Developers such as ASME, API, NFPA, and many others, peel back the layers of regulatory dialog, parse the rhetoric, and assess nuances in those regulations, such as the earlier statement, and then define those latent implications to the user in a manner that will make such underlying requirements much more apparent.

Within the FDA organization is the Office of Regulatory Affairs (ORA). This is the department that carries the responsibility of inspecting facilities that manufacture in-process material, drug product, food, or cosmetic product and whose job is to enforce regulatory requirements that such facilities are obliged to follow.

FDA inspectors, working through the ORA to inspect new and operating drug manufacturing facilities, are guided by three resources: the regulations set forth under CFR Title 21, its counterpart USC (US Code) Title 21 Chapter IX, and their FDA training guidelines. Training for FDA inspectors plays a big role in how they perceive, not only the rule of law under the USC but also to understand the nuances and implications of the unwritten variants within the many complex guidelines and laws the manufacturer is obliged to follow under CFR Title 21.

One of the difficulties lies in the fact that many regulations governing the manufacture of food, drugs, and cosmetics are, in many cases, intentionally vague. This is due in large measure to two basic facts:

- Much of the manufacturing in the drug, food, and cosmetic industries is proprietary and specialized. It would be impossible to write detailed requirements that would apply to all the varied manufacturing schemes without constraining or interfering with innovation and without inhibiting new concepts in design and manufacturing.
- The criteria that the inspector must base their field analysis on is relative by nature and is subject to a subset of nuances that would be impossible to capture in words, making broad statements in the CFR a necessity.

It helps to somewhat understand the perception of the FDA inspector in carrying out their fundamental responsibility of ensuring that the regulations relative to the product being manufactured are being met. Not their mind-set but rather their training portfolio. There are a set of "Inspection Guides" and "Inspection Technical Guides" used in the FDA inspectors' training that are available in Appendices B through J found in the back of this book. What is found in this book can also be found at www.fda.gov/iceci/inspections. At this site you will also find access to other guides used by FDA inspectors, such as the following:

- Field Management Directives: These are mainly for internal management.
- IOM: Investigations Operations Manual.
- Guide to International Inspections and Travel.
- Medical Device GMP Reference Information.
- QS Regulation/Design Controls.

Point being, that FDA regulations are written in a manner that is somewhat tangential to formal regulations in that the inspectors' guidelines allow, indeed it prescribes for them the means to make on-site judgment calls with respect to interpreting the meaning of a regulation based on their firsthand assessment. And this is where the BPE Standard comes to the aid of the designer, engineer, and end user. The BPE Standard compiles and assimilates information such as that which is contained in, not only the regulations themselves but also in such guides and training documents as those mentioned previously.

So when a regulatory statement is made to the effect that, as mentioned earlier, *…surfaces that contact components, in-process materials, or drug products shall*

not be reactive, additive, or absorptive… the Standard expands on such a statement by determining, from that, just what it is the FDA will require of the end user in showing proof that they are in compliance. That is why documentation and traceability are such a significant requirement in the BPE Standard. All material used in the construction of drug manufacturing that comes in contact with the process or product will require a paper trail that is not insignificant. Meaning, verifiable material documentation, from that of gaskets and seals to modular assemblies and from weld filler material to instrument probes, will be required and will need to be traceable to their manufactured source.

1.6.1 Documentation

Using Section 1.6 as a premise, this section will describe the type of documentation necessary in providing evidentiary proof that the material expected to be in contact with process and product fluids are acceptable, are in accordance with FDA dictates, and are fabricated, assembled, and installed in accordance with the ASME BPE standard.

1.6.1.1 Trust but Verify

Whether you are a raw material supplier, a component manufacturer, a fabricator, a service provider, or a distributer, you are a link in a supply chain. And as such, you, as well as the engineer or end user, should be continually checking upstream in that supply chain to ensure that consistently compliant material, components, and services are delivered to your doorstep. This may involve periodic audits of a provider's QMS manual or even an on-site audit. The QMS and other facets of quality assurance (QA) will be discussed in greater detail in Chapter 6.

