

**The new U.S. FDA regulations on
biocompatibility and reprocessing for medical devices**

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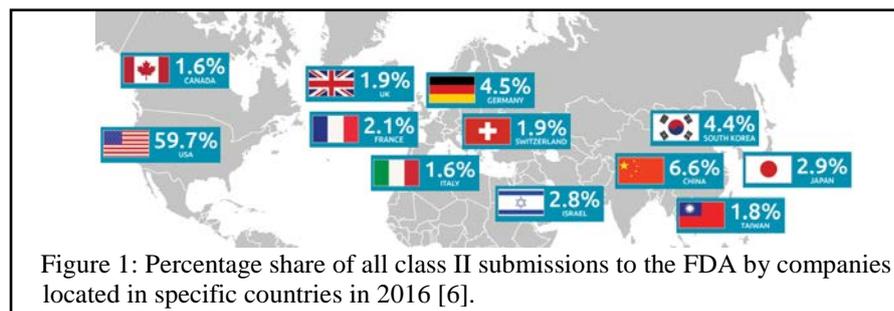
1 LIST OF ABBREVIATIONS

510(k)	Pre-market submission made to the FDA for new & modified Class II devices
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care
AAMI	Association for the Advancement of Medical Instrumentation
AdvaMed	Advanced Medical Technology Association
ANSI	American National Standards Institute
ASTM	American Society for Testing and Materials
CDC	Centers for Disease Control
CEN	European Committee for Standardization
CFR	Code of Federal Regulations
CDRH	Center for Devices and Radiological Health
CGMP	Current Good Manufacturing Practices
DHF	Device History File
DMR	Device Master Records
EO	Ethylene Oxide
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FFF	Final Finished Form
GLP	Good Laboratory Practices
HCT	Human Cells, Tissues.
ICDB	Infection Control Devices Branch
IDE	Investigational Device Exemption
IFU	Instructions For Use (<i>e.g.</i> , user’s manual)
ISO	International Organization for Standardization
MDMA	Medical Device Manufacturers Association
MDR	Medical Device Reports
MtF	Memo-to-File
ODE	Office of Device Evaluation
OOS	Out of Specification
PETA	People for the Ethical Treatment of Animals
PIP	Poly Implant Prothèse
PMA	Pre-Market Application made to the FDA for Class III devices
QSR	Quality Systems Regulations
SAL	Sterility Assurance Level
SDO	Standards Developing
SOP	Standard Operating Procedures
TIR	Technical Information Reports
USC	United States Code
USP	United States Pharmacopoeia
QAU	Quality Assurance Unit

*Note: Because this paper focuses on the U.S. FDA, American English (“AmE”) will be used.

2 INTRODUCTION

The United States is the biggest medical device market in the world, with a market size of approximately US\$148 billion [1]. The U.S. share of the global marketplace value of the global medical device market in 2015 was approximately 43%. The Food and Drug Administration (“FDA”) controls access to this market. In one study that was sponsored by the Medical Device Manufacturers Association (“MDMA”), Stanford University researchers asked 204 medical technology companies about the U.S. regulatory process. The reported average cost to take a product from concept to market is US\$31 million, and that roughly 77% of that amount is spent on tasks related to FDA regulation [2]. A major part of those costs involves issues of biocompatibility, reprocessing, and/or sterilization [3]. Therefore, it is clear that these three regulatory areas represent important topics for many medical device manufacturers [4]. Importantly, the FDA rules regulating these three issues have undergone substantial changes in the past two years [5]. The image below shows the top twelve countries that submit to the FDA a class II medical device submission [6]. More than 40% of all medical device applications to the FDA come from outside the United States. Therefore, it is imperative that a straightforward analysis is made of the recent FDA guidances on biocompatibility, reprocessing, and sterilization, along with their effects on the regulatory submission process for new devices in the United States.



The present master thesis intends to provide an understanding into how the new FDA guidances affect the development of new medical devices. This paper begins with a comprehensive overview of how the FDA regulatory framework affects biocompatibility, reprocessing, and sterilization. Not only does the FDA approve medical devices, but FDA inspectors also examines medical devices at their manufacturing facilities. Many quality problems that the FDA identifies have to do with manufacturing failures related to either biocompatibility, reprocessing, or sterilization. This paper shows that the FDA only makes major changes to its regulatory requirements after there are a large number of injuries or deaths from problems in medical devices that the FDA had previously cleared. This thesis discusses several cases where medical device failures led directly to the FDA publishing new rules/guidances on biocompatibility, reprocessing, and sterilization. Finally, a thorough analysis is made on the new guidances to clarify several difficult issues for medical device manufacturers. This master thesis is intended to provide not only an overview of FDA requirements, but to function as a guide for both researchers and engineers to improve their medical device design and development process.

FDA guidances function as a benchmark that medical device companies can use to plan their development program for new devices [7]. The publishing of guidance documents is one of the main principal regulatory controls that defines the FDA's understanding of a policy on a regulatory issue [8]. As of 2017, there are now 760 different guidances on the FDA website that regulate medical devices [9]. The FDA only requires clinical data for less than 10% of all Class II device submissions [10]. Often, FDA guidances comprise the only source of information on the precise requirements that manufacturers must obey to obtain regulatory approval for their device.

Section 3 of this paper summarizes the FDA regulatory process for premarket submissions. Section 4 discusses how both regulatory and quality failures are the leading source for changes in FDA guidances. Section 5 focuses on how the FDA uses its "quality systems regulations" to make sure that companies conform with the regulations on biocompatibility, reprocessing, and sterilization.

Sections 6 and 7 of this master's thesis examines the most recent FDA biocompatibility guidance from 16 June 2016 ("*Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'*"), which focuses on topics such as [11]:

- NEW**
- when to consider using animal testing vs. *in vitro* testing;
 - sample preparation of nanoscale, bio-absorbable, and *in situ* plasticized materials;
 - the assessment of extractables and leachables.

Sections 8 and 9 discuss the new FDA reprocessing guidance from 17 March 2015 (*Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*), which concentrates on the following areas of interest [12]:

- NEW**
- procedures for validating the instructions for cleaning, disinfection, or sterilization;
 - simulated use testing for validating methods & instructions; and
 - uncommon sterilization methods (*e.g.*, use of flexible bags, assorted sterilants, sound waves, ultraviolet light, and microwave radiation).

Lastly, section 8.16 has a separate analysis on the most recent FDA sterilization guidance from 21 January 2016 ("*Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*") [13]. Sterility questions are common with device reprocessing and biocompatibility:

- NEW**
- the FDA's bifurcation between "established" versus "novel" sterilization methods;
 - a thorough discussion of hydrogen peroxide, ozone, and flexible bag systems; and
 - the FDA will inspect the manufacturing facilities of companies that employ novel sterilization methods before clearing premarket submissions for such devices.

3 THE FDA REGULATIONS ON PREMARKET SUBMISSIONS (I.E., 510(K) AND PMA)

The Center for Devices and Radiological Health (“CDRH”) is responsible for assuring the safety, effectiveness, performance, and quality of medical devices used to treat, prevent, and diagnose diseases [14]. The Medical Device Regulation Act of 1976 authorized the FDA to regulate both the safety and effectiveness [15] of medical devices [16]. In 1982, the CDRH was created from an amalgamation of the “Bureau of Radiological Health” and the “Bureau of Medical Devices” [17].

The FDA's goal of defending consumer safety requires laborious pre-marketing reviews, but its mandate to foster innovation creates a simultaneous countervailing pressure. Congress has directed the FDA to employ the "least burdensome" methods of evaluating products in the premarket notification and premarket approval processes [18]. Following this mandate, the FDA has declared that premarket approval can sometimes be based on "well-designed bench and animal testing" rather than clinical tests [19]. Moreover, the FDA will consider the extent to which measures such as post-marketing trials can substitute for premarket scrutiny [20]. Though clinical data are normally not needed for most premarket notifications, the FDA responded to the "least burdensome" directive by emphasizing that "substantial equivalence" determinations should also be streamlined [21].

The FDA divides all medical devices into three separate classes based on the device's intended use and the possible jeopardy caused by the device to the patient [22]. The class level governs the necessary amount of evidence to sufficiently demonstrate both safety and effectiveness of the device [23]. Class I devices are mostly exempt from premarket notification and do not require FDA regulatory clearance before being marketed. Class I devices are considered to be “low-risk”, although the manufacturer must still fulfill all required “general controls” such as registering with the FDA.

Class II devices are normally required to clear the 510(k) regulatory process, where the manufacturer must demonstrate “substantial equivalence” to another legally marketed device in the United States. The FDA defines “substantial equivalence” by comparing the manufacturer's device to a comparator device in terms of its intended use, technological characteristics, and “safety & effectiveness” [24]. This guarantees that the technical features, of the manufacturer's newly proposed device, do not create any new safety or effectiveness issues for that precise device type [25]. Clinical trials are also not normally required for class II devices. Other requirements such as “special controls” may be imposed, such as specific labeling requirements and post-market surveillance [26]. If the FDA deems a device not to be substantially equivalent, the manufacturer can petition for reclassification or file a *de novo* application [27].

Class III devices are considered to be the riskiest devices and must utilize the PMA regulatory pathway. This normally includes a major clinical trial, FDA advisory panel review, and a pre-approval inspection of the manufacturing location. As of October 2017, the fee for a PMA is US\$310.764, while the fee for a 510(k) is only US\$10.566.

It is important to note that the 510(k) regulatory pathway is used by 98% of all products that undergo premarket review by the FDA [28]. In the fiscal year 2014, the FDA issued 2,368 different 510(k) clearances for class II devices, while only issuing 44 PMA approvals for class III devices.

4 REGULATORY AND QUALITY FAILURES HAVE BEEN THE PRECURSOR FOR MOST FDA GUIDANCES

There is evidence that the FDA only makes major changes to its regulatory requirements through new guidances when it is faced with serious threats from their mistakes or failures [29]. According to a report from the Brookings Institution, medical device problems contribute to approximately 3,000 deaths per year in the U.S. [30]. The American public often blames these medical device failures on overly lax regulations by the FDA [31]. These regulatory mistakes negatively affected the reputation of the FDA and potentially threatens its overall regulatory standing within the U.S. government [32].

The FDA has faced many calls to reduce its importance by copying the system used in the EU for medical devices, and utilize non-governmental third-parties to perform medical device approvals (*i.e.*, Notified Bodies) [33]. Major American medical device manufacturers like Medtronic have disparaged the FDA for “*strangling innovation with inconsistent regulation and lagging device approvals*” [34]. A survey of 350 medical device companies by the Institute for Health Technology Studies found that more than 75% of device manufacturers initially seek regulatory approval outside of the United States for their new medical devices [35]. In fact, in 2011, the U.S. Institute of Medicine (“IOM”) found that “*the current 510(k) process is flawed based on its legislative foundation*” [36]. Because the 510(k) process is used to approve most of the Class II medical devices in the U.S., this recommendation by the IOM would substantially reduce the size and importance of the FDA [37]. Subsequently, the FDA stated that it “*believes that the 510(k) process should not be eliminated but we are open to additional proposals and approaches for continued improvement of our device review programs*” [38].

In its self-defense, the FDA has also criticized the use of Notified Bodies in the EU medical device review process [39]. The FDA wrote in May 2012 about twelve different medical devices that were approved for use in the EU, which turned out to be dangerous, but that were not approved in the U.S. because of FDA oversight [40]. Furthermore, as proof of the superiority of the FDA regulatory system to the EU regulatory system, the FDA has highlighted the fact that Poly Implant Prothèse (“PIP”) was not able to sell its adulterated silicone breast implants in the United States because of biocompatibility problems [41]. Before January 2000, PIP had sold 35,000 implants in the United States [42]. However, in May 2000, the FDA sent an inspector to France, who subsequently wrote PIP a warning letter that accused the PIP implants as being “adulterated” and cited at least 11 deviations from good manufacturing practices [43]. However, AFSSAPS, the French agency in charge of medical devices that was responsible for regulating PIP, never saw the FDA warning letter before 2010 [34].

After the 2000 warning letter by the FDA, PIP was unable to sell their implants in the United States anymore. Because of the reduction in profit from losing access to the U.S. market, PIP then sought to recoup some of its lost income by severely cutting costs. At that point, PIP began to switch from “medical-grade” silicone which had to be externally purchased, to an in-house produced “industrial-grade” silicone. This change in material

resulted in a cost savings of 90% on PIP's previous silicone gel purchasing costs [44]. In some ways, because the FDA blocked all PIP sales in 2000 in the United States, the FDA might be considered to be indirectly responsible for the subsequent actions that led to the PIP scandal in Europe. An independent analysis of the industrial-grade silicone used by PIP in their implants showed that it contained more siloxanes than the original medical-grade silicone [45]. Following the PIP scandal in 2010, the European Commission embarked in 2012 on a full regulatory overhaul of the medical device regulations within the EU [46].

Specifically, the FDA criticized the EU for the following issues related to medical device oversight [47]:

- The lack of centralized oversight over the Notified Bodies;
- The decision to approve a medical device by any single Notified Body permits the legal marketing of that device throughout the EU;
- There is no publicly available evidence of the Notified Bodies' approval decisions; and
- An inefficient centralized collection of medical device adverse event reports related to device side effects (*i.e.*, EUDAMED).

Instead of replacing the 510(k) regulatory framework, the FDA decided to make important changes to the original 510(k) program with their “*CDRH Plan of Action for 510(k) and Science*” in November 2012 [48]. As part of this improvement plan, the FDA found that their biggest problem was the lack of sufficient predictability in the FDA device approval and clearance process [49]. The lack of uniformity by FDA reviewers creates several inefficiencies, increased costs to the medical device industry, and delays the introduction of new medical products into the market. Having inconsistent regulatory requirements by different FDA reviewers, as was shown by a report from Pricewaterhouse Coopers [50], creates particular challenges for small start-up companies to get investors or venture capitalist funding for new, early-stage technologies [51]. The lack of uniform regulatory decision-making also affects the introduction of new technologies, that the FDA had previously identified, as being critical to helping patients [52]. For example, the number of 510(k) applications that received a request for “additional information” has rapidly increased since 2002. These “additional information” requests greatly delay the clearance time for new devices [53]. Subsequently, the FDA identified in their 2012 review several root-causes of the problems related to the lack of predictability in their regulatory decision-making process [54]. These include the following challenges [44]:

- 1) Insufficient guidance for industry;
- 2) Very high turnover rates for FDA reviewers and managers at CDRH (*i.e.*, almost double that of the FDA's pharmaceutical and biologics regulatory divisions);
- 3) Insufficient training for both the CDRH staff and the medical device industry;
- 4) Extremely high ratios of front-line supervisors to employees;

- 5) Insufficient oversight by managers;
- 6) CDRH’s rapidly growing workload, caused by the increasing complexity of devices and the number of submissions that are reviewed;
- 7) Unnecessary and inconsistent data requirements imposed on medical device manufacturers;
- 8) Poor-quality submissions from the medical device industry.

One of the solutions that the FDA proposed was to begin to produce many more FDA guidances. Issuing guidance documents, and providing updates to older guidances, can provide greater predictability by laying out for companies what steps to take in preparing a device application or submission for approval or clearance [55]. The FDA is legally authorized to issue industry guidances under 21 CFR § 10.115 [56]. In the past, the FDA annually issued approximately 30 to 40 new guidances, which was not adequate to keep up with the mounting demand by the medical device industry or the changing regulatory environment [57]. As the need for new and updated guidances increases with the growth in types of devices, and as the rapidly changing scientific landscape makes current guidances outdated more quickly than in the past, the adverse impact of the FDA’s limited capacity to issue guidances will only increase if nothing was changed. Because of the focus on this issue, the number of FDA guidances has significantly grown since 2011 [58]. As part of the changes, the FDA updated their Standard Operating Procedure (“SOP”) on issuing guidance documents [59].

Device Problem	FDA guidance “solution”
Olympus and Fujifilm duodenoscope	The requirement for validated reprocessing instructions in the new reprocessing guidance.
Vaginal surgical mesh devices	Greater reliance on chemical characterization in the new biocompatibility guidance. FDA has also reclassified these devices from class II to class III.
“Metal-on-metal” hip implants	Greater reliance on chemical characterization in the new biocompatibility guidance. FDA has also reclassified these devices from class II to class III.
Contaminated backflow from water irrigation used during colonoscopies.	New FDA guidance on mitigating the risk of cross-contamination.

