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STAINLESS STEEL TUBING IN THE BIOTECHNOLOGY INDUSTRY

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This article describes in general terms, stainless steel types and their chemistry, tubing/piping fabrication standards, and fabrication procedures. It also addresses compliance with biotechnology and pharmaceutical standards, codes, and guides, as well as surface characterization, electropolishing, joining techniques, passivation, measurement and inspection for Cr/Fe ratios, corrosion types, and guidelines for hygienic systems.

— INTRODUCTION—

Chemical services of any kind may require special alloys for corrosion resistance, freedom from metal ion contamination, or both. Bioprocessing applications can have even more stringent requirements, due to the high degree of cleanliness required to convey sterile and non-sterile products or solutions. Tubing and/or piping systems, must, therefore meet these requirements in their fabrication, particularly when it applies to their product or solution contact surfaces.

Stainless steels are uniquely qualified not only because of their long service life, availability and fabricability, but also because they are non-corroding, non-contaminant, they can be polished to very smooth finishes, they are strong and rigid, they can withstand heat and chemical sterilization treatments, and they are easily welded.

— STAINLESS STEEL TYPES —

There are more than 70 standard types of stainless steel and many special alloys. These steels are produced in the wrought form (AISI - American Iron and Steel Institute - types) and as cast alloys (ACI - Alloy Casting Institute - types). Generally, all are iron based, with 12% to 30% chromium, 0% to 22% nickel, and minor amounts of carbon, columbium, copper, molybdenum, selenium, tantalum, and titanium. Following are descriptions of the most widely used stainless steels in the chemical processing industry (CPI):

Wrought stainless steels:

Martensitic: characteristically magnetic and hardenable by heat treatment are oxidation resistant. Type 410 being the most notable example. These alloys contain 12% to 20% chromium with controlled amount of carbon and other additives. Their corrosion resistance is inferior to that of austenitic stainless steels, and are generally used in mildly corrosive environments.

Ferritic: characteristically magnetic (because of the ferrite structure) but not hardenable by heat treatment. Contain 15% to as much as 30% Cr, with low carbon content (0.1%). The higher chromium content rates its corrosion resistance as good. Type 430 widely used in nitric acid plants is a typical example.

Austenitic: widely used in bioprocessing, are characteristically non-magnetic, not hardenable by heat treatment, and are the most corrosion resistance of the three groups. The many types of austenitic steels include the highly alloyed, the lower alloys in which Mn has been substituted by Ni (the 200 series), and the **18-8** group which includes types **304** and **316** and all their variations. Types **304L** and, **316L** are the workhorse materials of the bioprocessing industry, they have their carbon content lowered from about 0.08% to a maximum of 0.030% which minimizes the chromium carbide precipitation. These steels do not rust, are easily weldable and machinable, and are not reactive, additive, or absorptive to any extent where strength, quality or purity of the feed is compromised.

Cast Stainless Alloys:

Widely used in pumps, valves, and fittings. All corrosion resistant alloys have the letter C plus a second letter (A to N) denoting increasing nickel content. Numerals indicate maximum carbon. Typical members of this group are CF-8, similar to 304 stainless; CF-8M, similar to 316; CF3M, similar to 316L and CD4M Cu, which has improved resistance to nitric, sulfuric, and phosphoric acids.

High Performance Alloys:

Because the weaknesses sometimes encountered in the ferritic and 18-8 austenitic grades 304, 316 and variations thereof, new and better "super" stainless steels have been developed. These are **superferritic grades, duplex grades,** and **superaustenitic grades.** Of these three, the high-performance austenitic grades have all the weldability and fabricability of conventional 18-8 varieties, coupled with nitrogen induced strength comparable to the duplex grades and a very high resistance to chloride pitting and stress corrosion cracking. The most notable low carbon, high purity superaustenitic stainless steel (nickel-based alloy technology) is the 6 Mo (6% Molybdenum) known by its trade name **AL-6XN** or "6 Moly" stainless steel. Its basic chemical composition being 20.0-22.0 Cr, 23.5-25.5 Ni, 6.0-7.0 Mo, 0.18-0.25 N, 0.03 C max, and Fe balance, it is the material of choice for many modern high performance piping systems, and is available in standard pipe sizes and all commercial sizes of tubing.