1.6.1.2 Source Verification of Material, Product, and Services

Documentation is the foundation of HP piping systems. From a manufacturer's QMS to an installing contractor's turnover package and everything in between, proper documentation provides assurance, traceability, and accountability for material, components, and services procurement of anyone in the supply chain leading up to an installed process system. Such documentation provides the following:

- Assurance, as to procurement and delivery of proper construction material and that the work was done in accordance with specifications.
- Traceability, in that all material that comes in contact with the process or product is traceable back to its original Material Test Report (MTR) or Certificate of Compliance (C of C) for its original chemical composition.
- Accountability, in that all personnel responsible for the welding, assembly, installation, and testing of process or product contact systems are identified and on record.

It is not enough to verify and document that the welding of two sections of tubing was done properly and in compliance with a governing code or standard. The chemical properties and mechanical properties of the material from which each section of tubing was formed has to be traceable back to the mill from which it was originally melted.

A batch of melted material and chemical additives is referred to as a heat of material. Each batch, or heat of material, also referred to simply as a "heat," has its own characteristics, or fingerprint, if you will. These characteristics are based on the heat's chemical composition and its mechanical properties. Each heat of material is assigned a specific heat number and will carry that number with it throughout its recorded life cycle and product evolution.

As it is separated into various product forms, the heat number is subsequently marked on each of its separate forms of material as it moves from mill to market. The document that contains the material's chemical and mechanical properties, plus other information as identified in the bulleted list in the following, is referred to as a Material Test Report, Mill Test Report, Certification Report, Certified Material Test Report, or simply a Test Report.

Figure 1.6.1, is a simple diagram that represents the path taken from mill to market by tube and tube fitting products, such as the tubing itself and various fittings made from tube such as elbows, tees, laterals, etc. Welded tubing is manufactured from sheet material. The sheet material formed at the mill is rolled on to spools. These spools are then either slit into skelp (strips of metal) at the mill or sent to a tubing manufacturer in bulk coils to be slit as needed. The bulk coils of steel, prior to entering the production line, are, as mentioned, slit into skelp and then formed and welded longitudinally into tubing. Some of that tubing will be used by fitting manufacturers and formed into various fittings such as elbows, tees, and laterals.

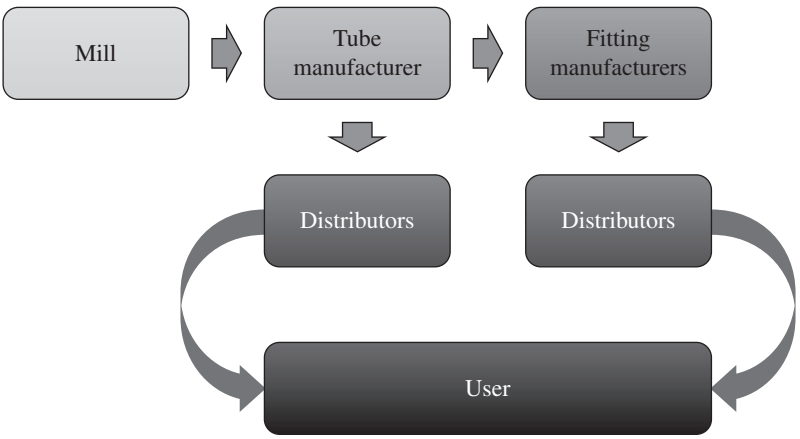

Figure 1.6.1 Mill to market of tube and fitting products

As the material moves along its path from mill to market to become an end product and to then be distributed to users of the product in constructing HP facilities, it requires one more thing—its MTR. The MTR has to be requested by the purchaser and will contain a requested laundry list of information applicable to the material. As an example, ASTM A450 states that,

> "When specified in the purchase order or contract, the producer or supplier shall furnish a Certified Test Report certifying that the material was manufactured, sampled, tested, and inspected in accordance with the Specification, including year date, the Supplementary Requirements, and any other requirements designated in the purchase order or contract, and that the results met the requirements of that Specification, the Supplementary Requirements, and the other requirements."