Table 1: List of major medical device problems that led to some of the newest FDA guidances.

5 HOW THE QSR AFFECTS BIOCOMPATIBILITY, REPROCESSING, AND STERILIZATION

After a medical device is either cleared or approved by the FDA, the CDRH will then eventually conduct an inspection of the establishment responsible for the device. This post-approval inspection is used by the FDA to make sure that the device complies with the required quality requirements [60]. For foreign manufacturers, it is important to note that the FDA often conducts inspections outside of the United States. These FDA inspections include observations on a manufacturer's reprocessing, biocompatibility, and sterilization processes [61]. For example, in 2015, the FDA conducted 90 inspections in Germany, 44 inspections in Japan, and 30 inspections in France [62]. The FDA is allowed to inspect relabelers, contract manufacturers, design specification developers, repackagers, contract sterilizers, and several other types of establishments [63]. Medical device establishments must follow the FDA quality systems to help ensure that their products consistently meet applicable requirements and specifications [64]. For example, FDA inspectors are known to request data on the "disinfectant log reduction" [65]. On another occasion, a German manufacturer of guidewires named Epflex Feinwerktechnik GmbH was required to provide the FDA inspectors with a detailed explanation for their "cleanroom qualification" validation failure [66].

When companies do not comply with the FDA's quality requirements, they can be charged with civil and criminal penalties [67]. For example, B. Braun Melsungen AG had to pay US\$7.8 million in both civil and criminal fines for selling supposedly sterile syringes that were, in fact, contaminated with "Serratia marcescens" bacteria [68]. These devices caused at least five deaths and the hospitalization of more than 300 patients in the United States because the defective products generated an outbreak of bacterial infections [69]. Furthermore, both the quality control director and the plant manager who were responsible for manufacturing the B. Braun syringes, pleaded guilty to criminal conspiracy to commit felony violations of the FDA's regulations. Both employees were sentenced to 54 months in prison [70]. In referring to another case of a different medical device manufacturer selling products contaminated with bacteria, U.S. federal attorney Benjamin Mizer stated that "*device manufacturers that fail to comply with good manufacturing practices, thereby threatening patient safety, will be held accountable*" [71].

The quality systems regulation ("QSR") for medical devices in the United States is known as current Good Manufacturing Practices ("cGMP"), and are codified under 21 CFR § 820 [72]. When companies fail to meet their requirements under 21 CFR § 820, then the FDA may eventually file a "warning letter" on that company [73]. A foreign company with a warning letter may have their products seized by U.S. customs officials [74]. For example, "Innovative Sterilization Technologies, LLC" is a specification developer of a sealed sterilization container, which received a warning letter in 2016 for various quality control problems related to their device's sterilization problems [75].

Another company, "Collagen Matrix, Inc.", which is a manufacturer of collagen-based devices for use in oral/maxillofacial surgery, also was the recipient of a warning letter in 2016 [76]. The FDA explained that the packaging on their originally cleared product

consisted of only a plastic jar, surrounded by an outer blister package. However, “Collagen Matrix” had then altered the original packaging, which presented unique biocompatibility and sterilization validation concerns. The FDA noted that another 510(k) would be required to demonstrate that the plastics used in the new packaging did not give off leachables or extractables that could negatively affect the biocompatibility of the modified device’s materials [77]. In general, more companies can expect to receive warning letters in the future because of the new FDA guidances and stricter adherence to the rules by the FDA on issues of biocompatibility, reprocessing, and sterilization [78].

FDA inspections focus on failures in the medical device manufacturer’s development process, device design, raw materials, and employee training [79]. The FDA inspectors focus on complaints, medical device reports, servicing, product acceptance, change control, process validation, design control, and internal audits. Importantly, the FDA requires the manufacturer, or specification developer, to establish and maintain a design history file (“DHF”) for each type of device [80]. However, as the case of “Collagen Matrix” shows, companies can mistakenly believe that a change to a previously FDA cleared device incurs only an insignificant new risk. Nevertheless, a wrong decision may lead to a warning letter or legal prosecutions by the FDA [81].

If a company has already cleared a device with the FDA, and the original device was changed in any way, then the company would need to provide documentation on what changes were made [82]. Those changes would need to be first validated to maintain the same level of safety and efficacy as the original version of the device that was cleared by the FDA [83]. Normally, companies use a document called a memo-to-file (“MtF”) to note any insignificant changes to a previously FDA cleared device [84]. A thorough evaluation is especially needed when those changes involve any vagaries to the type of materials used on the device, its sterilization method, or reprocessing instructions [85].

6.1 GENERAL

Biocompatibility testing is used to determine the potential toxicity resulting from physical contact with a material or medical device. On 16 June 2016, the FDA issued the final version of their biocompatibility guidance (“*Use of International Standard ISO 10993-1, ‘Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process’*”) [11]. This final guidance replaces the draft guidance that was previously issued on 23 April 2013.

Biocompatibility testing is a subject where many medical device manufacturers struggle to comply with the FDA’s requirements [86]. For example, some companies think that simply because its patient contacting material is widely used in the industry, then it should not need to be tested for biocompatibility. However, the FDA expects that almost all patient-contacting devices will be subjected to biocompatibility testing, unless the manufacturer provides sufficient scientific evidence to justify why testing is not required (*e.g.*, materials and the manufacturing/processing are identical to a similar FDA approved or cleared device). Manufacturers should be able to identify what biocompatibility testing is required for their devices with this new FDA guidance [87].

The final guidance is mostly undifferentiated from the previous draft version, with a few notable exceptions [11]:

- NEW** • The FDA removed “gas pathways” and “color additives” from the final version of the guidance. Biocompatibility of these components will be encompassed separately in future FDA guidances.
- Attachment B of the new guidance outlines the information that the FDA would expect to see in a “device master file” for biocompatibility considerations.

6.2 HISTORY OF BIOCOMPATIBILITY AND THE FDA

In 1987, the FDA issued General Program Memorandum G87-1 “Tripartite Biocompatibility Guidance” on 24 April 1987 [88]. The G87-1 guidance was used by medical device manufacturers to select appropriate tests to evaluate the adverse biological responses to medical devices. The key element to the G87-1 guidance is a matrix that categorizes devices according to whether it is an external device on intact skin, or an internal device in contact with blood [89]. Also, the duration of contact is categorized as either transient (< 5 minutes), short-term (5 minutes - 29 days), or long-term (> 29 days) [90].

The G87-1 guidance built upon standards that had previously been published by AAMI, ANSI, and ASTM [91]. The problem with the old G87-1 guidance included the fact that there was no direction on how to handle whole devices, and it only related to biomaterials, but not metals or ceramics. Furthermore, as the complexity of biomaterial

technology increased and the types of biocompatibility assays proliferated, FDA testing requirements strayed further from the original G87-1 guidance.

The International Organization for Standardization's Technical Committee 194, comprised of members from both CEN and AAMI, produced the original ISO 10993 standard in 1992 [92]. Afterward, the FDA had a goal to harmonize their biological safety policy with the expectations of the international community. The FDA then issued a memo in 1995 known as “G95-1” that made compliance with a modified version of ISO 10993 mandatory in the United States [93]. With the latest revision of the ISO 10993 standard, the focus changed from how to determine which biocompatibility tests to perform, to a method that considers existing information before determining if biocompatibility testing is even required [94]. Furthermore, a major focus of the 1995 FDA guidance was to minimize the number of test animals by giving preference to chemical characterization and *in vitro* testing [95]. In 2016, the FDA incorporated the latest ISO 10993 revision and issued new a guidance that supersedes both G87-1 and G95-1 [11].

6.3 BIOCOMPATIBILITY REQUIREMENTS FOR MEDICAL DEVICES

For FDA premarket submissions, in general, the biocompatibility information for the proposed device in its final finished form must be provided, including any applicable reprocessing or sterilization [96]. For example, there are two types of biocompatibility tests for allergic reactions, such as irritation and sensitization tests. Nevertheless, a company has the option of using the following two alternative options to conducting biocompatibility testing:

1. If the premarket submission is for a modified device of a previously cleared FDA device, then a risk management analysis may be sufficient if both devices are sufficiently identical; or
2. Provision of a chemical characterization, in conjunction with supplementary biocompatibility information, that adequately addresses the potential biocompatibility risks of the device [97].

6.4 GENERAL PRINCIPLES FOR BIOCOMPATIBILITY TESTING ON MEDICAL DEVICES

Before 1987, there were no recognized standards for device biological safety testing [98]. Medical device manufacturers floundered around looking for tests that seemed applicable. For example, the U.S. Pharmacopoeia (“USP”) tests for drug containers were occasionally used when developing new syringes [99]. Unfortunately, several medical device suppliers and manufacturers still incorrectly believe that materials that comply with USP requirements are safe for medical device applications.

According to the newest guidance, the FDA uses seven general principles for its approach to biocompatibility evaluation [11]:

NEW

- a. The medical device manufacturer should take into consideration the chemical formulation for each component material, including adhesives, any impurities, and constituents associated with processing.
- b. The materials used in the final finished form of the device, and any possible “leachable chemicals” or “degradation products” should be gauged for their significance to the overall biocompatibility evaluation of the device. The FDA recognized standard ASTM F748 could be used to help companies to select the biological test methods for materials and devices.
- c. Any biocompatibility endpoints should take into account the nature, degree, frequency, duration, and conditions of exposure of the device materials to the human body.
- d. Any *in vitro* or *in vivo* biological safety experiments or tests should be conducted under the recognized Good Laboratory Practice (“GLP”) regulations including, the assignment of competently trained staff in the conduct of biocompatibility testing.
- e. When test data are provided, then the complete experimental data should be proffered to the FDA.
- f. If a previously FDA cleared or approved device has a change in its physical configuration, manufacturing process, chemical composition, or intended use – then the change should be evaluated with respect to any potential changes in biocompatibility.
- g. Any biocompatibility testing should be considered in conjunction with information obtained from other non-clinical assessments and post-market experiences for an overall safety assessment that incorporates all available relevant evidence [100].

6.5 UTILIZING CHEMICAL CHARACTERIZATION TO COMPLEMENT BIOCOMPATIBILITY TESTING

To avoid multiple biocompatibility tests, the FDA has begun to increase their acceptance of chemical characterization of medical devices as an alternative to *in vivo* testing [101]. Chemical characterization involves the utilization of analytical chemistry to identify and quantify the amount of chemicals extracted from a medical device, and an evaluation of the toxicological risk associated with the expected exposure. The preliminary chemical characterization should uncover any leachable materials [102]. The extractable compounds can then be used to form a “toxicological risk assessment” based on the expected biological response to the compounds [103].

After the recent public outrage involving “metal-on-metal” hip implants, it became evident that the reliance on only *in vivo* or *in vitro* testing does not show the overall safety of a device [104]. In the case of the metal-on-metal hip implants, all of those implants passed

their biocompatibility tests. Namely, none of the animals that were implanted with the metal-on-metal hip implants showed any health problems or weight loss. Also, the clinical studies on human subjects were too short to show the eventual wearing down of the hip implants [105]. Although the hip implants were safe when newly implanted, the unforeseen problems occurred only when the hip implants were inserted into actual patients, and the metal parts began to grind against each other for several years [106]. The devices quickly began to wear out, thereby “*generating high volumes of metallic debris that is absorbed into a patient’s body*” [107]. Because both the metal ball and the metal cup slide against each other when the implant recipient walks or runs, tiny metal particles can begin to come off the device and get into the bloodstream of the hip implant recipients [108]. However, if the manufacturers had conducted a chemical characterization analysis on their hip implants, then they would have found the potential danger before their implant patients suffered adverse events [109].

In the case of vaginal (urogynecologic) surgical mesh devices, the FDA required that Boston Scientific conduct a “*chemical characterization and biocompatibility of the final finished urogynecologic surgical mesh. The chemical characterization tests will identify and assess the chemicals present in the raw material and mesh*” [110]. Experts have estimated that at least 135,000 women have suffered from vaginal mesh devices because of unforeseen biocompatibility problems [111]. Just like in the case of the metal-on-metal hip implants, the vaginal mesh devices all passed their biocompatibility tests to receive an FDA clearance [112]. The complications from the vaginal mesh included infection and erosion of vaginal wall [113]. Many of adverse effects were related to the poor integration of the materials at the implantation site, resulting in both inflammation and the restriction of blood supply to the surrounding vaginal tissues. The FDA’s recent decision to change the classification status [114] of vaginal mesh devices from Class II to Class III will require the manufacturers to conduct many more tests to show the safety of their devices [115]. Presumably, this will include a chemical characterization of the vaginal mesh material [116].

Some of the options for chemical characterization include the following [117]:

- Fourier Transform Infrared Spectroscopy (FTIR);
- Differential Scanning Calorimetry (DSC);
- Liquid Chromatography-Mass Spectrometry (LC-MS);
- Inductively Coupled Plasma-Mass Spectrometry (ICP-MS); or
- Gravimetric Assays.

6.6 THE FDA ONLY APPROVES COMPLETE DEVICES, NOT SPECIFIC RAW MATERIALS

It is common for manufacturers to examine raw materials for biocompatibility, assuming that they can then leverage the findings to the final device [118]. However, manufacturers must also analyze any effects from the manufacturing process on the raw materials. For example, the mold-release agents can change the surface coating of the final device. Alternatively, if sterilization is required, then the sterilization methods such as

ethylene oxide could affect the biocompatibility of the device. Therefore, merely because a material is biocompatible by itself, does not automatically entail that the final device will also be biocompatible.

Nevertheless, the FDA states in their new biocompatibility guidance that no biocompatibility testing is required if the sponsor of the proposed device submits proof that “*each material, the type and duration of tissue contact, physical form, formulation, processing, component interactions, and storage conditions are the **same** as for the comparator device*”. [11]

If these seven factors are found in the proposed device, then “attachment F” of the new FDA biocompatibility guidance allows the device manufacturer to write the following statement in their premarket submission:

NEW *"The medical device in its final finished form is identical to [name] (previously marketed device) in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents)". [11]*

Consequently, biocompatibility testing does not address the device’s internal parts, such as computer chips or cables that do not have any direct physical contact with the patient [119]. Biocompatibility testing is only concentrated on both the device materials and how those materials are treated. Thus, the new guidance provides information on how to develop “coupons”, which are “prototype devices” that are equivalent to the final version of the proposed device. Representative coupon devices should be made from the same materials, and in the same proportions, but do not necessarily incorporate functional internal components such as computer chips or cables [120].

While the internal components of a medical device, such as the inside of the balloon catheter, are not normally supposed to make physical contact with the patient. If a balloon catheter were to burst inside a patient, then it could potentially expose the previously internal material component to the patient’s bloodstream [121]. Therefore, these types of “internal” components may still have to go through biocompatibility testing because of their risk.

NEW Many companies have “material master files” for most of their discrete materials that are used in their devices [122]. Unfortunately, many companies believe that they do not have to perform biocompatibility testing if there is a master file for their material. Although master files can significantly help in creating risk assessments, they are not a substitute for testing because the same materials may be treated differently during the manufacturing process of various types of medical devices.

In addition, the materials with master files, or the devices from which they are made, may not have undergone either cleaning, disinfection, or sterilization. Hence, before performing a risk assessment to establish a device’s overall biocompatibility, manufacturers must still assess the influence of the processing methods on the raw materials used to

produce the final medical device [123]. The guidance makes it clear that biocompatibility testing may not be required every time, so long as other information exists that demonstrates the biocompatibility of the device. Importantly, the FDA is quick to note that it does not approve individual materials. Specifically, the biocompatibility of the material is affected by device-specific features, including the manufacturing processes, duration of contact, and the tissue contact-type.

Historically, the FDA has theoretically believed that biocompatibility can be shown through alternative information (not just ISO 10993 testing) [124]. However, in the opinion of many experts, the FDA has rarely accepted alternatives to ISO 10993. One of the major reasons that materials are not considered interchangeable between different devices is because the manufacturing processes are often extremely different between the old predicate device and the new proposed device [125]. Frequently, the alternative information that companies use to try to avoid the ISO 10993 testing did not specifically consider biocompatibility issues, such as in the case of most clinical studies. Nonetheless, it is uncertain whether the FDA reviewers will become more accepting of alternative information to support biocompatibility [126].