Nickel-Based Alloys:

The most widely recognized are:
200 series, **Inco** (International Nickel Co.) series, such as commercially pure nickels Nickel 200 and 201, which are widely used in the chemical process industries.
300 series are precipitation and dispersion strengthened low-alloyed grades.
400 series are nickel-copper alloys (non-ferrous alloys), well known as **Monel** alloys.
500 series are the precipitation-hardened 400 alloys, such as **Monel** K500.
600 series also known as **Inconel** alloys are nickel-chromium alloys, such as Alloy 625
700 series also known as **Inconel** alloys are precipitation-hardened nickel-chromium alloys.
800 series are nickel-iron-chromium alloys also known as **Incoloy** alloys.
900 series are precipitation-hardened nickel-iron-chromium alloys.
1000 series are also known as **Hastelloy B -** 61% Ni, 28% Mo, 5.5% Fe, 1% Cr, available as wrought and cast, resistant to all concentrations of hydrochloric acid at all temperatures, and **Hastelloy C -** 54% Ni, 16% Mo, 5.5 Fe, 15.5 Cr, resistant to all concentrations of hydrochloric acid at room temperature, wet and dry chlorine, hypochlorite, and chloride solutions.

As noted in the previous descriptions, corrosion resistance is the paramount concern when it applies to the proper selection of materials applying to the chemical processing industry at large. The current selection process is an almost continuous progression of small steps, each step containing one or more alloys of increasing corrosion resistance that can be summarized as:

1. 304 and 316 stainless steels and their L grades
2. Austenitic stainless steels with higher Mo content
3. Duplex stainless steels group
4. Superaustenitics in particular "6Mo"
5. Ni, Cr, Mo family commonly called the "Alloy C family"
6. Cobalt based alloys with high corrosion and wear-resistance
7. Titanium alloys, referred as chemically pure (CP)

— CHEMISTRY--

Table I -- Chemistry Comparison

	304	304L	316	316L
Cr (%)	18.0 - 20.0	18.0 - 20.0	16.0 - 18.0	16.0 - 18.0
Ni (%)	8.0 - 11.0	8.0 - 13.0	10.0 - 14.0*	10.0 - 15.0
Cr (%)	0.08 max	0.035 max	0.08 max	0.035 max
Fe (%)	Balance	Balance	Balance	Balance
Mo (%)		2.0 - 3.0		2.0 - 3.0
Mn (%)	2.0 max	2.0 max	2.0 max	2.0 max
Si (%)	0.75 max	0.75 max	0.75 max**	0.75 max**
P %)	0.040 max	0.040 max	0.040 max	0.040 max
S (%)	0.030 max	0.030 max	0.030 max	0.005 - 0.017***

* 11.0 - 14.0 (A269) ** 0.030 (A269)

*** Sulfur has greatest effect on weld quality. Controlling sulfur facilitates orbital field welds by minimizing stabilization problems.

— TUBING/PIPING FABRICATION STANDARDS —

Austenitic stainless steel tubing and/or piping used in bioprocessing are produced following various specific industry standards:

ASTM A249/ASME SA249 *Standard Specification for Welded Austenitic Stainless Steel Boiler, Superheater, Heat-Exchanger and Condenser Tubes* **-** Scope covers pressure tubes made from austenitic stainless steels. (Types 304, 304L, 316, 316L, 317. 321, and other austenitic grades)

ASTM A269 *Standard Specification for Seamless and Welded Austenitic Stainless Steel Tubing for General Service* **-** Scope covers grades of nominal wall thickness, stainless steel tubing for general corrosion resisting and low or high temperature service. (Types 304, 304L, 316, 316L, 321, and other austenitic grades). Tubing sizes and thicknesses usually furnished to this specification are 1/4" inside diameter and larger and 0.020 in nominal wall thickness and heavier.

ASTM A270 *Standard Specification for Seamless and Welded Austenitic Stainless Steel*

Sanitary Tubing - This specification covers grades of seamless and welded austenitic stainless steel sanitary tubing intended for use in the dairy and food industry and having special surface finishes. Tolerances are much tighter than those specified in ASTM A269 and ASTM A312, allowing a closer alignment of tube to tube to fittings, which is necessary for compatibility with automatic orbital welding. Pharmaceutical quality may be requested, as a supplementary requirement. (Types 304, 304L, 316, 316L). This specification covers tubes in sizes up to and including 6".

ASTM A312/ASME SA312 *Standard Specification for Seamless and Welded Austenitic Stainless Steel Pipe* - Scope covers stainless steel pipe intended for high temperature and general corrosive service. (Types 304, 304L, 316, 316L, 317, 321, and other austenitic grades). In contrast to sanitary tubing, industrial piping and components are not compatible for sterile service due to their basic design and manufacturing techniques. However, due to the size limitations of sanitary tubing, industrial piping NPS (nominal pipe size) must be used in large-scale biotechnology or pharmaceutical facilities. When industrial piping and components are selected, high quality standards must be met, particularly where their internal finishes and fit-up is concerned, to assure that piping systems have a minimum of places for product entrapment, and that the systems are sanitizable and sterilizable.