It then goes on to state that,

> "In addition, the Certified Test Report shall include the following information and test results, when applicable:
>
> - Heat number,
> - Heat analysis,
> - Product analysis, when specified,
> - Tensile properties,
> - Width of the gage length when, when longitudinal strip tension test specimens are used,
> - Flattening test acceptable,
> - Reverse flattening test acceptable,
> - Flaring test acceptable,
> - Flange test acceptable,
> - Hardness test values,
> - Hydrostatic test pressure, Non-destructive Electric Test method,
> - Impact test results, and other test results or information required to be reported by the product specification."

The MTR originates at the mill or foundry from which the material is produced. Referring to the mill or foundry as the producer, this is the source of the original heat or batch of material, and they, the producer, will assign an original heat number to each batch or heat of steel. That heat number is then marked on the various forms of the steel from its initial billets, bars, and sheets to its final product in the supply chain.

As the product is modified by downstream tubing and fitting, manufacturers' information contained on the original MTR may get transposed on to the various manufacturers' personalized MTR forms, forms that better suit the needs of each manufacturer. This does not give the product manufacture a license to modify the chemical properties or the original heat number. And depending on the type of forming that is done in the manufacture of a component, the mechanical properties may undergo a transition. A transition that may alter the mechanical properties of a material such as its yield and tensile strength.

Because of this possibility, it is not a requirement to include the mechanical properties in the MTR of fittings (Ref. BPE Para. MM-6.3). If included they must comply with the specifications of the raw material from which they are manufactured.

1.6.1.3 Turnover Package

As an installing contractor, who is very likely the fabrication contractor, begins completing the installation of piping systems, a turnover process begins. This is the phase of a project in which the mechanical contractor turns over all required documentation related to each system that the contractor is responsible for. Typically the documentation package, referred to as a turnover package, is handed over to the owner or the owner's representative by systems, which is an organized way of handling what could be, and typically is, thousands of documents. It is between the owner and contractor to agree on the most efficient and organized way in which the handover of documentation is done.

If the turnover procedure is set up for the installing contractor to hand over the turnover documentation at the time each system or package of systems is completed, then the turnover packages can serve as notification to the owner that a system is completed and ready for their review. Once the package is logged in, an assigned inspection group can then go about verifying that all of the required documentation has been included, based on a predetermined set of criteria. This in turn triggers a walk-down of the installed system to verify its accuracy with the documentation and to verify its completion.

Within each turnover package, there are certain documents that are to be accrued by the contractor in the performance of their work and then transferred to the owner in a manner dictated by the owner or agreed to between the owner and contractor. This list of documentation is considered to be a minimum requirement under the BPE Standard but can be expanded on. That list includes:

- For materials
  - MTR
  - C of C
  - Material Examination Log
- For welding
  - Welding Procedure Specification (WPS)
  - Procedure Qualification Record (PQR)
  - Welder Performance Qualification (WPQ)
  - Welding Operator Performance Qualification (WOPQ)
  - Examiner Qualifications approved by owner or owner's representative
  - Inspector Qualifications approved by owner or owner's representative
- For weld documentation
  - Weld map
  - Weld log

- Weld examination and inspection log
- Coupon log

- For testing and examination
  - Passivation report
  - Spray ball testing
  - Pressure testing (actually a "leak test")
  - Final slope check documentation
  - Calibration verification documentation
  - Purge gas certifications
  - Signature log
  - Number of welds—both manual and automatic
  - Number of welds inspected expressed as a percentage (%)
  - Heat numbers of components must be identified, documented, and fully traceable to the installed system

An additional item, not a BPE requirement for the turnover package but a document that can nonetheless be added to the previous list, is a simple but effective method used to identify and number test circuits used in leak testing the installed piping systems. This will be explained along with a scheme for the leak testing process in Appendix A. The aforementioned list of documentation will be discussed and explained in the appropriate chapters throughout this book.