6.7 MINIMIZING THE REQUIREMENT OF ANIMAL TESTING

NEW

To help reduce animal testing, which is a major goal of the new biocompatibility FDA guidance, certain *in vitro* tests can be designed to replace some of the required biocompatibility testing that currently involves animals. For example, alternatives to animal testing have been shown for hemocompatibility, implantation, and chronic toxicity testing [127]. Before commencing with *in vitro* testing, it is crucial to incorporate the endpoints into the *in vitro* protocol to help justify the chosen tests [128]. PETA provides a list of alternative *in vitro* tests that they recommend. The FDA has placed much more importance in the material characterization, instead of just conducting *in vivo* animal testing [129].

6.8 THE IMPORTANCE OF RISK ANALYSIS FOR BIOCOMPATIBILITY TESTING

The most critical change in the final FDA biocompatibility guidance is the importance that the FDA gives to the manufacturer's risk-based assessment of biocompatibility. For example, the FDA guidance now starts with a section entitled "*Risk Management for Biocompatibility Evaluations*". Instead of simply evaluating the contact-type and "duration of contact" to resolve whether a new biocompatibility test is necessary. The biocompatibility guidance now proposes that before any testing is started, the company should first start by executing a risk analysis of the raw materials [130]. Only when any possible material hazards are first identified, then a "gap analysis" can be completed to ascertain what information is available to alleviate the identified risks [131].

The FDA provides instructions on how to complete such a risk analysis [132]. It also summarizes several types of information that may ease any biocompatibility risks (*e.g.*, the manufacturer's prior knowledge, relevant published literature, clinical information, animal

studies, and other formerly FDA cleared devices). The FDA requires that the biocompatibility section of the premarket submissions for new devices must start with a risk assessment, instead of the contact type and duration as detailed in the actual ISO 10993 standard. Nevertheless, the FDA would still expect that manufacturers will identify the contact type and duration of contact later on in the regulatory premarket application.

6.9 THE IMPORTANCE OF BIOCOMPATIBILITY IN MEDICAL DEVICE DEVELOPMENT

Biocompatibility is associated with the behavior of biomaterials. The term “biocompatibility” denotes the capability of a material to adequately function within a given biological situation [133]. The vagueness of the term mirrors the ongoing development of how biomaterials interact with the human body. As well as how those potential biological interactions affect the clinical effectiveness of a medical device (*e.g.*, catheters, hip implants, or endoscopes). Most medical devices are made out of more than one type of material, so it is not sufficient to only focus on the biocompatibility of one specific material [134]. Inevitably, evaluating the biocompatibility of a device is a risk assessment exercise. Fundamentally, the FDA does not recognize any “risk-free” device or material.

Biocompatibility needs to be considered at the onset of any medical device design. It is always preferable to only use previously known biocompatible materials in a medical device. The reason is that the immunological reaction and repair functions in the human body are so complicated, that it is not possible to define the biocompatibility of a material in relation to all cellular tissues within the body. On many occasions, companies must conduct an extensive battery of biocompatibility tests to determine if their device is wholly biocompatible. These tests are not designed to determine the biocompatibility of the tested material for all potential intended uses. The FDA has repeatedly stated that any biocompatibility testing can only identify the particular biocompatibility of the material within a specific device, such as with dental implants or drug delivery devices [135].

6.10 EFFECT OF DIFFERENT MATERIALS ON A DEVICE’S BIOCOMPATIBILITY

It is recognized that the surface properties of a material can significantly affect its biocompatibility. Some of the differences between material properties that companies must take into consideration include the specific material’s protein-binding ability, membrane selectivity, hydrophilicity (*i.e.*, “wettability”), hydrophobicity, lubricity, chemical barrier properties, and bonding properties [136]. Surface properties can also affect the thermodynamics of the surface-free energy of a device, as well as its reflectivity and other optical properties, corrosion & wear resistance, cellular transport properties, the amount of mineral deposition & encrustation, and the retention of static charge.

For reusable devices, the materials used in the construction of the device should be stable in the presence of recommended chemical agents and under the expected reprocessing conditions (*e.g.*, temperature, pressure, vacuum, and humidity) [137]. Manufacturers should demonstrate that a reusable device’s materials will not release any toxic byproducts after

repeated use and reprocessing. Materials should also be evaluated for their capacity to retain unacceptable levels of reprocessing chemical residuals as a result of any recommended cleaning, disinfection, or sterilization procedures [138]. If there is a potential for toxic byproducts or residuals, then manufacturers of both critical and semi-critical devices should perform extra biocompatibility testing on these potential threats [139].

If any materials in a device are adversely affected by the recommended cleaning, disinfection, or sterilization procedures – then the limits of reuse should be determined. The effect of the cleaning, disinfection, and sterilization processes on materials degradation should also be evaluated. When storage or transport conditions could affect the safety, functionality, or useful life of the device, then the device manufacturer should also recommend the acceptable range of storage or transport conditions in their user instructions [140].

6.11 CHANGES ON BIOCOMPATIBILITY FOR A PREVIOUSLY APPROVED DEVICE

It is common for a company to modify the materials used in their medical device, which has already previously received an FDA clearance or approval [141]. There are some reasons why a manufacturer would make a material change after a product has been granted FDA market clearance or approval. Some of the most common actions, which necessitate a change in a medical device’s component materials, are as follows:

- Discontinuation – Material discontinuation happens when the supplier/ producer of a material completely shuts down the production of a specific material;
- Policy Change – When a vendor/producer or regulatory body restricts the use of a material in the medical device market;
- Price Change – The price of raw materials can increase significantly, thereby requiring that the costs of medical materials to subsequently increase; or
- Device Improvement – Medical device companies tend to focus on innovation, and these endeavors may require a change in materials to improve their previously cleared or approved devices.

When embarking on the material change process, companies should evaluate the impact of the change on the design function, biocompatibility, packaging validation, and sterilization, as applicable. For minor material changes, the FDA would normally not require a new regulatory premarket submission. The company would just need to write a memo-to-file as documentation of their minor alterations and place it in their internal Device History File [142]. However, for any change that could substantially affect either the safety or effectiveness of a device, then the FDA would require a new regulatory submission, like a new 510(k) or PMA supplemental. For example, the FDA considers hip joints made of a “*metal/composite semi-constrained cemented prosthesis*” to be a class II device [143]. Conversely, the FDA considers hip joints made of “*metal constrained cemented or*

uncemented prosthesis” to be class III [144]. Subsequently, if a device changes classes, then a new premarket submission would be required.

However, not all material changes require a new regulatory premarket submission to the FDA. Even when the change is substantial, such as the recent decision by DuPont to alter the material for their Tyvek fabric, which is extensively used for packaging in the medical device industry. DuPont successfully conducted a biological evaluation of new Tyvek for medical packaging, using testing methodologies according to ISO 10993 and the United States Pharmacopoeia [145]. DuPont submitted to the FDA an amendment to their Device Master File for both Tyvek 1073B and Tyvek 1059B. DuPont was able to show that the “*performance of the new Tyvek material is functionally equivalent to the existing Tyvek material*” [146]. DuPont was also able to demonstrate that the “*results of the testing indicate biocompatibility — even after sterilization*” [147].

The majority of regulatory submissions to the FDA are 510(k) applications, where it is crucial to determine “substantial equivalence” to a comparator device. When a company seeks an FDA approval for its medical device, then the FDA will need the manufacturer to send test data concerning the safety and effectiveness of the proposed device. The FDA will weigh the proposed product's potential risks and benefits in deciding whether to approve. In addition, consideration of the product's risks can lead the FDA to impose extra requirements concerning product warnings and cautions in the user instructions or IFU [148].

6.12 THE ROLE OF FDA INSPECTIONS ON BIOCOMPATIBILITY

Normally, the FDA does not conduct a pre-inspection of the manufacturing facilities for Class II devices when it considers a regulatory premarket submission [149]. Therefore, although a device may receive regulatory approval to sell the device in the U.S., it may still receive a warning letter after the approval because the manufacturing process does not meet FDA standards [150]. For example, “CPR Medical Devices” is a Canadian company that sells hand-held resuscitator devices. On 13 December 2011, the FDA issued a warning letter to this company for not following the FDA requirement of “*addressing the needs of the patient*” in their design inputs for their Oxylator device [151]. Specifically, the FDA inspector discussed the lack of consideration for the biocompatibility of the material that was used in their Oxylator, and the potential adverse effect on the patient’s skin.

6.13 STERILE BARRIER SYSTEMS AND BIOCOMPATIBILITY CONSIDERATIONS

ASTM F2475 provides guidance on biocompatibility testing of sterile barrier systems [152]. Normally, before the preparation of a validation protocol for a sterilized packaging system, the biocompatibility of the sterile barrier system typically has been assessed [153]. For example, one journal article described how the chemical structure of magnesium was altered when it was exposed to different types of sterilization methods, with the effect of decreasing of surface hydrophilicity of the magnesium, thereby creating a potentially “*pernicious effect on the biocompatibility of sterilized magnesium alloys*” [154].

The medical device manufacturer should consider any potential interactions between the proposed device and the packaging system in advance of investing resources aimed at validating a sterile barrier system. An important aspect of the packaging system design validation is having an understanding of the different levels of packaging that might be used. A complete packaging system may have a sterile barrier system (*e.g.*, a pouch or tray), additional levels of protective packaging (*e.g.*, carton, shelf pack), as well as the shipping container [155].

When testing, the acceptance criteria for the packaging system is the integrity of the sterile barrier system for the primary package, which is judged by strength and reliability tests. In addition, secondary and tertiary levels of packaging – which provide dispensing, labeling, and protective functions – may often be discreetly evaluated in the protocol as they contribute to the efficacy of the complete packaging system [156].

6.14 THE POTENTIAL REGULATORY CONSEQUENCES OF CHANGES TO DEVICE MATERIALS

Any substantial changes to a previously cleared device (including any reprocessing or sterilization changes) will potentially affect the chemical or physical qualities of the medical device, and should be submitted in appropriate detail for the FDA to make an independent assessment within a 510(k) application. If a company decides not to submit a new 510(k) application to the FDA because the company believes that there are no potential problems to the safety or efficacy of the device from the alteration, then the company should include this information in an internal memo-to-file.

Changes in raw material vendors or specifications could present different types or amounts of residual chemicals, which could give rise to a toxic response, even if the base material has a long record of safety in similar applications. The FDA allows for the possibility that a chemical characterization, at the raw material level, may be adequate to show comparability and eliminate the need for device-level testing. It is important to consider that some changes may result in variations in physical properties and surface characteristics of the medical device, which could have an unforeseen biological response [157]. Even the impact of surface alterations, including at the micron level, should be analyzed when the chemical changes at the surface could lead to an adverse biological reaction.

6.15 USING THE RESULTS FROM A PREVIOUS BIOCOMPATIBILITY TEST

Because the cost of some biocompatibility tests may reach US\$120,000 or more, it is important for many companies to avoid performing more biocompatibility tests than necessary. It is a fact that many devices are made of materials that have a long history of innocuous use. Therefore, it may not be necessary to test for all endpoints delineated in ISO 10993 on these types of harmless materials, but only if the manufacturing process does not raise any new biocompatibility concerns [158]. Nevertheless, if the device materials,

manufacturing processes, and intended use are not identical to a previously legally marketed device in the United States, then the FDA requires additional biocompatibility testing to be performed.

Clause 4.1 in ISO 10993 states that an “*evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the device under design*” [159]. To conclude that no additional biocompatibility testing is needed, the manufacturer should provide evidence that their proposed device’s material is exactly like the materials used by the comparator device. In addition, the company can furnish proof that the comparator device is considered to be a “worst case” example, when compared to the proposed new device. In cases where there are differences, such differences should be explained and justified.

An illustration of a “worst-case” setup would be where a patient is exposed to 100% of the chemical, or 100% of the by-product that could be produced from the device. Alternatively, a worst-case scenario could be justified based on exhaustive extraction data from chemical characterization. As part of the chemical characterization, a company would need to consider the potential where a patient might come into contact with multiple devices, to calculate an estimated worst-case patient exposure level. For example, it is not uncommon for several stents to be used on a single patient during angioplasty. An “exposure evaluation” should investigate the following: (a) local versus systemic exposure potential, (b) any degradation chemicals, (c) and the route-to-route extrapolation of dose. Lastly, data needs to be provided to the FDA that shows the total amount of chemicals to which the patient may be exposed through 30-days, or a time-period that the device would plausibly encounter during expected clinical use.

The FDA also states that “*biocompatibility testing may not be needed if the device is made of materials that have been well characterized chemically and physically in the published literature; and have a long history of safe use*” [160]. Furthermore, it is possible to use earlier biocompatibility test results if the following factors are present:

- the manufacturer provides an explicit statement regarding any differences in materials or manufacturing between the new and the previous device; and
- the manufacturer explains why any differences between the new and previous devices are not expected to impact the biocompatibility of the new device.

6.16 FDA REQUIREMENTS FOR SHELF-LIFE TESTING

For shelf-life testing, it is up to the company to designate the expected shelf life for their device (*e.g.*, 12 months). The FDA declares that in order to establish a validated shelf life for the device, then “*repeated testing using the subject device may be required*” [161]. In the case of the TIGR surgical mesh, the manufacturer wrote that they would verify the 12-month shelf life by using three batches of the subject device and were to be “*evaluated*

for stability for 12 months at 25°C [162]. Therefore, the TIGR device would need to undergo biocompatibility testing after being stored for 12-months at 25°C.

Alternatively, in a recent webinar that discussed biocompatibility, the FDA stated that they would be willing to consider “time zero” as a “worst case” for shelf-life testing in terms of biocompatibility [163]. “Time zero” denotes the start of each new product generation. The FDA gave an example of a device where the chemistry changes over time for products, such as a sealant. In those cases, a company should not conduct biocompatibility testing at the end of the shelf life. According to the FDA, manufacturers would then perform “*biocompatibility of time-zero manufactured product and then have other types of information to look at whether or not it changes over time for shelf life*” [164].

6.17 BIOCOMPATIBILITY AND STERILIZATION CHANGES THAT REQUIRE A NEW FDA SUBMISSION

When a company alters their medical device with the aim of meaningfully changing their device’s safety or effectiveness (*e.g.*, due to adverse events or recalls), then a new regulatory submission to the FDA would be required [165]. Significant changes to a medical device could include changes to the materials used to manufacture the medical device, changes to the manufacturing process (*e.g.*, annealing, passivation, electropolishing, machining, or injection molding), and changes to the sterilization process. For example, the manufacturing residuals that may be present on the modified device will initiate questions on biocompatibility by the FDA. The FDA has written many warning letters to manufacturers that discuss problems associated with biocompatibility (see Appendix A).

Changes in the method of sterilization, cleaning, or disinfection has the potential to change material or performance characteristics of a device. This applies particularly to the biocompatibility properties of polymeric materials or surface coatings. When manufacturers make changes in sterilization, cleaning, or disinfection methods, they should then consider whether the material properties or specifications of the device could be significantly affected [166]. To determine whether a change to a device’s method of sterilization, cleaning, or disinfection could significantly affect the device’s material performance, the premarket submission sponsor should consider any known information on the sterilization, cleaning, or disinfection methods. The FDA recommends that the sponsor should then ascertain if there are any novel or significantly increased risks connected with using the new method with the device’s materials of manufacture [167]. If a sponsor decides that their cleaning, disinfection, or sterilization change could significantly affect the performance or biocompatibility of the device, then a new 510(k) or PMA supplemental is most likely required [168].

6.18 EFFECTS OF STERILIZATION, CLEANING, OR DISINFECTION ON BIOCOMPATIBILITY

Sterilization, cleaning, or disinfection changes may affect the biocompatibility of a device [169]. For instance, changes to an ethylene oxide (“EO”) sterilization process may

leave increased ethylene oxide residuals on the device surface, or changes to a cleaning process may incorporate chemicals that are inappropriate for use with a patient-contacting device. Manufacturers should consider whether cleaning, disinfection, or sterilization changes could significantly affect the biocompatibility of their device [170].