ASTM A358/ASME SA358 *Standard Specification for Electric Fusion-Welded Austenitic Chromium-Nickel Alloy Steel Pipe for High Temperature Service* - Scope covers pipe used for corrosion and high temperature service, normally not less than 8" nominal diameter. (Types 304, 304L, 316, 316L, 317, 321, and other austenitic grades).

ASTM A409/ASME SA409 *Standard Specification for Welded Large Outside Diameter Light-Wall Austenitic Chromium-Nickel Alloy Steel Pipe for Corrosive or High Temperature Service* - Scope covers pipe with nominal diameter 14-30" in schedules 5S and 10S. (Types 304, 304L, 316, 316L, 317, 321, and other austenitic grades).

— TUBING FABRICATION PROCEDURES —

There are two categories of tubular products — welded and seamless — and each has its advantages, disadvantages, and share of advocates.

Welded Tubing

Starts at the melting operation where special requirements on the alloy are placed to facilitate welding. The strip from which the tube is made may be supplied as either a hot or cold rolled coil. Cold rolled strip has the advantage of extremely close tolerances, smooth surface finish (ASTM A480/A480M-00 "Standard Specification for General Requirements for Flat-Rolled Stainless and Heat Resisting Steel Plate, Sheet, and Strip"), and excellent mechanical properties. Coils are slit into precise widths and then, put through a sequence of procedures, which will yield a close tolerance tube. These procedures are:
Forming, this includes the use of an entry guide, breakdown rolls, fin rolls, closure rolls.
Welding, this includes the use of rolls to close the seam, rolls to squeeze during the weld, and rolls to restrain the solidifying weld to prevent tearing.
Weld bead conditioning, which may be one of two types, *weld rolldown*, usually for thicker wall tubes, and *weld forging* for thinner wall tubes.
Sizing, which reduces the oversized tube to the proper diameter, roundness, and straightness.
Cutoff, which uses two types of cutting to establish the final length*: abrasive cutting*, which is the most popular since it does not require a die change with each size of tubing,

and *shear cutting* which generally requires a die to contain the tube to prevent deformation during the operation.

Seamless Tubing

Made by piercing, extrusion, and gun drilling of a metal bar. *Piercing* is a controlled tearing of a hole in a hot metal bar then ironing the sides to produce a smooth walled tube. Piercing is not a viable method for alloy tubing above 12% Cr. *Extrusion* is simply changing a billet or bar of metal into a tube by pushing it through a die over a mandrel; since extrusion is not generally limited by alloy content, it is very widely used to produce high alloy tube hollows. Prior to extrusion billets are soaked at a temperature above 1100°C (2000°F), glass is added to the ID and the billet rolled in a glass blanket and shoved into the extrusion container. The ram with an attached mandrel is pushed into the billet and the extrusion begins, then, the tube hollow is quenched in water to break the glass off the surface. Extruded tubes have several problems, namely high eccentricity and surface imperfections on both the ID and OD.

Gun drilling produces the best quality tube hollow, both dimensionally and freedom from surface flaws. The gun drilling process starts with a rotating round bar or billet that is fed over a stationary straight flute drill, chips are flushed out of the cavity, and by using intermediate inspection for concentricity it is possible to maintain the straightness of the hole. Although expensive, the quality of the tube hollow cannot be rivaled.

Secondary Fabrication

Occasionally it is necessary to cold reduce the tube hollow for dimensional or metallurgical reasons. Two methods are used:

Cold Drawing **-** Cold drawing is a tensile operation in which a tube is pulled through a die to reduce its diameter or to change its shape. There are three types of drawing: *sinking* (tube is pulled through a die without a mandrel), *mandrel* or *bar drawing* (uses a solid bar as a mandrel), and *plug drawing* (tube is pulled over a plug inserted into the die) the most accurate of the three.

Cold Pilgering **-** It is a compressive method for simultaneously reducing the OD, ID, and the wall thickness of tubing. It uses two opposing dies into whose faces are cut a tapered groove, half in each die. The dies rotate either 180° (more ductile alloys) or 360° (less ductile alloys) depending on the type of machine. Because it uses compression to shape the tube, very high reductions are possible, up to 90%, although the normal reductions are in the range of 65%.

— STANDARDS, CODES, AND GUIDES CRITERIA —

As mentioned in the introduction, tubing and/or piping fabrication must meet a high degree of cleanliness to convey sterile and non-sterile products or solutions, particularly when it applies to their product or solution contact surfaces. Following are the definitions of these surfaces, and an overview of some of the most important Standards, Codes, and Guides used in bioprocessing. Contact surfaces are *"all surfaces exposed to the product or from which liquids may drain, drop, or be drawn into the product"*, and solution contact surfaces are *"the interior surfaces of the circuit used exclusively for supply and recirculation of cleaning and/or sanitizing solutions"*.