1.7 An Essential Understanding of Codes and Standards

An understanding by those that write and develop codes and standards, an understanding that goes largely unacknowledged and unstated within codes and standards, is that codes and standards provide the **essential minimum requirements** necessary to achieve their intended goal. And that initiative is to provide guidance and establish requirements needed in order to achieve a safe working and operating environment within the scope and confines of that code or standard's responsibility. In other words the Standards Developer creates a line in the sand when it comes to writing and developing codes and standards for industry. A line that on one side provides prescriptive requirements and guidance to the user and on the other side refrains from becoming burdensome with excessive and overly conservative requirements. What the engineer should understand in working with codes and standards is that those minimum requirements should be treated as benchmark values and not as a crutch. Meaning that each circumstance should be considered on its own merit, and if good engineering judgment leads to more conservative values, then those values should be determined and applied.

Engineers should have awareness in the fact that ASME and other such Standards Developers walk a fine line in their efforts to create and establish guidance and requirements that create safety in the workplace while at the same

Case in Point

In an incident that occurred at a Texas refinery on February 16, 2007, a leak from a ruptured liquid propane pipeline in a propane deasphalting (PDA) unit caused an explosion that ripped off a nozzle on a PDA extractor column causing ignited propane to erupt from the now-opened nozzle on the column at a velocity sufficient to create a jet fire (Figure 1.7.1).

The blowtorch-like flame discharged toward a main pipe rack approximately 77 ft away. As the temperature of the nonfireproof structural steel of the pipe rack reached its plastic range and began to collapse in on itself, the piping in the rack, which contained additional flammable liquids, collapsed along with it (Figures 1.7.2 and 1.7.3).

Due to the loss of support and the effect of the heat, the pipes in the pipe rack, unable to support its own weight, began to sag. The allowable bending load eventually being exceeded from the force of its unsupported weight, causing the rack piping to rupture spilling its flammable contents into the already catastrophic fire. The contents of the ruptured piping, adding more fuel to the fire, caused the flames to erupt into giant fireballs and thick black smoke.

While the engineer was certainly in compliance with the governing code, with regard to fire proofing, a thorough risk analysis may have determined that the 50 ft avoidance perimeter stated in the standard might not have been sufficient for such an installation. Proprietary circumstances, therefore, make it the imperative responsibility of the engineer or the owner to make risk assessments based on specific design conditions; conditions that may require good engineering practice to push design beyond the minimum requirements of an industry code or standard when such analysis dictates.

Figure 1.7.1 From plant surveillance camera 90 s after ignition. Courtesy: U.S. Chemical Safety and Hazard Investigation Board

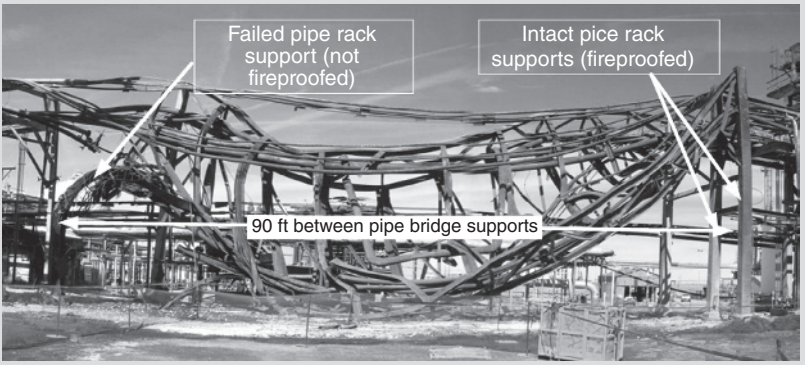

Figure 1.7.2 View of PDA unit pipe rack. Courtesy: U.S. Chemical Safety and Hazard Investigation Board