Before starting any biocompatibility testing, the medical device manufacturer should analyze whether the tested device is representative of a product family [171]. A company could argue to the FDA that not all devices in a “product family” need to be tested if one “representative device” had already been previously tested [172]. Therefore, medical device manufacturers should categorize their devices into the following groups:

- The type of material that is used in making the device;
- The device shape and size;
- Types of expected soils in contact with the device;
- The number cleaning cycles (if any); and
- The number sterilization cycles (if any).

6.19 USING NEW MATERIALS

NEW

The FDA wrote that even a change to an “internal component part” of a previously 510(k) cleared device, which has no direct patient contact, would need a new 510(k) if that new component could change the structure or durability of the device [173]. For example, if there was heat applied to the new internal part, in order to join it with the part of the device that does have patient contact, then the application of heat could have changed the chemistry of the surrounding materials in the previously cleared device. The application of heat could weaken the device’s material strength. These types of unforeseeable consequences are another reason why the device sample used for the final biocompatibility testing needs to be in its final finished form (“FFF”). Therefore, if the device is supposed to be sterile or reprocessable, then it should be sterilized or reprocessed before being sent to the biocompatibility testing.

6.20 DIFFERENCES BETWEEN THE FDA-MODIFIED MATRIX AND THE ISO 10993 MATRIX

Just like ISO 10993, the new FDA guidance also includes a matrix as a framework for their recommendations on the “biological effects evaluation”, grounded on the various factors previously discussed [174]. In addition, the FDA agrees with the framework established in ISO 10993 for the classification of both the nature and duration of patient contact with the device’s material (*e.g.*, cumulative effects with repeated use).

NEW

The FDA writes in the new biocompatibility guidance that acute systemic toxicity, irritation, sub-chronic toxicity, genotoxicity, and implantation endpoints must be considered for all devices/tissue exposures, something that is not necessarily required by ISO 10993. In addition, the FDA has added a separate column for material-mediated pyrogenicity, which ISO 10993 incorporated as a subclass of acute systemic toxicity [175]. Additional

evaluations, beyond those recommended in ISO 10993, may be demanded by the FDA if either the manufacturing processes or novel materials are employed (*e.g.*, materials or processes that have not been previously used in a legally U.S.-marketed medical device with the same type and duration of contact).

The ISO 10993 standard does not stipulate either a specific method or test outcome. ISO 10993 permits the company to select various tests and methods, and does not always include an acceptance criteria. Consequently, in order to allow the FDA to evaluate conformance, the device manufacturer must give an explicit reason for the selected ISO 10993 test, as well as the principles used to determine their device's acceptance criteria.

6.21 BIOCOMPATIBILITY EVALUATION ENDPOINTS

For certain medical devices, different biological endpoints may require an evaluation using the FDA-modified matrix, including either additional or fewer endpoints than indicated by ISO 10993 [176]. If the manufacturer is unclear about which group a device falls into, then device categorization information can be obtained informally via e-mail or by contacting the appropriate FDA review branch for details [177].

For example, the FDA has previously found that devices that were used to drain fluids, such as catheters, were considered to be “externally communicating devices” instead of “surface devices” contacting mucosal membranes. In addition, reproductive and developmental toxicity should be addressed for novel materials, devices that can be used with pregnant women, and devices designed for reproductive organs. Finally, degradation information should be stipulated for any devices, device components, or materials remaining in contact with tissue.

When devices are designed to come into contact with mucosal membranes for longer than 24-hours (*e.g.*, neonatal feeding tubes), then toxicities that would not be detected with short-term assessments could occur. In this instance, the FDA recommends that implantation testing in a “clinically relevant model” with acute and sub-chronic endpoints should be performed.

Devices with incidental blood contact, which may introduce leachables, should include added biocompatibility information pertaining to an irritation endpoint. One example includes devices used in extracorporeal circuits, which the FDA requires genotoxicity testing due to the high surface area and the accompanying increased potential for chemical leaching [178]. Any potential leachables may then be introduced into the patient's circulation. For potentially pyrogenic materials, companies should conduct a separate evaluation. The FDA recommends that it may not be suitable to use data from an acute systemic toxicity or implantation study instead of a separate pyrogenicity evaluation. The FDA recommends that any pyrogenic studies should include periodic temperature measurements (*e.g.*, every 30 minutes for the first three hours) and must be conducted in an appropriate animal model, such as with rabbits [179].

Permanent devices in contact with mucosal membranes, such as hip implants, must be tested for chronic toxicity. The FDA recommends that there could be adverse biological responses associated with the long-term contact, which might not be detected with short-term assessments.

In addition, the FDA recommends that companies should conduct a carcinogenicity evaluations through a risk assessment. Including all permanent devices in contact with breached or compromised surfaces and all permanent externally-communicating and implanted devices. For example, the chemical information and data from the published literature regarding genotoxic and nongenotoxic carcinogens are useful to assess carcinogenicity.

6.22 SAMPLE PREPARATION

The FDA guidance document requires that the devices which are tested must be representative of actual production lots and must use the same design, materials, assembly, and packaging procedures [180]. For example, the FDA guidance on “Conventional and High Permeability Hemodialyzers” [181] specifies that sub-component testing is suggested because of the large surface area of the membrane module of hemodialyzers. In this case, the FDA recommends that the hemodialyzer should be filled with the appropriate solvent in accordance to the suggestions from ISO 10993-12. However, if non-membrane components are examined discretely, then the FDA permits the company to use the ISO 10993-12 recommendations for test article preparation as an alternative.

6.23 TEST REPORT REQUIREMENTS

The FDA requires that complete test reports must be provided for all tests performed. The test report should proclaim the specific acceptance criteria for every test to be considered successful. If the test approach is not in accordance with an FDA guidance document or FDA-recognized standard that includes demarcated acceptance criteria, then a justification for the proposed acceptance criteria should be provided by the manufacturer [11]. An example of acceptance criteria that the FDA has previously agreed to, according to several experts, is the following:

- No visible soil after cleaning;
- Protein rate $\leq 3 \mu\text{g}/\text{device}$ (ISO 15883-1);
- HCT rate $< 2.5 \mu\text{g}/\text{cm}^2$ (AAMI TIR 30);
- Endotoxin $\leq 2.1 \text{ EU}/\text{cm}^2$ (AAMI TIR 30); and
- Reduction of at least a 10^6 in recoverable bacteria – total aerobic bacterial count.

7.1 GENERAL

The main goal of a biocompatibility testing is the protection of patients [182]. The FDA requires that the manufacturer perform some research beforehand to gather all relevant data on each component materials of the device, as well as on similar devices with an established clinical history. Existing data may be adequate to determine the biocompatibility of either components or the entire device. Therefore, potentially avoiding the need to conduct certain biocompatibility assessments.

The number of necessary tests will also be contingent on the designated use of the device and the manner/duration in which it will be in contact with the body [183]. When preparing for a biocompatibility test, it is also important that any testing must be conducted under Good Laboratory Practice (“GLP”). GLP compliance is required for all biocompatibility test reports that are included within FDA 510(k) or PMA submissions [184].

7.2 WHAT ARE THE FDA PREREQUISITES FOR BIOCOMPATIBILITY TESTING?

The best starting point for understanding biocompatibility requirements is ISO 10993. Part 1 of the ISO 10993 standard is an overall analysis on the selection of tests. Part 2 encompasses the animal welfare requirements. Parts 3 through 19 of the ISO 10993 standard are guidelines for detailed test procedures. If either vendor or supplier data is used, then manufacturers must acquire exact duplicates of the original study reports from the source. It is critical that the laboratory, which creates the reports, have a good reputation of cGMP/GLP compliance (see section 7.6 below) and has an AAALAC accreditation or another similar animal welfare certification [185]. The FDA will only recognize test reports from laboratories that meet these requirements. It is an industry standard that manufacturers will conduct at least some confirmatory testing of their own (*e.g.*, cytotoxicity and hemocompatibility studies). Part 18 of ISO 10993 provides guidance on how to conduct a chemical characterization, which manufacturers may use to show that a device has a low overall risk of a negative biological effect. Data from the clinical trials of the proposed device or clinical experience with similar devices containing similar components/materials, can also help show that the proposed device is biologically safe.

7.3 PRE-ASSESSMENT OF DEVICE MATERIALS MINIMIZES RISK.

Many manufacturers begin their biocompatibility assessments by first conducting some inexpensive *in vitro* studies such as cytotoxicity and hemocompatibility testing [186]. Preliminary material screening tests also help to ensure that the manufacturer is not forced to redesign their device due to biocompatibility test failures. Manufacturers should take into account that some specific tests do not permit the use of amalgamated samples, such as implant studies.

7.4 TESTING MATERIALS VERSUS A COMPOSITE OF THE FINISHED DEVICE

The FDA recommends that manufacturers should gather safety data on every component and material used in a device [187]. They should conduct testing on the finished device as specified by ISO 10993 and the FDA guidance. However, if the biocompatibility results are not acceptable for an amalgamated sample, then it can be difficult to track down the specific component or material that is causing the problem [188]. Manufacturers may end up delaying their regulatory submission while they repeat testing on the individual device components. If disinfection or sterilization is required in the final finished form of the device, then it is important that all biocompatibility studies use test samples that have already been disinfected or sterilized under identical methods that will be used in the finished product [189].

7.5 CONDUCTING BIOCOMPATIBILITY TESTS

For the FDA, companies may perform material characterization and analysis of the device's components. These tests, if performed, would be carried out before any biocompatibility assessment [190]. This includes removing leachable materials from the device or components at high temperatures; the leachable extracts are then examined for any dangerous chemicals or cytotoxicity. After the *in vitro* testing has been finished, then *in vivo* testing can be started based upon the product's intended use [191]. Completion times for tests can vary from one-month to one-year, depending on the required test that is required by ISO 10993. Subchronic or chronic implantation testing can take even more time [192]. After the tests are completed, and all data has been collected, the FDA recommends that an expert interpret both the data and test results [193]. The expert can then decide on whether the existing data provides enough information to make a conclusion on the device's biocompatibility.

7.6 IS GLP REQUIRED FOR BIOCOMPATIBILITY TESTING?

The FDA requires that any study designed to assess the safety of a medical product in non-clinical models, such as biocompatibility studies for medical devices, needs to be conducted according to the Good Laboratory Practice requirements [194]. GLP includes the following items:

- Quality Assurance: independent monitoring of research processes;
- Resources: organization, personnel, facilities, and equipment;
- Characterization: test items and test systems;
- Rules: protocols, standard operating procedures (SOPs); and
- Results: final report and raw data.

a. Resources

According to 21 CFR § 58.33, the Study Director occupies a pivotal point of control for any biocompatibility study [195]. The Study Director must be aware of all events that may potentially affect both the quality and integrity of the testing [196]. This responsibility is manifested in a signed and dated “GLP Compliance Statement”, which must be included with all study reports.

b. Characterization

According to 21 CFR § 58.105, for non-clinical studies intended to evaluate safety, the FDA requires that the Study Director must have comprehensive knowledge about the test item [197]. The manufacturer’s batch records for the specific lot from which test samples are selected, can be a reliable source of data on device characterization [198].

c. Results

According to 21 CFR § 58.185, GLP study results must be analyzed by the Study Director [199]. GLP does not permit any “Out of Specification” (OOS) processes [200]. However, any confounding or contributing factors that could result in misinterpretation of study results by the FDA can be explained by the Study Director in the test report.

d. Quality Assurance

According to 21 CFR § 58.35, the FDA requires that a Quality Assurance Unit (“QAU”) must be created and charged with assuring that GLP compliance is achieved [201].

8.1 BACKGROUND

On 17 March 2015, the FDA published a final version of the guidance on “*Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*” [13]. This new guidance made several changes to what the FDA considers acceptable for reusable devices [202]. A medical device intended for reuse should be designed to ensure that it will function safely and effectively during its useful life, when it is reprocessed according to the device manufacturer’s instructions [203]. Legally, pursuant to 21 USC § 352(f), a device must have labeling that bears adequate directions for use for the device operators [204].

NEW

Manufacturers of reusable medical devices must demonstrate that their product instructions of reusability are sufficient for the cleaning, disinfection, testing, repackaging, and aeration for the device, as applicable. Labeling instructions for reuse require validation of the recommended cleaning/disinfection or cleaning/sterilization instructions. The FDA assigns the responsibility on both developing and validating the methods for effective reprocessing of reusable medical devices on the manufacturer (see Appendix B). Manufacturers must also prove that any stated disinfection or sterilization recommendations are effective for their device [205].

8.2 THE PROPER HANDLING PROCEDURES FOR THE REPROCESSING OF REUSABLE MEDICAL DEVICES

Medical workers who work with reusable devices are often unable to correctly evaluate the quantity of microbial contamination on a reusable device [206]. Therefore, it is important that the product labeling, professional practices, and institutional infection control procedures help guide the people who are responsible for reprocessing devices. According to the FDA, the proper handling procedures for the reprocessing of reusable medical devices is done by carefully adhering to the steps described below [207]:

- a) Protective covers are discarded.
- b) Reusable devices are segregated from waste. The devices are wiped clean of visible soil, and kept moist.
- c) The soiled devices are then placed in a container and transported to a dedicated cleaning work area.
- d) The devices are then disassembled to facilitate cleaning and subsequent microbicidal steps.
- e) Thorough cleaning with an FDA-cleared compatible detergent and rinsing to remove unsafe residues. During this cleaning process, the user can use enzyme cleaners, ultrasound baths, and brushes.

- f) If the user is cleaning a non-critical device that is unlikely to be soiled from body fluids or a source of cross-transmission, then the thoroughly cleaned device may be returned to service.
- g) Otherwise, the device should be sent for final processing with a terminal microbicidal process (*e.g.*, either disinfection or sterilization).
- h) For low-level or intermediate disinfection for non-critical reusable devices, the user should follow the instructions of the disinfectant and the label-recommended contact time.
- i) For high-level disinfection, the devices should be treated using a validated high-level disinfection method, which is device-specific. The devices should then be rinsed to remove any chemical residues and dried before storage.
- j) For terminal sterilization, the validated sterilization instructions must be followed. When the terminal process is completed, then the devices may be returned to service.

For example, the “Fujifilm Corporation” received a warning letter from FDA inspectors because their reprocessing validation for their duodenoscope did not include an evaluation on the effects of reprocessing of their device’s O-ring [208]. Fujifilm only “*conducted one full cycle run of ethylene oxide (EO) sterilization for validation, but did not justify how one full run is indicative of the process being consistent and reproducible*” [209]. Therefore, Fujifilm’s action was unacceptable because the FDA requires that all reprocessing instructions must be validated under 21 CFR § 820.30(g), and performing a validation test with only “one full cycle run” was not considered adequate by the FDA [210].

In addition, a medical device should be designed in a way that healthcare personnel can both fastidiously clean and successfully disinfect or sterilize the device, throughout the device’s designated use life [211]. If a company does not properly validate their reprocessing method, then the FDA is likely to send them a warning letter. For example, “Eminent Spine LLC” received a warning letter in 2010 because they had not validated the cleaning procedure from their instructions to ensure that the cleaning procedure effectively removes body fluids and tissue debris [212]. Eminent Spine LLC told the FDA that their new validation testing would include the surgical instruments, which are considered to be the worst-case because they are the most difficult to clean [213].

8.3 FDA REGULATORY OVERVIEW OF THE REPROCESSING PROCESS

The FDA describes reprocessing as being “*validated processes used to render a medical device, which has been previously used or contaminated, fit for a subsequent single use*” [13]. Device reprocessing is designed to remove soil and contaminants by initial

cleaning. Disinfection or sterilization aims to inactivate any remaining microbes. The reprocessing of reusable devices involves the following three sequential steps [214]:

- Point of Use: This includes immediate cleaning steps and measures to prevent the drying of soil and contaminants inside and on the device.
- Thorough Cleaning: After the point-of-use processing, the soiled or contaminated device should be taken to a specially reserved cleaning area.
- Disinfection or Sterilization: The manufacturer must recommend whether the device should be disinfected or sterilized.