Standards

ASME Bioprocessing Equipment (BPE-1997/BPEa-2000)

American National Standard that covers, either directly or by reference, requirements for materials, design, fabrication, examination, inspection, testing, certification (for pressure systems), and pressure relief (for pressure systems) of vessels and piping for bioprocessing systems, including sterility and cleanability (Part **SD**), dimensions and tolerances (Part **DT**), surface finish requirements (Part **SF**), material joining (Part **MJ**),and seals (Part **SG**) for the bioprocessing systems in which the pressure vessels and associated piping are involved. This Bioprocessing Equipment Standard does not address all aspects of these activities, and those aspects that are not specifically addressed should not be considered prohibited.

Requirements of this Standard apply to:

1. All parts that contact the product, raw materials, and/or product intermediates during manufacturing, process development, or scale-up.
2. All equipment or systems that are critical part of product manufacture, such as Water For Injection (WFI), clean steam, ultrafiltration, intermediate product storage. and centrifuges.

3-A Sanitary Standards

3-A Sanitary Standards for Polished Metal Tubing for Dairy Products, Number 33-00
Published by the International Association for Food Protection (IAFP) formerly known as the International Association of Milk, Food and Environmental Sanitarians (IAMFES), these standards cover the sanitary aspects of polished metal tubing used to conduct dairy products in processing lines or systems that also may include sanitary fittings. These standards do not apply to tubing used in pneumatic conveying systems for dry milk and dry milk products. For tubing, these standards refer to the use of AISI 300 series stainless steel, and compliance with ASTM A270.

3-A Accepted Practices for Permanently Installed Product and Solution Pipelines and Cleaning Systems Used in Milk and Milk Product Processing Plants, Number 605-04:
These standards apply to cleaning of rigid cleaning solution lines and for the mechanical cleaning (CIP) unit which circulates the pre-rinse, rinse, cleaning solutions and post-rinse liquids used for cleaning and sanitizing the product pipelines and process equipment.

ASME B31.3 Process Piping

American National Standard that covers piping typically found in petroleum refineries, chemical, pharmaceutical, textile, paper, semiconductor, and cryogenic plants, and related processing plants and terminals. Certain piping within a facility may be subject to other codes and standards, including but not limited to: (a) **NFPA Fire Protection Standards:** fire protection systems using water, carbon dioxide, halon, foam, dry chemical, and wet chemicals, (b**) NFPA 99 Health Care Facilities:** medical and laboratory gas systems, (c) **Building and Plumbing Codes,** as applicable, for potable hot and cold water, and for sewer and drain systems.
It must be noted that B31.3 does not address hygienic tubing and/or piping: it applies mostly to inspection, examination, and testing of systems.

Codes

cGMPs - Code of Federal Regulations (CFR), Title 21 - Foods and Drugs

Chapter I - Food and Drug Administration (FDA), Department of Health and Human Services

Subchapter C - Drugs - General (Part 200)

Part 210 *Current good manufacturing practice for finished pharmaceuticals* (human and animal)

Part 211 *Current good manufacturing practice for finished pharmaceuticals* (human and animal)

Part 225 _Current good manufacturing practice for medicated feeds_ (animal)
Part 226 _Current good manufacturing practice for type A medicated articles_ (animal)

Subchapter F - Biological Products (Part 600)

Part 600 _Biological products: General_ (human and animal)
Part 610 _General biological products standards_ (human and animal)
Part 680 _Additional standards for miscellaneous products_ (human and animal)

NOTE: These parts are the substantive current good manufacturing practices as contained in Appendix 4 of the Pharmaceutical GMP Annex. U. S. Food and Drug Administration.

Guides

Baseline® Pharmaceutical Engineering Guides (ISPE)

A series of industry publications developed in partnership with the US Food and Drug Administration (FDA). Each volume in the series is a collaborative effort of industry leaders representing a broad cross-section of manufacturers and other industry experts. The Guides document current industry practice for facilities and systems used for production of pharmaceutical products and medical devices. They are intended to:

- Establish a baseline approach to new and renovated facility design, construction, commissioning, and qualification that is based upon clear understanding of the type of product and its manufacturing process.
- Prioritize facility design features based upon the impact on product and process.
- Avoid unnecessary spending on facility features that do not contribute to consistent production of quality products.