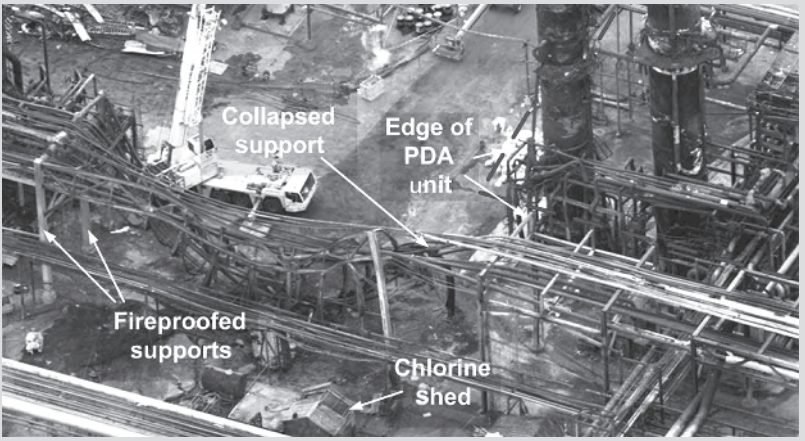

Figure 1.7.3 Aerial view of PDA unit with PDA extractor columns in the upper right. Courtesy: U.S. Chemical Safety and Hazard Investigation Board

time trying not to step over that line of infringement, getting into the area of overregulation, and undue influence. Knowing this should embolden the engineer and designer to look beyond these basic requirements and recommendations when necessary to determine whether particular design conditions fall within the conditional parameters set forth by the standard or whether conditions are such that more conservative values or a more conservative approach should be considered.

1.8 Source of BPE Content

Content of the BPE Standard is developed from three primary sources. That being:

- Government regulations
- Generally accepted principals and practices of the industry
- Research and testing done by BPE membership
  - R&T is prompted by the recognition of the membership that standardization or clarification is needed to support and/or inform the industry.

1.8.1 Government Regulations

Much of the requirements stipulated by the FDA for the bioprocessing industry and the pharmaceutical industry in general, along with industry itself, create a context within which the BPE Standard is developed and maintained. Government regulations (top-down directives) are assessed and analyzed by the various BPE SCs to determine what the designer, constructor, and facility owner will need to know and do in order to comply with these many regulations.

As an example, under Title 21 of the FDA, Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart D Section 211.65—Equipment Construction, it states:

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

In essence the statement in subparagraph (a) is telling the manufacturer of pharmaceutical products that the material of construction of the equipment and components that make up a process system, such as tubing, fittings, valves, seals, pressure vessels, etc.—those items that come in contact with the process or product—shall not alter it in any way that would be counter to its processing design nor can any lubricants or sealants, under paragraph (b), applied to processing equipment, come in contact with the process or product.

The various SCs within the BPE Standard take such government regulations and interpret them in a manner that, when added to the Standard, provides the necessary guidance to the designer and constructor on what needs to be done in order to meet those requirements.

The core of design within the BPE Standard resides mainly within Part SD. And this is not to diminish the content of the other parts of the Standard.

On the contrary, each of the ten parts that make up the Standard are integral with one another. Each providing essential information necessary in designing and constructing piping systems that meet the HP demands of FDA regulations in conjunction with the safety and integrity requirements of the ASME B31.3 Process Piping Code.

1.8.2 Generally Accepted Principals and Practices of the Industry

Each segment of industry, over time, develops an ever-evolving set of metrics that include a range of materials that seem to be more compatible with respect to service conditions within that industry; design methods developed that have, over time, proven to provide the best results; quantitative values that seem to achieve the needed result; and so on. These metrics are principles and practices developed by designers, engineers, constructors, and product manufactures that, over time, become integral and essential in achieving safety and efficiency in the workplace while meeting regulatory and design requirements. These can be referred to as "generally accepted principals and practices of the industry." The bioprocessing industry is no different.