Cleaning, disinfection, and sterilization are distinctly different parts of the reprocessing process [215]. For example, the definition of cleaning for the FDA is “*the physical removal of soil and contaminants*” [13]. Furthermore, the process and chemical agents used for cleaning should be designed to effectually remove both soil and contamination. Specifically, effective cleaning should include the following:

- minimize any potential soil transference from one patient to another;
- thwart the accumulation of residual soil throughout the product’s expected use life;
- permit subsequent disinfection/sterilization steps, if required.

Unlike cleaning, both disinfection and sterilization processes are intended to kill microbes. Therefore, the methods and agents employed for both disinfection and sterilization should be designed to achieve microbicidal effects. The cleaning process should be validated separately from either the disinfection or sterilization steps. Nevertheless, it is still standard practice in the medical device industry to omit a disinfection validation test when the manufacturer has already successfully conducted a cleaning validation. Many companies incorrectly assume that a successful validation of the cleaning process is enough to prove that the disinfection process would also be validated. However, this reasoning is incorrect because of the clear differences between cleaning and disinfection. Importantly, manufacturers are required to only use cleaning and disinfection chemical agents that have been previously cleared by the FDA. Therefore, the chemical manufacturer is responsible for supplying evidence of the efficacy of its solutions, and not the medical device manufacturer.

Lastly, the FDA recommends that manufacturers should consider alternative medical device designs to facilitate effective reprocessing. For example, manufacturers should replace features that are challenging to reprocess with the following improvements:

- single-use parts (in order to avoid reprocessing altogether);
- include flush ports and
- specify any dedicated cleaning accessories.

8.4 THE OLYMPUS DUODENOSCOPE REPROCESSING SCANDAL AND ITS REGULATORY CONSEQUENCES

In early 2015, an FDA-related scandal became important news in the United States that involved outbreaks of infections at several U.S. hospitals [216]. At least 40 people at U.S. hospitals have died since 2012 after suffering infections from contaminated duodenoscopes that were sold by Olympus Corp [217]. A congressional investigation concluded that Olympus knew of two independent laboratory reports that found their closed-channel model duodenoscope could shelter and spread microbes, even after following the suggested reprocessing instructions from Olympus [218]. After more than 25 infections from their duodenoscopes were registered in both Dutch and French medical facilities, Olympus alerted their European customers in January 2013 that their duodenoscope could become contaminated [219]. At the same time, Olympus told their U.S. executives not to issue a similar warning to American hospitals about the potentially fatal infections from their defective duodenoscopes. In one internal company e-mail from 31 January 2013 that was made by Ms. Laura Storms, a vice-president of regulatory affairs for Olympus, she asked a question to her managers on whether the U.S. subsidiary of Olympus “*should also be communicating to our users the information that [Olympus Europe] is communicating to their European users?*” [220]. These secret internal e-mails were shown to the public because of the lawsuits against Olympus in the United States.

In response to Ms. Storms’ question, Mr. Susumu Nishina, the company’s chief manager for quality in Tokyo, wrote on 6 February 2013 an e-mail reply that there is no “*need to communicate to all the users actively*”, when an internal Olympus assessment of the risk to patients found it to be “*acceptable*” [221]. Many of the Olympus executives involved in this matter are now under criminal investigation in the United States or are awaiting extradition from Japan [222].

Olympus is the manufacturer of 85% of the duodenoscopes used in the United States. Nevertheless, Olympus never brought this information to the FDA and did not alert any American hospitals, physicians, or patients about the risk of infection until February 2015. Additionally, although at least a dozen separate American hospitals traced antibiotic-resistant infections directly to duodenoscopes, these hospitals did not notify the FDA about these infections even though they are legally obligated to do so [223]. In fact, not a single American hospital, which experienced the duodenoscope infection outbreaks, sent the required adverse event forms to either the FDA or the duodenoscope manufacturers [224].

Therefore, the FDA was incapable of comprehending the frequency and severity of the duodenoscope infection outbreaks until it was too late [225]. Eventually, Olympus agreed to “*revamp an internal mechanism inside the reusable device that had been almost impossible to disinfect before being used in the next patient*” [226]. After the infection outbreak from the unprocessable duodenoscopes, the FDA cautioned that the microscopic fissures inside the Olympus instruments could still retain “*residual body fluids and organic debris*”, even after reprocessing [227]. This breakdown in the FDA’s device safety reporting system, to rapidly identify the duodenoscope antibiotic-resistant infections and superbug

infections, has become a wakeup call for the U.S. Congress. Without a comprehensive post-market device surveillance system, future medical device failures are likely to go unobserved, with life-threatening consequences [228].

The FDA also found that many hospitals only had a single duodenoscope in their facilities due to the prohibitive costs per duodenoscope device (e.g., >US\$45,000). Subsequently, the hospitals could not alternate between different duodenoscopes, which would have been necessary to keep up with the recommended sterilization standards. The time spent reprocessing the duodenoscope after using it during a procedure was time that the hospital could not perform another endoscopic retrograde cholangiopancreatography (“ERCP”) procedure on a different patient.

In 2015, the FDA was severely criticized by the U.S. Congress because of duodenoscope devices linked to drug-resistant bacteria outbreaks at U.S. hospitals. Many U.S. Senators believed that the FDA “*failed to recognize the prevalence of duodenoscope-linked infections and respond quickly*” [229]. The FDA began investigating the problematic duodenoscopes in September 2013, after reports of infections surfaced, but “*wasted valuable time*” according to the U.S. Congress in getting necessary data from Olympus, Pentax, and Fujifilm on whether they could prove that their devices could be adequately reprocessed. Unsatisfactorily to the U.S. Congress, the FDA did not warn any U.S. hospitals about the issue until after a “superbug” outbreak occurred at the UCLA's Medical Center in Los Angeles, California in February 2015 [230].

NEW

The problems related to the duodenoscope scandal from 2013 to 2015, partially forced the FDA to finalize its guidance for reprocessing in March 2015 [231]. The guidance was first published as a draft version in 2011. In 2016, a new law was passed in the U.S. called the “21st Century Cures Act” [232]. Section 3059(a) of this new law required the FDA to publish a list of reusable devices where any premarket submission must include validated instructions for use. In addition, the manufacturer must produce validation data for the cleaning, disinfection, or sterilization (as applicable) of the device. It is clear that the recent duodenoscope led to this new legal provision [233]. The FDA had already been focusing on this area, but this law solidifies the extra requirements on manufacturers on reprocessing questions. In addition, section 3059(b) of the 21st Century Cures Act also requires that the FDA must publish a final version of their guidance on class II device modifications and 510(k) submissions.

8.5 WHAT HAPPENS IF THE METHOD OF REPROCESSING IS CHANGED

The design process of a reprocessible medical device should focus on the intended functions of the device [234]. The function of the medical device is affected by the ability and training of the person who uses it, how the device works, what it does, where it is used, and the reason why it is used [235]. It is also important to review any changes made to a previously cleared device [236]. For example, Olympus made significant changes to its

duodenoscope device, which was previously cleared by the FDA, without first notifying the FDA of their changes by submitting a new regulatory submission [237].

Olympus had a duodenoscope that was marketed under the name “TJF-Q160V” that was cleared by the FDA in 2008 [238]. With this duodenoscope, the elevator wires were exposed and could be directly cleaned and subjected to high-level disinfection or sterilization [239]. However, Olympus made an update to their “TJF-Q160” and sealed the elevator channel. This updated version of the device was called “TJF-Q180V”, and Olympus decided that they could

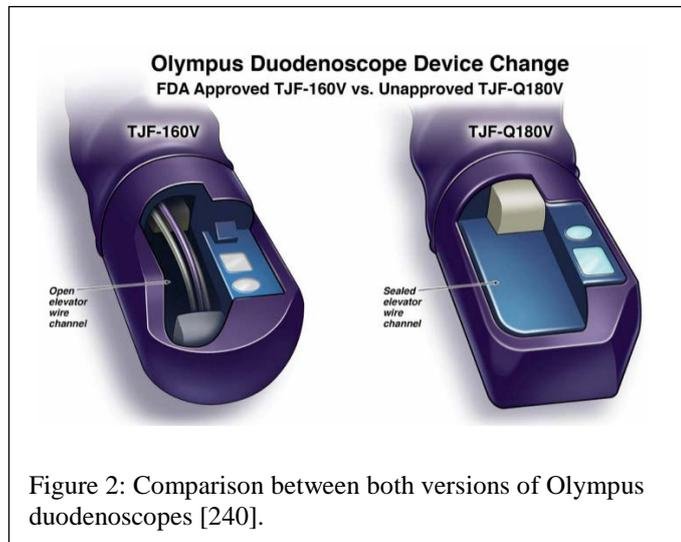


Figure 2: Comparison between both versions of Olympus duodenoscopes [240].

sell it in the U.S. with only a memo-to-file (see also sections 3 and 6.11 above), instead of a new 510(k) regulatory submission. Olympus even updated the instructions for use by stating that “*the elevator wire channel of the TJF-Q180 is sealed and does not require reprocessing*” [240]. However, the “sealed” channel turned out to not be impenetrable and eventually allowed microbes to live inside the channel.

The decision on when to file a new 510(k) submission for a change to an existing device that was previously cleared by the FDA is governed by the FDA guidance document K97-1 [241]. With K97-1, manufacturers only need to submit a new 510(k) when a modification could appreciably affect the device as stated in 21 CFR § 807.81(a)(3). However, many companies have abused K97-1 by claiming that almost any change that they make to a previously approved device should only be considered to be “insignificant” change, and does not require a new 510(k) or PMA submission to the FDA [242].

In March 2014, Olympus was informed by the FDA that they must submit a new 510(k) submission for their “sealed” elevator channel duodenoscope, which had never been specifically cleared for marketing in the U.S. by the FDA [243]. The FDA stated that the design changes that Olympus made to their original “TJF-Q160” model, resulted in a “closed” elevator channel instead of the “open” elevator channel, which was the original design of the device that the FDA had actually cleared. The FDA had decided that the changes that Olympus made to the original version of the duodenoscope device were actually “*significant and impacted the safe use of the device*” [244]. Olympus consequently submitted a new 510(k) for their modified “TJF-Q180V” duodenoscope [245].

8.6 DEVICES THAT MUST VALIDATE THEIR REPROCESSING METHODS

NEW

Under 21 USC § 352(f), a device must have labeling that bears adequate directions for use [246]. In order to guarantee that a reusable device is ready for its next patient, it is critical that the manufacturer's reprocessing instructions are thoroughly validated, and that licensed practitioners can use the device safely [247]. This is especially important because there has been a steady progression towards product designs that are much more problematic to successfully reprocess. The FDA has identified a group of medical devices that present an increased threat of microbial transmission and a prohibitive risk of infection if they are not effectively reprocessed [248]. The devices identified by the FDA that belong to this subset are listed in Appendix D of this master's thesis. The FDA has based their classification on the information garnered through device recalls, medical device reports, infection occurrences, published literature, and manufacturer-initiated surveillance studies [249].

Although FDA guidances are not normally legally binding, the FDA is legally bound to require companies to perform reprocessing validation tests on the list of devices described in Appendix D [250]. Nevertheless, many experts agree that companies should always try to comply with the FDA guidance that regulates their specific device because it is almost impossible to show any scientifically proven alternative to an FDA guidance. [251]. In principle, manufacturers do not have to follow such recommendations as found in FDA guidances because they are not binding. However, the consequences of not following an FDA guidance can be problematic and more burdensome than just following the guidance [252].

8.7 FACTORS TO CONSIDER WHEN PERFORMING VALIDATION TESTING ON REUSABLE DEVICES

NEW

It is important to note that any validation tests must be conducted using FDA-cleared equipment, such as any sterilizers or sterilization accessories (*e.g.*, biological indicators, physical/chemical sterilization process indicators, sterilization wraps) [253]. The new reprocessing guidance provides general considerations for reprocessing instructions in the device labeling. The guidance specifically discusses that companies should consider reprocessing challenges early in the design process, especially with devices that have parts that are difficult to reprocess, such as "elevator channels" and "shaft-within-lumen configurations".

The FDA guidance also describes what documentation will be required from manufacturers in their 510(k) application to demonstrate the validation of the reprocessing process. This guidance applies to those devices that are intended to be reprocessed in hospitals before being reused in either the same or different patients [254]. However, this new reprocessing guidance does not apply to the reprocessing of single-use devices, which is controlled by a separate FDA guidance from 2000 with the title of "*Reprocessing and Reuse of Single-Use Devices*" [255]. Similarly, the new reprocessing guidance does not

apply to any processes intending to remove or inactivate “transmissible spongiform encephalopathy” agents because the FDA has not approved or cleared any medical devices for this specific intended use [256].

8.8 ACCEPTABLE REPROCESSING CRITERIA FOR THE FDA

The FDA has written many device-specific reprocessing guidances that apply to different types of devices, such as the “Guidance Document For Washers And Washer-Disinfectors Intended For Processing Reusable Medical Devices” [257]. Therefore, it is important for each manufacturer to look for any FDA guidances that may apply to their exact device, because the FDA may have special requirements for different types of devices. All FDA guidances can be accessed by searching the FDA’s Guidance Document Database, which is available online [258].

In addition to the official FDA guidance on reprocessing medical devices, there are also several standards published by various standards developing organizations (“SDO”) that the FDA believes is “*helpful when developing labeling instructions for reusable medical devices*” [12]. These standards complement the FDA reprocessing guidance by going into much greater detail on various methods and procedures on reprocessible devices. It is important to use the FDA-recognized test methods available from these SDOs. A searchable database of FDA recognized consensus standards can be found on the FDA website as well [259]. For example, in the new reprocessing guidance, the FDA states that “*Technical Information Reports (TIRs) developed by the Association for the Advancement of Medical Instrumentation (AAMI) provide technical information for manufacturers and users*” [12]. These TIRs include the following:

- AAMI TIR 12 – A guide to designing, testing, and labeling reusable medical devices for reprocessing in healthcare settings.
- AAMI TIR 30 – A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices.

In addition to TIRs, the following standards are also recommended by the FDA for reprocessible devices:

- ANSI/AAMI ST79 – Offers comprehensive instructions on steam sterilization and sterility assurance in healthcare facilities.
- AAMI/ANSI ST81 – Offers the information requirements that the manufacturer of the reusable medical device must provide to ensure the device maintains its performance specifications.

Lastly, the FDA also works closely with the Centers for Disease Control (“CDC”) on the topic of reprocessible medical devices, although the CDC is not a regulatory agency. For example, the FDA issued a joint “Safety Communication” with the CDC in 2009 that

cautioned hospitals about the hazards to patients if endoscopes are not correctly cleaned and recommended steps to reduce these risks [260]. Consequently, the FDA recommends in its new reprocessing guidance document that medical device companies should follow any relevant guidelines or recommendations from certain professional organizations, such as the CDC [261]. Specifically, the CDC publishes an important document called the “*Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008*” that deals with various topics on reprocessible devices [262].

Nevertheless, clinical practice procedures do not always consider or correctly address all FDA regulatory requirements. For example, some professional organizations may recommend using disinfectants in ways that may not necessarily comply with FDA regulations. Importantly, compliance with the applicable FDA regulations is required for all medical devices in the United States and have legal precedence over any other type of recommendations from third-parties.

Whenever a manufacturer attempts to validate their device’s reprocessing instructions using the FDA guidance and an FDA-recognized standard or guideline, whenever the initial validation test results are a failure by being outside of the device’s specifications, then it is important that any unsuccessful test must be recorded by the company and not deleted. For example, “GeoTec, Incorporated” received a warning letter from FDA inspectors when one of their electrode lots failed an initial internal validation test, and were subsequently retested by the company [263]. However, the FDA noted that the documentation of the rework was not recorded in the GeoTec’s device history file, even though it should have been contemporaneously recorded.

8.9 FOCUS ON LABELING COMPREHENSION

The 2015 reprocessing FDA guidance provides detailed information on the required user instructions. However, the guidance clarifies that the device users must be able to comprehend the instructions. The FDA guidance proposes that manufacturers consider using the final version of the reprocessing instructions in any usability testing. The FDA requires usability testing to be conducted on the reprocessing instructions.