The Guides include five product manufacturing operation based guides (vertical guides),| and three support system/function based guides (horizontal guides):

1. Volume I - Bulk Pharmaceutical Chemical (1996)
2. Volume II - Oral Solid Dosage Forms (1998)
3. Volume III - Sterile Manufacturing Facilities (1999)
4. Volume VI - Biotech (in progress)
5. Volume IV - Water and Steam Systems (2000)
6. Volume V - Commissioning and Qualification Guide (2000)
7. Volume VII - Packaging and Warehousing

— SURFACE CHARACTERIZATION —

"Surface finishes are all interior surface finishes accessible and inaccessible, that directly or indirectly come in contact with the designated product in bioprocessing equipment and distribution system components". Reference should be made to ASME BPE Standard, Part **SF**, "Stainless Steel and Higher Alloy Interior Surface Finishes".
Part SF comprises: Scope (SF-1), Objective (SF-2), Applications (SF-3), Material (SF-4), Typical ggg Stainless Steel Interior Surface Anomaly Characteristics (SF-5), Classification of Interior Surface Finishes on Weldments for Process Equipment and Components (SF-6), Inspection and Techniques Employed in the Classification of Interior Surface Finishes (SF-7), and Description of Various Surfaces Available on Stainless Steel and Higher Alloys (SF-8)

Surface finishes have been quantified utilizing different names and measurement units, such as Grit Numbers, USA Finish Numbers, Common Name, Ra (Microinch), Ra (Micron), Rmax (microinch), Rmax (Micron), RMS, ISO number, Japanese Standard, etc. Each of these many roughness parameters has a specific use, but this variety of systems has also provided a broad and sometimes overlapping range, and a high degree of confusion. (See Table II)

To be complete and unambiguous, a universally recognized and accepted surface roughness specification and measurement standard must be considered, and final criteria shall be determined by that standard (**Ra** values) rather than by polishing methods. Following the definition of the standard:

> **Arithmetic Average Roughness (Ra).** The arithmetic average height of roughness component irregularities from the mean line measured within the sample length (L). This measurement conforms to ANSI/ASME B46.1 "Surface Texture - Surface Roughness, Waviness and Lay"; the surface is measured and normally described using the arithmetic derivation **Ra** (formerly known as AA or Arithmetic Average in the U.S., and CLA Centerline Average in the U.K.) usually expressed in microinches, and measured with profilometers and/or borescopes.

Refer to Tables SF-1 through SF-8 of ASME BPE for acceptance criteria of interior surface finishes for tubing, fittings, valve bodies, and vessels.

Table II—Surface Measurements Comparison

RMS (Microinch)	**RMS** (Micron)	**Ra** (Microinch)	**Ra** (Micron)	**Grit** Size
80	2.03	71	1.80	80
58	1.47	52	1.32	120
47	1.20	42	1.06	150
34	0.86	30	0.76	180
17	0.43	15	0.38	240
14	0.36	12	0.30	320
		4 - 8		320 EP
		10		400

— ELECTROPOLISHING —

In addition to purely mechanical finishes, sanitary tubing is also available in a number of highly polished surfaces.

These surfaces are accomplished by an electrochemical process also known as "chemical machining" and/or "reverse plating" that is far superior to any available mechanical process for the **removal** (as metallic salts) of surface imperfections in stainless steel. Electropolishing levels and brightens the material surface by anodic dissolution in an electrolyte flowing solution with an imposed electrical current. When the proper combination of electrolyte current temperature is attained, the high points of surface irregularities, or high current density areas, are selectively removed at a greater rate than the remainder of the surface, resulting in improved surface measurements.

Electropolishing typically uses mixed acids solutions sometimes with organic additives (electrolyte), and a cathode that is pulled through the inside of the tube. The tube becomes the anode, so it preferentially dissolves, removing metal from the peaks and not from the valleys. Normally the cathode would be plated if the solution chemistry did not cause the metals to dissolve as fast as they are plated.

In addition to appearance, electropolished tubing has five primary advantages:

1. Extremely smooth surface, which minimizes adherence of debris on the electropolished surface.
2. An increased chromium to iron ratio on the electropolished surface to improve corrosion resistance.
3. Creation of a passive layer that is free from iron contamination.
4. Improved ability to visually detect surface defects.
5. Improved mechanical property performance through minimization of stress risers.

— JOINING TECHNIQUES —

Connections between tube and tube or tube and fitting, and even tube/fitting to equipment during system fabrication and/or erection can be accomplished by diverse means. However, it is paramount to understand the requirements for hygienic system cleanliness integrity. ASME BPE defines hygienic as "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". It becomes clear that in order to achieve the required cleanliness levels, a system, shall as much as possible reduce the use of joints where impurities entrainment may occur, such as flanges and threaded joints (must be avoided), or even hygienic clamps. Thus. systems shall, preferentially be joined using butt-welding practices only.