Much of what constitutes safety and design practices in the BPE Standard, or in the B31.3 Piping Code, comes from this huge resource—that of the workplace. From the engineer working on a new concept to the designer taking a new approach at making something work or from a fabricator working a design into a physical reality to a plant operator making it function properly, each of these workplace functions develop their own set of methods, equations, and principals in carrying out their job responsibility. From these efforts, principals and practices evolve into quasi-industry standardization. In the absence of any standardization, these are the fundamentals that the workplace relies on.

The problem with such industry-derived principals and practices is the fact that in most cases there is no record of what their basis for acceptance is or how such practices were arrived at. When such principles and practices are adopted and accepted into a standard or code, they are then assessed, evaluated, and clarified as to their validity and application and whether or not they should be adopted as a recommendation or requirement in the code or standard.

1.8.3 Research and Testing Done by the BPE Membership

In consideration for adopting and refining various generally accepted principals and practices of the industry, a code or standard will vet the premise of the value or action by testing its premise under a controlled and documented procedure. Much of this testing and research is either done wholly by the membership or is coordinated by the membership in using third-party testing contractors.

When referring to "membership," I am making reference to an SC Task Group (TG) with, on average, five members whose assignment is to resolve issues that require at-length discussions or research and testing to accomplish the task.

When the issue has been resolved in TG, a proposal is written and submitted to the SC for review and comment and/or balloting for approval to be entered into the Standard.

Not all proposals are based on generally accepted principals and practices of the industry. Some are simply a case of the BPE membership understanding the need for standardization and clarification of various subject matter such as those listed in the following, which are currently being worked on:

- Maximum acceptable dead leg
- Standardized clamp joint pressure ratings
- Hold-up volume
- Lyophilization system
- Chromatography
- Filtration

Topics such as those listed previously, and many more I might add, are discussed as to the merits of including them in the BPE Standard. Like the other ASME codes and standards, the BPE goes to great lengths to avoid including superfluous information in the Standard. If a topic is covered elsewhere by another Standards Developer in a sufficient manner, there is no need to expound on that same topic in the BPE Standard. If such a topic needs to be touched on in the BPE Standard for any reason whatsoever, it simply references the document that already addresses that topic. This prevents conflicts that might otherwise occur over time when a topic contained in one document is somewhat duplicated or paraphrased in another.

During the time this book was being written, research, analysis, and testing had been recently completed for determining maximum dead leg requirements and for establishing hygienic clamp joint pressure ratings. Both are topics of considerable interest to the bioprocessing industry. Up until this point in time, maximum dead leg values were theoretical, and standardized pressure ratings for the hygienic clamp joint assembly were proprietary to each manufacture and inconsistent throughout the industry. Results of the testing and research for both of these topics are expected to appear in an upcoming issue of the BPE Standard.

1.9 ASME B31.3 Process Piping Code Chapter X

Two members of the B31.3 TG, on what would eventually become Chapter X of that Code, were invited to attend the 2007 meeting of the BPE in Philadelphia. They graciously accepted, and at that meeting they gave a presentation to the main committee as to what this TG was working on. As a side note, there is a great deal of harmonization between codes and standards committees, which is due in large part to the fact that so many members are on multiple committees within organizations such ASME (BPVC, B31 Committees, B16 Committees, etc.) as well as interorganizational committees (ASME, API, CGA, NFPA, etc.) in much the same manner.

This creates an integrated network of communication between code and standard committees and their affiliate organizations in arresting and resolving any conflicts that might otherwise exist in the pages of these codes and standards.