The manufacturer should perform a usability study with the same type of expected users (e.g., doctors, nurses, or hospital cleaning staff) who will be performing the recommended reprocessing steps of the device. The manufacturer should then ask for user comments regarding the instructions for use [264]. The FDA recommends that manufacturers should not use their own employees for usability testing due to potential bias.

8.10 USABILITY AND MEDICAL DEVICE REPROCESSING

The FDA has found that many problems in reprocessing have a root-cause in the lack of sufficient usability testing. Many companies simply publish their reprocessing recommendations without testing the instructions in “real-world” conditions [265].

Subsequently, the FDA recommends that all medical device companies with reprocessable devices must comply with both IEC 62366 and ANSI/AAMI HE75 [266]. The FDA has also published several guidances that focus on “Human Factors” engineering, which all medical device manufacturers need to follow [267]. In order to improve overall usability, manufacturers should develop uniform reprocessing instructions for their product families, and not have separate instructions for every version of their respective devices. Especially when many hospitals and medical centers purchase the same type of device from the identical manufacturer, in order to make training more consistent for their staff. Companies must do their best to learn about any post-marketing usability problems on the reprocessing of their device [268]. The principal situations where errors in usability would negatively affect the reprocessing process would include the following:

- Actions requiring substantial dexterity or strength;
- Actions that require good visual acuity; or
- Actions that are not standard practice at that medical facility.

On many occasions, information on the potential usability issues for many types of devices may be found by reviewing the following sources of information [269]:

- The company’s internal user complaint files;
- Published literature;
- The FDA’s medical device reporting system (for adverse reports); and
- FDA safety alerts and other public health notifications.

8.11 HOW TO CONDUCT USABILITY TESTING

The FDA requires that companies need to validate their reprocessing instructions to ensure that the device operators will be able to successfully understand the instructions [13]. This type of usability testing needs to include the following five features [270]:

1. The usability study participants should be representative of the professional staff that would perform these actual reprocessing procedures. For example, if users would be wearing “personal protective equipment”, then the validation study participants should wear the same protective equipment as well.
2. Test members must use the final version of the device instructions to perform an actual reprocessing procedure. Additionally, usability test participants may verbally describe what they would prefer to do, as they read the instructions.
3. If the “medical facility environment” might potentially affect the use of the instructions and reprocessing of the device, then these environmental attributes should be copied in the study (*e.g.*, not having specialized cleaning equipment).
4. The manufacturer must judge the participants’ adherence to the instructions and identify the nature of any user errors or problems that occur. They may wish to visually and audibly record the testing session for later analysis.

5. After the test members have finished obeying the instructions, the company must inquire whether the participants had problems in successfully performing the reprocessing, and allow the participants to independently describe their experience. The manufacturer should also provide a written questionnaire that the participants can fill out, these questionnaires should be included in the “usability report” that is included in the 510(k) or PMA submission. The company should ask specifically about any errors, problems, or hesitations that were observed by the participant during the testing. The participants should furnish their opinion regarding any phrasing or wording in the instructions that they found perplexing, ambiguous, or inadequate. The company should record the participants' responses and comments. If the manufacturer makes significant changes to the instructions or reprocessing method after the usability testing, then they should revalidate the altered instructions for use or reprocessing method in a new usability test [13].

8.12 HOW TO VALIDATE THE METHOD OF REPROCESSING

The new FDA reprocessing guidance provides numerous recommendations for manufacturers to follow when validating their reprocessing methodology. For example, (a) cleaning must be validated under “worst case” situations, (b) artificial soils should be clinically important, (c) and any reprocessing must use the weakest dilutions, shortest time, and lowest temperature [13]. The FDA reprocessing guidance serves as a resource for drafting reprocessing validation protocols to ensure that all factors have been appropriately considered by medical device companies. For example, the FDA recommends that all manufacturers of reusable devices should conduct their reprocessing validation studies under certain parts of ISO 17664 “*sterilization of medical devices – information to be provided by the manufacturer for the processing of resterilizable medical devices*” [271]. ISO 17664 provides recommendations on the development of reprocessing instructions so that the device can be reprocessed safely in real-world practice, even for non-sterile devices.

8.13 CLEANING VALIDATION

Cleaning is the first step in reprocessing reusable medical devices. The FDA divides the various cleaning methods into two categories: manual and mechanical/automated [272]. When performing cleaning validation tests, the efficacy of the cleaning instructions should be based on the assessment of required cleanliness and allowable residual levels. The biological residues, total organic carbon levels, and cytotoxicity testing should be utilized to compute the expected chemical detergent residues. The manufacturer must evaluate the lessening of the residues from soils and chemical reagents, after the cleaning process.

1. Manual Cleaning - The FDA recommends this method for delicate or complex medical devices (*e.g.*, flexible endoscopes, air powered drills, microsurgical devices, and lensed instruments).
2. Mechanical (automated) Cleaning – This method of removing soiling and microbes through an automatic cleaning and rinsing process utilizes thermal disinfection processes or chemical disinfectant rinses.
3. Ultrasonic Cleaning Methods – This provides the most efficient way of removing soil from some medical devices. Ultrasonic technology uses sound waves in a liquid as a cleaning method, in a process known as “cavitation” [273]. The sound waves in the liquid produce bubbles that burst on contact with surfaces, which then removes soil from the device’s surface. This cleaning method is especially useful to remove soil from hard-to-reach joints, crevices, or internal lumens. Because instruments may still be contaminated with patient debris like blood or stool after manual brushing, many reprocessing guidelines recommend using an ultrasonic cleaning to remove fine debris that could otherwise be inaccessible and remain on the instrument.

Companies can measure the presence of bacteria, proteins, lipids, carbohydrates, hemoglobin, or endotoxins by using one of the following FDA recommended methods:

- *In-situ* method;
- Indirect sample elution;
- Viable bioburden assessments;
- Total organic carbon; or
- Protein, Hemoglobin tests.

Disinfection may be performed by manually soaking a device in a container with a liquid chemical germicide solution that is regulated by either the FDA or EPA, or it can be accomplished by using automated equipment such as washer-disinfectors [274]. The most frequently used chemical disinfectants contain chemical agents such as hydrogen peroxide, chlorine compounds, quaternary ammonium compounds, phenols, ortho-phthalaldehyde, or glutaraldehyde.

8.14 WHAT IS CONSIDERED TO BE A “WORST-CASE” CONDITION

The FDA believes that any reprocessing method must be validated under “worst-case” conditions [275]. Furthermore, the FDA recommends the use of AAMI TIR 30 in the framework of a cleaning validation as the first step of reprocessing. AAMI TIR 30 includes a list of test methods and acceptance criteria for reusable devices [13]. The cleaning validation protocols should specify predetermined cleaning test end-points. The medical device manufacturer must designate the most challenging locations on the proposed device that can be adequately cleaned during routine processing.

a. Artificial soil

The FDA recommends that the artificial soil (*e.g.*, simulated blood and mucus) chosen for the validation testing should permit at least two clinically relevant soil components to be quantified for validation testing (*e.g.*, “total organic carbon” and protein levels) [276]. It is also important that the artificial soil should be formulated to be the worst-case for the device’s intended use.

b. Inoculation sites

The FDA recommends using artificial soil to inoculate the proposed device in all patient contacting locations, including all locations that are potentially problematic to clean [277]. If the device includes any functional procedures such as articulations, flexures, and manipulations – then the validation testing should be conducted under worst-case conditions that include those functional procedures. Lastly, if it is likely that after the device is used on a patient, that the soil might be allowed to dry by the user, then the validation testing should allow soils to dry out (*e.g.*, longest expected duration). Therefore, many companies allow the soil on the device to dry for at least 24-hours during the validation test, with the intention to make the cleaning much more difficult.

c. Simulated use environment

Devices at risk of the accretion of soil with repetitive use should be tested under those simulated use conditions. Any validation studies for the FDA should use devices that have undergone simulated use. The manufacturer’s validation studies should incorporate multiple full use cycles and should be designed to assess the accumulation of soil over time. The number of simulated use cycles that the manufacturer uses should be scientifically justified [278]. Manufacturers should also conduct all functional procedures for which the device is designed, in order to soil the device in a manner that characterizes the worst-case conditions. However, due to the complexity of creating a cleaning protocol that the FDA will agree to, many companies hire a consultant to assist in creating a validation test protocol. Some of the most popular consultants include NAMSA, XuHi, Nelson Labs, UL-MDT, Pacific BioLabs, and ToxiCon.

d. Examples of worst-case conditions

- If the instructions propose a 5 to 15-minute pre-soak, then the validation protocols should specify 5 minutes for the pre-soak time.
- If the instructions suggest manually clean at $35^{\circ}\text{C} \pm 3^{\circ}\text{C}$, then the validation protocols should be set at 32°C .
- In general, “worst-case” implies shortest times and lowest allowable temperatures. However, for enzymatic detergents, the lowest temperature must be based on the recommended temperature for the enzymatic detergent.

- If the device’s process validation uses automated medical washers, washer disinfectors, or ultrasonic cleaners – then the worst-case would include both the highest and lowest settings for the recommended cleaning equipment.
- If a device consists of lumens, ports, or channels that must be flushed during cleaning, then the validation testing should include the formal flushing specifications such as the recommended flush time, flush volume, flow rate, and the number of repetitions (*e.g.*, 5 mL flush, performed three times).

8.15 DISINFECTION

Both the FDA and CDC define disinfection as “*a process that eliminates many or all pathogenic microorganisms, except bacterial spores, on inanimate objects*” [279]. Disinfection procedures are not designed to guarantee the same level of safety as sterilization processes for reusable devices. The FDA advises that the manufacturer must validate their disinfection procedures and instructions. For bioburden limits, companies can utilize information from ISO 11737 (“*sterilization of medical devices -- microbiological methods -- part 1: determination of a population of microorganisms on products*”) and ISO 14644 (“*cleanrooms and associated controlled environments*”), which provide information on bioburden limits for medical devices, components, raw materials, and packaging [280]. Importantly, the lethality of the disinfection process may vary, depending on the nature of the disinfectant that leads to the following subcategories.

- High-Level Disinfection – A lethal process utilizing a sterilant, under less than sterilizing conditions. The process kills all forms of microbial life, except for some bacterial spores.
- Intermediate Level Disinfection – A lethal process using an agent that kills viruses, mycobacteria, fungi, and vegetative bacteria. But does not eliminate bacterial spores.
- Low-Level Disinfection – A lethal process using an agent that kills vegetative forms of bacteria, some fungi, and lipid viruses.

a. Manual disinfection

A successful cleaning validation ensures that appropriate cleaning is achieved according to the normative and internal requirements by first wetting the entire instrument with a cleaning solution. Consequently, it is important that the instrument can be completely soaked with the disinfection agent applied manually [281]. If the cleaning validation has proven wettability, then the efficacy validation with the disinfectant that was conducted by the disinfectant supplier can be used as evidence by the manufacturer to the FDA.

b. Automated, thermal disinfection

Manufacturers should use ISO 15883 to develop their device instructions for automated disinfectors [282]. ISO 15883 stipulates that the “A0 value” for washer-

disinfectors has to be maintained. The A0 concept gives parametric control on the thermal disinfection cycle and its relationship to the inactivation of microbes through moist heat. An “A0 value” of 3.000 is recommended for programs used to process surgical instruments [283]. A0 = 3.000 can be achieved with a disinfectant application time of 5-minutes at a temperature of 90°C. Consequently, the thermal disinfection process with an application time of 5-minutes at 93°C ensures an adequate disinfection. Entire wettability of the surface is also assured during the process step of thermal disinfection, as proven for the cleaning process validation.

c. Automated, chemical disinfection

A successful cleaning validation ensures that appropriate cleaning is achieved according to the device’s requirements, by saturating the entire instrument with a cleaning solution. If the cleaning validation has proven wettability, then the efficacy validation with the disinfectant conducted by the chemical supplier is transferable for the disinfection process [284]. It is important to note that the FDA does not recognize any medical devices that can be reprocessed when contaminated with transmissible spongiform encephalopathy. Therefore, processes regarding the removal or inactivation of TSE agents such as prions from contaminated medical devices, are not part of the new FDA reprocessing guidance.

8.16 STERILIZATION

ISO 11737-2 defines a sterile medical device as being one that is free from viable micro-organisms [285]. If a reusable medical device must be sterilized before use, then the FDA recommends that the company must validate that the sterilization method does not negatively affect the reusable device. This is to ensure that any proposed sterilizable device is compatible with FDA-cleared sterilization equipment, and the sterilization instructions are technically feasible for implementation by users. For reusable devices that are intended to be used as sterile instruments, labeling should include a sterilization process that has been validated to attain a sterility assurance level (“SAL”) of 10^6 (or 10^3 for devices that only contact intact skin) [15]. Although, the EU solely permits a SAL of 10^6 for all types of human contact. Medical device companies that require sterilization as a final step to reprocess their device, must follow ISO-11138 (“*sterilization of health care products – biological indicators*”), which specifies performance requirements for biological indicators [286]. It is an industry practice to manufacture, package, and label a device as supposedly “sterile” at one manufacturing facility, and then ship the device to a contract sterilizer in order to genuinely sterilize the device [287].

The most commonly used sterilization methods in healthcare facilities are described below:

8.16.1 FLASH STERILIZATION

“Flash” steam sterilization was originally defined as sterilization of an unwrapped object at 132°C for 3 minutes at 12 kg in a gravity displacement sterilizer [288]. The FDA recognizes flash sterilization as a commonly used method of sterilization [15]. At present, the mandatory time for flash sterilization is contingent on the type of sterilizer, as well as the kind of device being sterilized (*i.e.*, porous vs. non-porous items) [289]. Many manufacturers have a preference for the wrapped method of sterilization [290].

Experts classify flash sterilization as a modification of conventional steam sterilization, which allows for rapid penetration of steam [291]. Generally, flash sterilization has not been considered to be a common sterilization method because of: (a) the lack of rapid biological indicators to measure the performance, (b) the absence of protective packaging ensuring sterilization, (c) the chance for adulteration of processed items during the movement to the operating room and, (d) the sterilization cycle parameters are negligible (*i.e.*, time, temperature, pressure).

To reduce these concerns, many hospitals have done the following:

- placed flash sterilization equipment nearer to operating rooms to simplify aseptic delivery;
- extend the contact time to confirm microbial lethality (*e.g.*, 4 minutes at 132°C);
- used biological indicators that provide results in a single hour; and
- utilized protective packaging that permits steam penetration.

Many reusable sterilization container systems have been designed and validated for use with flash cycles [292]. However, it is a fact that when sterile items are left in the open to the air, they will eventually become contaminated. Therefore, the longer a sterile item is exposed to air, the greater the number of microbes that will settle on it. For example, there have been several adverse events that were associated with flash sterilization. In one case, the hospital found that several craniotomy infections originated from plate implants that were incorrectly flash sterilized. It is also important for the staff to wear heat-protective gloves in order to prevent burns. Patient injuries may be avoided by either air-cooling the instruments or by the immersion of the device in a sterile liquid.

Flash sterilization is often used to process patient-care items that cannot be packaged, sterilized, and stored before use. Flash sterilization is not designed as a substitute to buying additional instruments or to conserve time. Furthermore, the FDA does not recommend flash sterilization for implants [15]. Nevertheless, flash sterilization may be obligatory for particular types of devices such as plates and orthopedic screws [293]. If flash sterilization of an implant is required, then detailed record keeping is essential (*i.e.*, load identification and biological indicator result). The record keeping will also assist in tracking any potential surgical site infections. With this data, the hospital could assess the reliability of their sterilization process [294].

8.16.2 STEAM STERILIZATION

ANSI/AAMI ST79 provides a comprehensive guide to steam sterilization and sterility assurance in healthcare facilities. Steam sterilization is both the most widely used method and the most dependable sterilization procedure [295]. Steam sterilization is non-toxic, inexpensive, rapidly microbicidal, sporicidal, and quickly heats & penetrates fabrics [296]. Sterilization is attained by exposing the device to saturated steam at elevated temperatures (*i.e.*, 121°C to 134°C) [297]. Devices are placed in an autoclave and heated through pressurized steam to kill all microbes. Normally, companies select an exposure time of steam for their device between 3 to 15 minutes.