Automatic Orbital Welding

Welding technologies have improved significantly to meet the increasing requirements of pharmaceutical and microelectronics industries. Tubing and/or piping welding for the biotechnology and pharmaceutical industries used to be simply qualified to ASME Section IX of the Boiler and Pressure Vessel Code with reference to ASME B31.3. However, in response to specific quality requirements imposed by higher levels of complexity in bioprocesses, ASME has developed guidelines that do not necessarily replace the present code, but rather reference existing standards applicable to the industry for equipment design and fabrication. These guidelines are contained in ASME BPE Part **MJ**, Material Joining. This Part comprises: Scope (MJ-1), Materials (MJ-2), Joining Processes and Procedures (MJ-3), Weld Joint Design and Preparation (MJ-4). Filler Material (MJ-5), Weld Acceptance Criteria (MJ-6), Inspection, Examination, and Testing (MJ-7), Procedure Qualification (MJ-8), Performance Qualification (MJ-9), Documentation Requirements (MJ-10), and Passivation (MJ-11).

Hand executed Gas Tungsten Arc Welding (GTAW), commonly referred as Tungsten Inert Gas (TIG), has lost much popularity as an acceptable technique for bonding sanitary piping systems. Since the advent of automatic orbital welding equipment, the use of "316L" grade stainless steel with highly polished interior surface has become mandatory if overall results of this precision welding process are to be achieved.

The automatic orbital welder is used to fusion weld thin wall tubes and fittings together in a totally inert environment, without the use of filler materials or special weld preparation, pieces, or machining. Essentially, an arc established between a tungsten electrode (installed in a rotor within the weld head) and the tubing, accomplish the fusion weld. It consists of a series of spot welds in which the main welding current penetrates the material and the background current chills the puddle The quality of the fusion joint that is made by this equipment is predicated on the use of two pieces of material of the same thickness, and grade or type. Therefore, great care must be exercised in material and component selection. In operation, the two pieces of material tube-to-tube or tube-to-fitting are placed in the welding head. This head, which contains the tungsten electrode, is provided with clamping jaws, which securely holds the parts to be welded in position and in alignment with the tungsten. At the same time the entire area to be welded is enclosed in this welding head, forming a purge chamber which is filled with shield gas, usually argon, during the entire weld sequence to prevent oxidation of the welded material. Meanwhile, the inside of the tube can be purged free of oxygen and allow the entire area to be completely covered with argon gas. The weld cycle is preprogrammed and set in the machine; therefore the entire operation is *automatic*. The tungsten rotates around the weld seam on an internal gear, while the head remains stationary. When complete, the head can be opened and immediately removed from the welded section.

-- PASSIVATION --

A final treatment/cleaning process used to restore (by introduction of oxygen) the disturbed, chemically inert surface or passive layer of stainless steel piping, tubing and/or equipment, by removing/dissolving free iron or other anodic contaminants from the surfaces of corrosion-resistant parts, an leaving chromium and iron oxides as the primary metal components. Welding of the piping systems as well as process conditions affect the thin chromium oxide film, with some oxides of iron and nickel, that forms on stainless steel naturally and almost instantaneously in contact with air, making it "passive" and resistant to corrosion. Because welding disturbs that passive layer by reducing the chromium and increasing the iron, thus altering the chrome/iron ratio (measure of corrosion resistance), upon completion and approval of the weld, the weld surface and adjacent boundary area must be brought back to a passive state. Additionally, normal operating conditions in typical Water For Injection, Reverse Osmosis, Deionized Water, Clean Steam, Clean In Place and process piping often lead to formation of the most prevalent form of self catalyzing corrosion called "rouge", which is a colloidal form of rust containing iron, chromium and nickel in various forms. This problem is accentuated by the use of high temperature, aggressive process chemicals and ultra pure water, and can be overcome only by restoring the surface to its passive state.

Methods and tests for cleaning and passivation of critical water, product, and process piping systems are described in ASTM A380 "Standard Practice for Cleaning and Descaling Stainless Steel Parts, Equipment, and Systems".
Passivation can be accomplished by one of two methods:

Chemical Oxidation

The most common method of passivation and usually the most cost effective. It can be performed by many techniques including the use of mineral acids or citric-based chelant systems. Warm dilute nitric acid and other mineral acids are effective on removal of iron; however, they will not remove many of the inclusions or other surface metal contaminants. Citric acid and Ammonium Citrate (Ammoniated Citric Acid) together with other chelants dissolves surface contaminants and iron compounds. They also allow the dissolved ions attached to the chelant, to be flushed from the system with rinse waters. A number of events can trigger the need for repassivation. Generally, any change to the system, including additions and deletions, rewelding. or exposure to a highly corrosive agent may be cause for system repassivation followed by revalidation.