Work on this new chapter of the B31.3 Process Piping Code was initially proposed to the B31.3 committee in 2004. Once approved, its initial writing was influenced to a large extent by a TG composed mostly of individuals representing the semiconductor industry. Consequently the terminology, design and testing methodology, and quantitative values were based mainly on that of the semiconductor industry. The initial draft of Chapter X was therefore based largely on the requirements and guidelines of the semiconductor industry rather than HP piping in general. It was not written broad enough to encompass other industries that also required HP piping systems, such as the pharmaceutical, bioprocessing, food and dairy, and biofuel industries. The requirements of the semiconductor industry are far more stringent but for altogether different reasons than those of the bioprocessing industry. To make this proposed Chapter X work, it had to have a broader scope. Focus of the future Chapter X had to therefore change from an UHP philosophy, which relates mainly to the semiconductor industry, to that of a simple HP philosophy in an effort to broaden its scope of use.

The reason that B31.3 Chapter X High Purity had to exist at all is due to the fact that B31.3 is a construction and safety code for pressure piping, whereas the BPE Standard is chiefly about design and cleanability. The safety component within the BPE Standard defaults, by reference, to B31.3. The problem, prior to the 2010 publication of B31.3, was that no content existed within B31.3 acknowledging the BPE Standard, or the mechanisms used in HP piping, such as orbital welding, weld coupons, hygienic clamp joints, and other such BPE-related topics. The advent of Chapter X thereafter would be closing the loop on HP piping.

1.9.1 B31.3 Chapter X as Supplement to the Base Code

In B31.3 the base code is considered to be the content found in Chapters I through VI. These chapters are essentially written for metallic piping intended for fluid services that can be categorized under B31.3 as normal and Category D fluid services. These are the basic essential elements with regard to designing, constructing, and installing steel piping within the scope of what is considered normal and Category D fluid services. Any requirements beyond those essentials, such as requirements for nonmetallic piping, high-pressure piping, toxic or hazardous fluids, etc. are considered supplemental to those base requirements.

The supplemental requirements for nonmetallic piping and piping lined with nonmetallic materials can be found in Chapter VII. Nonmetals were initially introduced to the Code in its 1976 publication but were not given their own chapter until the 1980 publication. The paragraphs in Chapter VII are numbered with respect to the paragraphs in the base code with the added prefix A.

Supplemental requirements associated with handling toxic fluids, defined by ASME B31.3 as Category M fluid services, can be found in Chapter VIII.

This chapter was first added to the Code in its 1976 publication. The chapter establishes more stringent requirements for toxic fluid services and was also developed to supplement the base code. The paragraphs in Chapter VIII are numbered with respect to the paragraphs in the base code with the added prefix M.

Chapter IX, added in the 1984 publication, provides supplemental requirements for operations involving high-pressure fluids. The paragraphs in Chapter IX are numbered with respect to the paragraphs in the base code with the added prefix K.

The most recent addition to those supplemental chapters is Chapter X High Purity Piping. This new chapter was first included in the 2010 issue of the ASME B31.3 Code. The 2010 issue was actually published in March 2011. As in Chapters VII, VIII, and IX, Chapter X is supplemental to the base code, so that the respective base code paragraphs included in Chapter X carry the added prefix U to identify them with the HP requirements in Chapter X.

1.9.2 Harmonization of the BPE Standard and B31.3 Chapter X

ASME B31.3 Chapter X was born out of the harmonization efforts that interconnect the various Standards Developer organizations as well as the committees within those organizations. Members of the BPE Standard worked with members of the B31.3 Chapter X subgroup to help in drafting Chapter X until its approval and publication. During this process members of BPE also became members of B31.3 and Chapter X. One such member, Dr. Barbara K. Henon, took on the responsibility of serving as the first liaison between the two committees in providing a liaison report at each of the code and standard meetings to keep both the B31.3 Code and BPE Standard committees updated as to the changes that were taking place in each of those documents. I have since taken over that roll as of 2014 and continue to do so at this writing.

The liaison approach has kept both the Code and the Standard well in tune and abreast of one another with respect to HP piping system requirements. And over the foreseeable decades, well into the future, this same intercommunication is expected to be maintained in much the same manner as it is today.