Nevertheless, steam sterilization can cause corrosion or combustion of lubricants with dental handpieces, as well as a reduction in light transmission in laryngoscopes. In addition, steam sterilization is not appropriate for many materials due to the high temperatures [298]. Sterilized packages must be permitted to dry before being taken out of the autoclave to reduce the risk of contamination. Once a sterilized device is removed, then it has to be allowed to cool down to the surrounding normal air temperature [299]. The goal of steam sterilization is to subject each device or component to direct steam contact, at the necessary temperature & pressure, for the manufacturer's stated time.

There are four parameters of steam sterilization:

- Steam – The preferred steam for sterilization is “dry saturated steam” and entrained water (*i.e.*, dryness fraction $\geq 97\%$).
- Pressure – Is used to reach the necessary high temperatures to neutralize microbes rapidly.
- Temperature – The two most frequent temperatures are 121°C and 132°C. High temperatures are needed to guarantee microbicidal activity.
- Time – The most common time period is 30-minutes at 121°C within a gravity displacement sterilizer. Alternatively, 4 minutes at 132°C within a pre-vacuum sterilizer.

The steam flush-pressure pulsing process withdraws air quickly by repeatedly oscillating between a “pressure pulse” and a “steam flush” at high pressure [300]. Characteristic sterilization settings are 132°C to 135°C, with an exposure time of 4 minutes for porous loads and instruments. For successful sterilization, it is important that the steam envelop all of the device's surfaces [301]. To safeguard ideal conditions, many autoclaves include a display that shows both the internal temperature and pressure levels. Biological indicators and “indicator tape” that switches color are also used to measure the functioning of the autoclave. Many manufacturers recommend that the chemical tape must be positioned on both the inside and outside of the sterilized packages. Alternatively, biological indicators spread many spores within the autoclave, and the spores are then allowed to incubate for 24-hours. If all the spores have been terminated, then the sterilization process can be deemed to be successful [302].

ISO 17665 specifies the prerequisites for the development, validation, and routine control of a moist heat sterilization process for medical devices [303]. Steam sterilization validation testing must be conducted under ANSI/AAMI ST79. For this testing, devices are inoculated with a known population of microbes, and the devices are then autoclaved and tested for sterility. Moist heat sterilization processes covered by ISO 17665 includes:

- Saturated steam venting systems;
- Saturated steam active air removal systems;
- Air steam mixtures;
- Water spray; and
- Water immersion.

8.16.3 GAS PLASMA (STERRAD) STERILIZATION

Historically, sterilization was done mainly through using moist heat in the form of steam autoclaves, as well as dry heat [304]. However, most hospitals currently possess a greater number of diverse types of expensive and complex devices. Therefore, fast turnaround is a top priority, while extreme heat is not a possibility for all instruments. Using EO gas has been one of the main sterilization methodologies for delicate instruments. However, one negative issue for EO is the slow completion time in EO cycles, because of the required aeration of loads to diminish the EO residuals. The standard EO concentration consists of 500 to 1.150 mg/L, temperatures from 38°C to 62°C, exposure times from 1 to 6 hours, and humidity from 40% to 80% [305]. Some of the other types of gas sterilization that the FDA has previously cleared include peracetic acid liquid ($\text{CH}_3\text{CO}_3\text{H}$), O_3 gas, and ClO_2 gas [306]. These alternative sterilization processes use lower amounts of sterilizing agents, produce non-toxic residuals, and are compatible with most materials.

Currently, one of the most popular sterilization systems in the United States is the STERRAD family of devices, which is owned by Advanced Sterilization Products [307]. STERRAD uses hydrogen peroxide (H_2O_2), vapor, and low-temperature gas plasma to sterilize most devices quickly, with no harmful residues. With this hydrogen peroxide gas plasma sterilizer, the plasma is generated following the exposure and removal of the gas by a vacuum. In the STERRAD procedure, the plasma is important because it helps in the purging of any peroxide residuals from the sterilizer load. One of the benefits of low-temperature H_2O_2 gas is that temperature-sensitive plastic materials can be easily sterilized without warping or weakening the plastic.

Usually, the STERRAD process takes about 75-minutes for wrapped and dry instruments [308]. Inside the chamber, a deep vacuum is drawn. A mixture of 59% aqueous H_2O_2 is then vaporized into the chamber. The device or component is subsequently swathed in the H_2O_2 vapor. After that, the chamber pressure is lowered, allowing for the generation of low-temperature gas plasma. Radiofrequency energy is harnessed in the chamber with a special amplifier, thereby creating the plasma. After the sterilization processes, the gases recombine to form H_2O vapor, O_2 gas, and other innocuous byproducts.

The devices are then desiccated and pouched for either immediate usage or placed within sterile storage. Therefore, any potential risk of recontamination is greatly reduced. Also, because the devices can be stored in a sterile manner until they are needed, the hospital saves valuable time [309]. Lastly, the STERRAD system takes up minimal room and necessitates no extra venting or separate water connections. Most experts believe that there are only a few shortcomings with using gas plasma sterilization [310]. For example, H₂O₂ should not be used to sterilize liquids, powders, or strong absorbers. Additionally, there is a risk of anodized aluminum becoming discolored after several treatments with H₂O₂ vapor [311]. Paper products should also not be used because these materials can soak up large amounts of H₂O₂. Lastly, there are several types of glues that are not endorsed for use with H₂O₂ vapor (*e.g.*, polysulfide-based adhesives).

For gas sterilization, the FDA recommends that manufacturers should contemplate the importance of packaging [15]. Normally, devices are placed inside trays that have been previously validated and tested to confirm effective sterilization. The tray can also be double-wrapped in a polypropylene wrap to furnish a sterile barrier. For both industrial or terminal sterilization, individual devices can be deposited within heat-sealed pouches, which permit sufficient dispersal around the device. [312].

8.16.4 NEW FDA GUIDANCE ON STERILIZATION

NEW

One of the most recent final guidances that the FDA has issued is the guidance for the “*Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*”, which was released on 21 January 2016 [15]. The FDA held a webinar on 11 February 2016 for this new guidance, where FDA officials described in detail some new aspects of this new final version of the sterility guidance [313]. The draft version of this sterility guidance was initially issued in December 2008 [314]. A device can be either sterilized in its final packaging by the manufacturer or sterilized by an end user as part of reprocessing a reusable device. It should be noted that the FDA recommends that manufacturers of sterile devices should only send out their devices, when they are finally sterilized within its final packaging [315]. In accordance with AAMI/ANSI ST67, Manufacturers should not send out devices that are labeled as being “sterile”, when the end user is expected to sterilize the device for the first time.

This new sterilization guidance focuses on devices that are characterized as sterile by way of “microbial inactivation”. The sterility guidance differentiates between “established” sterilization methods and innovative sterilization methods. Unfortunately, according to AdvaMed, it is improbable that many new 510(k) submissions will conveniently fall into this regulatory framework [316]. Importantly, the original draft guidance from 2008 was going to categorically exclude both heparin and “saline lock flush solutions” from being used for terminal sterilization. However, this restriction was not included in the final version of the FDA guidance in 2016.

The FDA categorizes established methods of sterilization as those that are included within an FDA-recognized standard (*e.g.*, ISO 11737-2) and is well-accepted (*e.g.*, dry heat,

EO, steam, and radiation). In addition, even when a sterilization method is not included within an FDA-recognized standard, if the FDA has already cleared a sterilization method as part of a previous 510(k) or PMA, then a manufacturer can cite that as a precedent [15]. These established methods include H₂O₂, flexible bag systems, and O₃.

Novel sterilization methods are defined as new methods “*for which there exists little or no published information*” [15]. Novel methods include completely new sterilization methods, variations in parameters of established methods, and mixtures of established sterilants that the FDA has not previously reviewed. The guidance does not address how significant the alterations must be in order for a previously established method to be considered “novel”. The new FDA sterilization guidance specifies that the FDA will inspect any device manufacturing plants that utilize “novel” sterilization methods, prior to allowing that device to be marketed within the United States. However, the guidance does not show how the FDA will manage the inspectional findings that result from such pre-clearance inspections. For example, it is not clear what happens if the inspection results are not satisfactory. Presumably, the 510(k) or PMA submission will then be placed on hold [317]. In addition, the acceptance criteria to pass the inspection are not obvious. Traditionally, the FDA has not considered QSR compliance as part of their decision-making process on whether to clear or approve a device premarket submission [318]. In fact, the ability of the FDA to legally employ QSR compliance in making a regulatory approval decision [319] appears to be restricted by law under 21 USC § 360c(f) [320].

For devices sterilized by established methods, the sterilization information in the 510(k) submission should include the following particulars [15]:

- A depiction of the sterilization chamber;
- If the sterilizer or sterilization method has been previously cleared by the FDA, then provide: (a) the 510(k) number of the sterilizer; (b) the model number of the sterilizer; and (c) if the proposed sterilization cycle is duplicated in a previously cleared cycle or has it been altered [321].
- Radiation amount, if the device is sterilized via radiation [322];
- Packaging validation testing results [323]. In addition, the packaging for terminally sterilized medical devices should follow both ISO 11607-1 and ISO 11607-2 [324]. Importantly, the FDA recommends that any sterile device should be sterilized in its final packaging [325].

The FDA mentions that any sterility validation testing should use ISO 14937 in order to validate the sterilizing agent and sterilization process for all devices [326]. The validation test normally consists of the proposed device being contaminated with bacterial spores [327]. The device then goes through the recommended sterilization cycles and is tested afterward for sterility to ascertain if the required SAL had been achieved [328]. Manufacturers should be aware that sterilization errors constitute one of the biggest reasons for FDA warning letters to manufacturers (see Appendix C).

9 FDA'S SIX CRITERIA FOR REPROCESSING INSTRUCTIONS

NEW

The FDA reprocessing guidance includes an official list of six criteria that medical device companies must follow to show that the reprocessing instructions are clearly understandable by users [13]. This information must be included in any new premarket application [329].

9.1 CRITERION 1 – LABELING SHOULD REFLECT THE INTENDED USE OF THE DEVICE

The FDA requires that the reprocessible device's labeling must include instructions for a reprocessing method that reflects: (a) the physical design of the device, (b) its intended use, and (c) the expected soiling & contamination [13].

9.2 CRITERION 2 – USERS SHOULD THOROUGHLY CLEAN THE DEVICE

For reprocessible devices, instructions or diagrams for adequate disassembly should be included in the cleaning instructions [13]. However, many manufacturers prefer that their devices not be disassembled for reprocessing because this increases the reprocessing procedure time. A big selling point for many manufacturers of reusable devices is the speed with which their device can be reprocessed and put back into service, as compared to their supposedly slower competitors. Users may also misplace parts of the device or incorrectly reassemble the device. Nevertheless, the only permitted exception to disassembling a hard-to-clean device, is when the manufacturer can validate effective cleaning without disassembly [330]. In such circumstances, the only proper validation method is to scientifically scrutinize the contaminated devices that are cleaned after disassembly. If the manufacturer recommends the use of protective covers, then their labeling must include the recommendation to use only legally marketed protective covers.

Lastly, the ability to adequately flush the device is important to remove any retained soil from the inside of the devices during the cleaning procedures. For example, it is a standard operating procedure for hospitals to use a "water bottle" for irrigation purposes during colonoscopy procedures. The water is focused on the endoscopic lens to sweep away debris from the lens or, in some types of endoscopes, to wash away the "gastrointestinal mucosa" in the body. Unfortunately, it is also customary that the same "water bottle" is used over and over again with many different patients during the day, thereby greatly increasing the hazard of cross-contamination with blood, stool, and other body fluids that could go back into the endoscope's channels and tubing in a process called "backflow".

NEW

In order to help thwart backflow from happening, the FDA published a new guidance in 2016 called “*Mitigating the Risk of Cross-Contamination from Valves and Accessories Used for Irrigation Through Flexible Gastrointestinal Endoscopes*”, which tells endoscope manufacturers that one or more pieces inside the irrigation system must have a “backflow-prevention valve”. Furthermore, this special valve must be verified by the manufacturer with “*quantitative chemical and microbiological assays to test its ability to prevent backflow under simulated conditions*” [331]. Furthermore, according to the new FDA guidance, any part of the distal irrigation system (*i.e.*, the area between the backflow-prevention valve and the patient) must be intended to be either reprocessed or discarded as a single-use part, before using the device on the next colonoscopy patient.

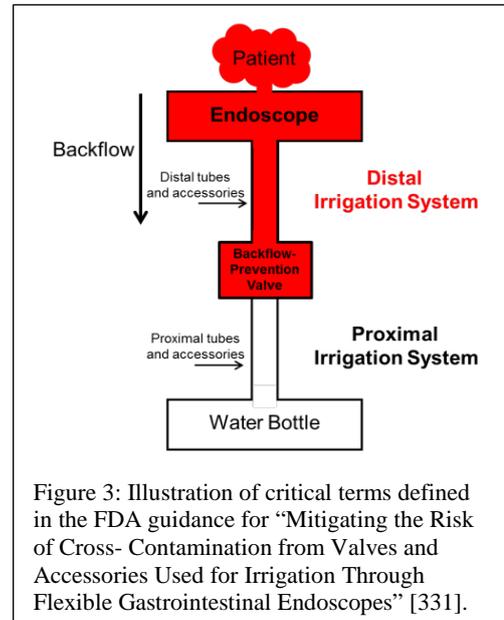


Figure 3: Illustration of critical terms defined in the FDA guidance for “*Mitigating the Risk of Cross-Contamination from Valves and Accessories Used for Irrigation Through Flexible Gastrointestinal Endoscopes*” [331].

9.3 CRITERION 3 – THE APPROPRIATE MICROBICIDAL PROCESS SHOULD BE PROVIDED

The evidence used to demonstrate a successful reprocessing methodology for the device should be validated and then stated in the IFU. Any validation results should show that both the soil and contaminants have been effectively removed, and that the device is substantially free of any viable microbes. The FDA uses the “Spaulding classification” scheme for critical, semi-critical, and non-critical devices [332]:

a. Critical Devices

Critical devices are considered by the FDA to be “*devices that are introduced directly into the bloodstream or which contact a normally sterile tissue or body-space during use*” [13].

b. Semi-Critical Devices

These types of devices come into contact with unbroken mucous membranes or skin. The FDA recommends that heat-stable devices (*e.g.*, rigid endoscopes) should be processed by steam sterilization [333]. Heat-labile devices are susceptible to alteration or destruction at high temperatures and should be processed with a “low temperature” reprocessing method such as hydrogen peroxide (H₂O₂) sterilization [334] or ozone (O₃) sterilization [335]. It should be noted that the FDA claims

that EO sterilization is not ideal for certain device types, such as duodenoscopes.

c. Non-Critical Devices

Non-critical devices are instruments whose surfaces only contact the intact skin and do not penetrate the skin. If a cleaning product can damage the proposed device, then the manufacturer's device labeling should include a warning not to use that product to reprocess the device.

9.4 CRITERION 4 – INSTRUCTIONS SHOULD BE TECHNICALLY FEASIBLE

Reprocessing instructions must be technically viable in the intended location (*e.g.*, health care setting or home use) [336]. Furthermore, the equipment and accessories needed to implement the instructions have to be clearly defined (including detailed descriptions & part numbers) and readily available for the users to obtain. The type of sterilizer, manufacturer-validated sterilization cycle parameters, and accessories must be accessible to the users. However, dry heat and chemical vapor sterilization are less common, and should not be recommended in most circumstances. Lastly, radiation sterilization is only normally used in manufacturing facilities for terminal sterilization, and not in medical facilities for the reprocessing of reusable devices.

Designing the manufacturer's reprocessing instructions, in accordance with the conventional parameters, provides assurance that the reprocessing instructions are compatible with existing FDA-cleared reprocessing equipment. For example, the manufacturer cannot recommend that their device undergo cleaning in a washer that has not been previously cleared by the FDA. Information on other cleaning methods may be found in AAMI TIR 12. For example: (a) accessories (*i.e.*, sterilization wraps, pouches, cassettes, and containers); (b) biological indicators and chemical indicators [337]; (c) as well as liquid chemical sterilants and disinfectants [338]. The reprocessing instructions should match these three specific process parameters.