"In Situ" Electropolishing

Electropolishing of small assemblies welded on the workbench can be accomplished with relative ease by the same techniques used to electropolish lengths of tubing. Electropolishing in place for complex systems may become more difficult. As with tubing, irregularities on weld surfaces will be leveled and a protective surface oxide layer will be formed by electropolishing the weld surface.

— MEASUREMENT AND INSPECTION FOR CrlFe RATIOS —

Testing the surface with a color change technique known as the **"Ferroxyl Test for Free Iron"** as outlined in ASTM A380, checks the effectiveness of the passivation procedure by indicating the presence of free iron at the surface. The testing solution is applied to the surface being tested; a blue stain appears within 15 seconds of application, indicating the presence of free iron. Ferroxyl test offers no quantitative information as to the amount of chromium oxide or iron at the surface.

With better passivation techniques (primarily citric and other chelant materials), new measurement techniques have been developed. Test methods now at the forefront, are:

AES (Auger Electron Spectroscopy)
An alternative surface analysis that can also detect all elements with an atomic number greater than that of helium with the additional ability to analyze sub micron-diameter features. It is not as quantitative as ESCA and cannot determine the chemical state of an element. The primary advantage of Auger is that when combined with etching, a chemical depth profile can be measured rapidly and it can image the distribution on the surface of spatial limitation resolution of 100 to 1,000 angstroms (depending on the equipment capability).

XPS (X-Ray Photoelectron Spectroscopy) or ESCA (Electron Spectroscopy for Chemical Analysis)
It is a surface-sensitive technique capable of detecting all elements with an atomic number greater than that of helium. ESCA provides data on the outermost several atomic layers of a material, and has a sensitivity in the order of 0.5 atomic percent. A primary advantage of ESCA is that it can both determine and quantify the chemical state of the elements detected (i.e. metallic state or oxide state).

— CORROSION TYPES —

Stainless steel in the passive state appears in a relatively noble position in the galvanic series and is usually cathodic (See Table III). Therefore, not subject to attack. However, under certain conditions all or portions of a piece of stainless steel may become active. This active surface becomes anodic to the more noble mass and in the presence of an electrolyte a galvanic cell is set up and attack will occur. The rate of attack will vary with different electrolytes and the area relationship of the anode and cathode.

Electrolytic or Stray Current Corrosion

Stray electric currents may produce pitting attack on stainless steel. The rate of attack with an AC current is considerably less than DC and in most cases insufficient to be considered.

Chemical or Crevice Corrosion

This probably is the most common cause of pitting of stainless steels. Whenever a solid or semi-solid material adheres or lies against a stainless steel surface in contact with an electrolyte, pitting may occur. The relative anode and cathode areas and the type of electrolyte will influence the rate of attack. This type of corrosion will spread as products of corrosion deposit on other areas of the metal form new cells which cause further pitting. Regular, efficient cleaning with correct cleaning agents will minimize these types of attack.

Stress Corrosion and Corrosion Fatigue

This type of corrosion cracking is a result of residual or applied stresses. Metal under stress is slightly anodic in relation to the unstressed metal of the same analysis. Austenitic steels under stress are subject to attack when exposed to certain corrosive agents. The Halogen salts are probably the most serious offenders. It is important to design installations that eliminate sources of stress such as applied loads, vibration, flexing and excessive expansion and contraction due to temperature changes.

Erosion Corrosion

Certain liquids or gases moving at high speeds may cause erosion corrosion, though these same materials if motionless would not affect the stainless steel. It is believed that the attack is due in part to the destruction of the passive layer on the surfaces. The action of fluids in rapid motion is not always destructive, in some cases the scouring effect keeps the stainless steel free of deposits and sludge that may cause other types of corrosion.

Galvanic Corrosion

A type of localized corrosion that occurs when two different metals come in contact in the presence of an electrolyte. The least noble metal in the galvanic series becomes sacrificial to the more noble.

Stainless Steel Pitting Characteristics Evaluation

PP (Potentiodynamic Polarization). An electrochemical test (ASTM G61 "Cyclic Potentiodynamic Polarization Standard Practice") that measures the point at which pitting corrosion begins. PP uses an electrolytic cell to directly measure the corrosion rate. By using the test piece as the working electrode, initiation of localized corrosion is shown by the potential at which the current density increases rapidly. This point is called the "pitting potential". The lower the current density at this point, the more resistance to pitting corrosion. The current density is measured in micro-amps per square centimeter.

Table III — The Galvanic Series

**Anode-corroding end,
least noble, electro-negative**

Magnesium
Aluminum
Zinc
Cadmium
Steel or Iron
Cast Iron
Chromium (active)
Stainless Steel (active)
Soft solder
Tin
Lead
Nickel
Brass
Bronze
Copper
Silver solder
Chromium (passive)
Stainless Steel (passive)
Silver
Graphite
Gold

**Cathode-protected end,
most noble**

Source: Dillon, Rahoi. and Tuthill - BioPharm - June1992

— GUIDELINES FOR HYGIENIC SYSTEMS —

Hygienic. As defined in ASME BPE "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".

General Considerations

All hygienic/sterile designs involving the use of stainless steel tubing or piping should conform to the applicable requirements of ASME BPE, ANSI B31.3, E-3-A, and FDA regulations, latest editions. Some of these considerations are:

- Direct connections between sterile and non-sterile parts are not permitted.
- Positive pressure should be maintained within the systems to prevent contaminants from entering; this does not apply to pathogen containing systems due to the danger of leakage to the environment. Alternate methods of preventing contaminates from entering a pathogen system must be investigated.
- Consideration of a steam seal should be given to vessel connections, which are not in use, for example sample valves should have live steam entering on the exit side.
- Where the media or product is heat sensitive such as in the case of antibiotics, sterilization can be accomplished by using a 0.2 micrometer sterile filter to remove organisms.
- In clean rooms, filling lines, or other post purification processes, exposed piping should be minimized. Such piping should be routed in encased chases with exposed branches as short as possible.

Guidelines

General Design Guidelines for sterility and cleanability applicable to all bioprocessing equipment, components, assemblies, and systems are detailed in ASME BPE Part **SD**. This standard addresses Cleanability (SD-3.1), Sterility (SD-3.2), Surface Finishes (SD-3.3), Materials of Construction (Sd-3.4), Fabrication (SD-3.5), Static 0-Rings, Seals, and Gaskets (SD-3.6), Connections and Fittings (SD-3.7), Exterior Design (SD-3.8), Containment (SD-3.9), Miscellaneous Design Details (SD-3.10), System Design (SD-3.11), and Drainability (SD-3.12).

Specific Guidelines for sterility and cleanability applicable to all bioprocessing equipment, components, assemblies, and systems are detailed in ASME BPE Part **SD**. This standard addresses Instrumentation (SD-4.1), Specialty Fittings and Hoses (SD-4.2), Centrifuges (SD-4.3), Filtration Equipment (SD-4.4), Pumps (SD-4.5), Process (Hygienic) Valves (SD-4.6), Vessel Design (SD-4.7), Agitators and Mixers (SD-4.8), Heat Exchange Equipment (SD-4.9), Cell Disrupters (SD-4.10), High Purity Water and Steam Systems (SD-4.11), WFI Generators and Clean/Pure Steam Generators (SD-4.12), Micro/Ultrafiltration and Chromatography Systems (SD-4.13), Sterilizers/Autoclaves (SD-4;.14), and C IP Systems and Design (SD-4.15).

— DEAD LEGS —

"Dead legs", or areas of entrapment in a vessel or piping run that could lead to contamination of the product, must be minimized. In a piping system a dead leg is "a pocket, tee, or extension from a primary piping run that exceeds a defined number of pipe diameters from the ID of the primary pipe". It is denoted by the term *LID* or *L/A*, where *L* is equal to the leg extension perpendicular to the normal flow pattern or direction, A is the annular gap width, and *D* is equal to the ID (or inside dimension) of the extension or leg. In some existing standards, the dimension *L* is measured from the centerline of the primary pipe. <u>For bioprocessing systems, and *L/D* of 2:1 is</u>

achievable with today's design technology for most valving and piping configurations.
For more details refer to BPE Part SD-3.11.1

About the Author

Michelle M. Gonzalez is the Senior Corporate Engineer at Amgen, Thousand Oaks, California. She has nearly 35 years of experience in facilities design and engineering. Since relocating to the United States in 1965, she has held positions of increasing responsibility in mechanical engineering with firms such as Shell Oil, Kaiser Engineers, Bechtel Corporation, Fluor Daniel, and Amgen. For the last 17 years she has focused her professional expertise in the pharmaceutical and biopharmaceutical industries. Ms. Gonzalez holds an MS in architecture from the Pontificia Universidad Javeriana in Bogota, Colombia. She is a lecturer at the Stanford School of Engineering, member of the ISPE Baseline Biotech Guide Task Team, and ASME BPE subcommittees on dimensions and tolerances, and surface finishes. She is also an active member of ISPE as a speaker, writer, and chapter committee member.