The FDA maintains a list of FDA-cleared liquid chemical sterilants and high-level disinfectants on its website [339]. Designing validation protocols, in accordance with the list of sterilants and disinfectants from the FDA, assures that solutions will be compatible with existing FDA requirements. Furthermore, the FDA advises that "a range of cycles" should not be used for identifying the recommended number sterilization cycles for reusable devices. If sterilization is included in the labeling, then the FDA requires that the manufacturer must provide an exact number of necessary sterilization cycles.

9.5 CRITERION 5 – REPROCESSING INSTRUCTIONS SHOULD BE COMPREHENSIVE

To ensure the reprocessing instructions are comprehensive, the FDA recommends that the manufacturer should include all of the elements below [340]. If any element is not

applicable to the proposed device, then the manufacturer should state this in their premarket FDA submission and provide a justification [341]:

a. Cleaning equipment

It is common for hospitals not to have all the necessary equipment to reprocess a reusable device correctly [342]. In one example, a medical facility did not have adequate ventilation in order to avoid the staff from suffering “*headaches, nausea, chest pains*” because of the toxic fumes that emanated from reprocessing an endoscope [343]. Therefore, the FDA recommends that manufacturers provide clear instructions on what accessories are needed for safe reprocessing. The IFU should also identify any required test kits, special tools, sizes & types of brushes, flush port connectors, connector size specifications, trays, specific types of sterilization wraps or containers, and part numbers [344]. One of the problems that were found during the Olympus duodenoscope scandal was that some hospitals were using US\$1 toothbrushes to clean their US\$30,000 duodenoscopes, when those toothbrushes were not designed to clean those devices because the bristles were not capable of effectively reaching inside small gaps and crevices of the device [345].

b. Point-of-Use wiping

If not provided with proper instructions, many medical facilities will use incorrect cleaning methods or chemicals during the initial processing step. For example, a facility that was reprocessing the Olympus Fiberscope was incorrectly “*wiping down the exterior of the devices with an unknown cleaning agent and flushing the channels with a surgical scrub solution*” [346]. Therefore, the FDA requires that labeling should include specific instructions for the initial point-of-use processing.

c. Disassembly and reassembly

As shown by a reusable device from Tontarra Medizintechnik GmbH, a hospital using their device mistakenly disassembled “*a no-take-apart device*” [347]. It is up to manufacturers to clearly indicate, in the device’s instructions, if the device can be disassembled or not. The FDA recommends that if the device includes removable parts, then the reprocessing instructions should include step-by-step systematic instructions for disassembly and reassembly of the device.

d. Cleaning solutions

A common reprocessing error is the use of incorrect chemicals, as was the case with an adverse event report on a Fisher & Paykel device [348]. In that case, the device was cracked because of the use of non-compatible cleaning solutions. The FDA recommends that any instructions should recommend only specific cleaning agents. These cleaning agents must be compatible with the device, and must be effective in cleaning the device. Certain products (*e.g.*, quaternary ammonium compounds and alcohols) may be used for both the removal of soil and the disinfection of microbes [349].

e. Rinsing

The critical importance of properly rinsing after reprocessing is often overlooked. There was a recent incident involving a Steris device where the operator "*flicked out the aspirator from the cup opening and was splashed with liquid resulting in exposure to, and a burning sensation around, her mouth and lips*" [350]. Rinsing instructions should include the recommended type & quality of rinse water, duration of rinse, and temperature. The device manufacturer may refer to the detergent supplier's labeling to assist in developing their validated rinsing instructions. The FDA also recommends that manufacturers refer to the current version of AAMI TIR 34 to ascertain the optimal water quality for final rinsing [351]. The FDA does not recommend saline solutions as the final rinse, because salt-water solutions may lead to corrosion and a build-up of residues. The manufacturer should warn that regular tap water often has endotoxins and should be avoided.

f. Lubrication

It is common for manufacturers to recommend the use of lubricants to enhance the performance and longevity of the medical device. An adverse event report on a Bard Core Biopsy device is an example of what happens when an instrument is not properly maintained, in which case the lubricant will do little to increase its longevity [352]. The reprocessing instructions should recommend the lubricating agents (*e.g.*, water-soluble lubricants) that are compatible with the medical device, if applicable [353]. The manufacturer should validate the device reprocessing methods using the lubricating agents under the expected "conditions of use" of the device. The FDA cautions that manufacturers should be careful when using oil-based or silicone-based lubricants, as they may cover and shelter unwanted surface microbes.

g. Visual Examination

The "instructions for use" should include a warning that if the device is not deemed to be visually clean, then the user should either repeat the relevant cleaning steps or safely dispose of the device. Additionally, the visual inspection instructions should identify the exact visual acceptance criteria (*e.g.*, look for any signs of corrosion, discoloration, pitting, or cracked seals).

h. Recommendations for Disinfection/Sterilization

The FDA recommends that reprocessing instructions should specify at least one validated microbicidal method for disinfection or sterilization [354]. The manufacturer should also specify the packaging and load characteristics in the labeling. For example:

- Weight – The Device instructions should stipulate a maximum weight of loaded trays. In the case of one STERRAD device, the hospital had seen residue on their instruments after being sterilized with the STERRAD device. It was subsequently discovered that the hospital was incorrectly loading the shelves with too much weight, when the STERRAD 100nx sterilizer was only validated using a load

weight of 4.85 kg per shelf [355]. Any manufacturer should follow the recommendations in the current FDA-recognized version of AAMI ST77 and the specific sterilizer specifications.

- Materials – There should be a warning against including incompatible materials within the sterilization load (*e.g.*, cellulose incompatibility with H₂O₂ sterilization).
- Device Design – A warning must state that the user must only sterilize devices with dimensions or characteristics (*e.g.*, lumen specifications or powered hand-pieces) that are compatible with the labeling of the specified sterilizer and sterilization cycles.
- Chamber load – The recommended chamber load should be described, based on a validation study. For example, the manufacturer should specify if the validation was conducted in either an “empty load” or in a “full load” that represents a worst-case scenario. This is illustrated by an injurious event involving the STERRAD, where the medical technician opened the chamber after canceling one cycle, with the result that some hydrogen peroxide came into contact with their hands [356].
- Drying – Labeling should also include a validated “minimum drying time”.
- Sterility Maintenance – Labeling should identify the packaging that is FDA-cleared [357].

i. Removal of any sterilant residuals

Residuals have the potential of harming the hospital staff if not properly removed. For example, in 2009 a hospital employee was severely injured when cleaning a Steris device because the cup that she was handling contained residual quantities of buffer and peracetic acid, some of which spilled onto the edge of the processing tray and wounded her [358]. Although the employee was wearing gloves, her forearm came into contact with the residue and caused second-degree burns [359]. Therefore, the FDA requires that the instructions include information on reducing sterilant residuals (*e.g.*, by aeration), after using a sterilization process that may leave sterilant residuals on the device [360]. On devices that are intended to be sterilized by EO, the labeling should recommend an aeration time that results in a reduction of EO residuals to acceptable levels. The FDA counsels that manufacturers refer to the current FDA-recognized version of AAMI ST41 and ISO 10993-7 for acceptable levels of EO residuals [361].

j. Reuse Life

The reuse life of any device is affected by the method of cleaning, disinfection, or sterilization that is used on the device. For example, Ethicon Endo-Surgery described how one of their handpieces which contained an O-ring, began to deteriorate after being subjected to sterilization [362]. This facilitated moisture to go inside the handpiece. Ethicon describes how the type of sterilization could affect the life of the handpiece. Specifically, the slowest and most gradual (*i.e.*, STERRAD) is the best method for prolonging the use of their handpiece. While faster sterilization methods, such flash sterilization, can lead to a

shortened device life. That is why the FDA requires that all devices should have an expected service life, based on its design and intended use [363]. The reusable medical device's labeling should, therefore, include either of the following information:

- declare the expected number of times that the device can be safely reused, based on validation testing; or
- provide the user with a means to determine whether the device has surpassed its expected use life (*e.g.*, leak testing a lumen, or visual signs of corrosion).

k. Additional Labeling Recommendations

During a surgery involving a Medtronic shunt component, the “*surgical team became aware that the newly implanted shunt may be contaminated, as it was noticed at that point that packaging materials indicated ‘non-sterile’*” [364]. In a different incident involving an Integra suture, the hospital reported that the packaging confusingly indicated that the device was “*both sterile and non-sterile*” [365]. Any potential confusion on whether a device is non-sterile must be eliminated by writing “non-sterile” directly on each individual device label, and not just on the shipper carton. In addition, warnings should be provided on devices that may have unsealed crevices, through which liquid disinfectant could enter into the interior of the device. A malfunction involving the Eli Lilly Injector Pen is a case in point, where the hospital staff noticed liquid ingress and corrosion in several areas of the injector pen, including a “*jelly-like substance in the crevices*” [366]. The FDA cautions that the use of clinical practice guidelines does not always correctly address all FDA regulatory requirements, and that compliance with FDA regulations is required. In addition, manufacturers are allowed to refer to the labeling of other devices used in reprocessing, such as an “endoscope washer-disinfector”, as long as the referenced labeling is relevant and consistent with the reusable device's labeling. Lastly, it may also be appropriate to highlight situations where damage to the device may affect the reprocessing procedure.

9.6 CRITERION 6 – REPROCESSING INSTRUCTIONS SHOULD BE UNDERSTANDABLE.

Whenever a hospital does not follow the manufacturer's instructions, it is the responsibility of the manufacturer to make sure that usability problems are not the root cause of the user errors. For example, in the case of an adverse event from an Olympus device, the hospital using the Olympus Rhino-Laryngofiberscope only began to correctly reprocess the device after the Olympus service specialist went to the hospital and personally showed the medical staff the proper reprocessing methods for the device, such as fully submerging the endoscope [367]. Reprocessing instructions should be clear, legible, and provided in sequential order from the initial processing step through the terminal processing step [368]. Any graphics should be supplemented with a descriptive text in English. The FDA may permit pictures with no accompanying text if the meaning of the pictures is described in the user manual. Lastly, the instructions should be validated using usability testing to ensure that users will be able to understand and to follow them.

10 CONCLUSION AND OUTLOOK

Regulatory affairs in the United States is a very active topic, with an ever-changing array of rules, regulations, and requirements. From the beginning of the FDA in 1938 until now, companies have had to manage continuously changing requirements that are placed on their medical products to receive approval to sell. Regarding the specific topics of this thesis such as biocompatibility, reprocessing, and sterilization – there are several unknown issues that the new FDA guidances have yet to clarify.

Firstly, it is not known if FDA reviewers will begin to accept more readily the fact that chemical characterization can be used as a substitute for animal testing. The traditional approach of always conducting animal testing to prove the biocompatibility of a new device is something that might disappear, if the FDA were to continue to place a spotlight on utilizing chemical characterization as a substitute for animal testing. Just because an animal does not lose weight after several weeks after being implanted with the device's material, does not inevitably signify that the materials are necessarily safe.

Many device failures that eventually lead to patient injuries or deaths are related to errors in the instructions for use. The FDA's new focus in recent years on human factors / usability testing should improve the instructions for use.

With the growth of antibiotic-resistant bacteria, there is a continued need for further developments in different types of disinfectant or sterilization methods. Perhaps the increased use of single-use devices, which do not need to be reprocessed, will help in reducing the risk from ineffective reprocessing methods or spreading superbugs.

For many medical device manufacturers, chemical processes continue to become more popular, particularly those based on oxidizing agents for either disinfection or sterilization. The advantages over traditional steam sterilization seem to be overwhelming (*e.g.*, improved material compatibility, faster-reprocessing cycle time, and lowers costs). It is clear that many of the FDA's regulatory decisions are based on unforeseen medical problems that occur in clinical settings (*i.e.*, duodenoscopes, metal-on-metal hip implants, and vaginal surgical mesh). It is an open question whether the FDA will be able to prevent future problems instead of just reacting to problems after they have already occurred.

In conclusion, medical device manufacturers need to continue enhancing their collaboration between sterile processing, biomedical engineering, and the overall medical community. Manufacturers may want to include the help of an "infection preventionist" in their product development process, who may assist in risk reduction. Also, it is crucial that the sterile processing managers and the quality assurance department collaborate to monitor any problems with their products in the market. The cumulative effect of collaboration, monitoring, and documentation has shown positive outcomes in reducing potential problems related to errors in infection controls or biocompatibility.

11 SUMMARY

The U.S. Food and Drug Administration (“FDA”) regulates all medical devices in the United States. As part of its regulatory duties, the FDA provides guidance documents on various regulatory topics as mandated by the U.S. code of federal regulations. Since 2015, the FDA has begun to issue many substantial revisions to their guidance documents that directly affects the regulatory framework on biocompatibility, reprocessing, and sterilization.

These regulatory issues are of paramount importance for many companies because of the potential high costs involved in changing their internal design, controls, manufacturing, and quality systems. This master’s thesis examines the various changes made by the FDA in recent years on the inter-related topics of biocompatibility, reprocessing, and sterilization. Some of the major changes by the FDA involve an increase in the importance of chemical characterization, a reduction in the use of animal testing, a requirement for an independent validation of the user instructions for reusable devices, and increased usability testing.

The principal reasons for these major policy changes by the FDA are shown to be the major device scandals that recently involved duodenoscopes, metal-on-metal hip implants, and vaginal surgical mesh implants. Along with several other regulatory failures that made national news headlines in the United States, the FDA began to revise several of their previous medical device guidances. The information from this master’s thesis can be used by medical device developers and manufacturers, especially when they are located outside of the United States and lack sufficient regulatory affairs resources to provide independent advice and recommendations on these important FDA changes. A thorough analysis is made of the new FDA guidances to clarify several potentially difficult questions for medical device manufacturers, specifically the following guidances: (1) “*Use of International Standard ISO 10993-1, ‘Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process’*”, (2) “*Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*”, and (3) “*Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*”. This master’s thesis is intended to provide not only an overview of the current FDA requirements, but to function as a guide for both researchers and engineers to improve their medical device design and development process.

12 APPENDIX A – FDA WARNING LETTERS FOR BIOCOMPATIBILITY PROBLEMS

Company	Date of Issue	FDA URL for the Warning Letter (Biocompatibility failures)
Collagen Matrix Inc	09/20/2016	https://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm522402.htm
Renovis Surgical Technologies, Inc.	05/05/2016	https://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm501776.htm
Aros Surgical Instruments, Corp.	09/25/2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm468225.htm
Zynex Medical, Inc.	06/27/2014	https://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm403237.htm
Ultradent Products, Inc.	03/17/2014	https://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm389625.htm
Medical Device Resource, Corp.	09/20/2013	https://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm369495.htm
Fresenius Medical Care, AG & Co. KGaA	03/05/2013	https://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm344711.htm
H & H Associates	04/30/2012	https://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm302628.htm
Mayer Laboratories, Inc.	07/05/2011	https://web.archive.org/web/20110720104207/https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm262027.htm
SenoRx, Inc.	07/19/2005	https://www.fda.gov/iceci/enforcementactions/warningletters/2005/ucm075488.htm

13 APPENDIX B – FDA WARNING LETTERS FOR REPROCESSING PROBLEMS

Company	Date of Issue	FDA URL for the Warning Letter (Reprocessing failures)
Bellus Medical	13 Sept 2016	https://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm520649.htm
Grams Medical Inc.	17 Mar 2016	https://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm497792.htm
GeoTec, Inc.	30 Sept 2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm465790.htm
Fujifilm Medical Systems U.S.A., Inc.	12 Aug 2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm458453.htm
Hoya (PENTAX) Corp.	12 Aug 2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm458487.htm
Olympus Medical Systems, Corp.	12 Aug 2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm458510.htm
Zeppessis Reprocessing, LLC	09 Aug 2013	https://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm365433.htm
NeuroTherm, Inc.	11 July 2012	https://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm312312.htm
Millar Instruments	7 May 2012	https://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm308649.htm
Stingray Surgical Products	03 May 2012	https://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm309452.htm
Eminent Spine, LLC	20 July 2010	https://web.archive.org/web/20110909212016/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm234102.htm
General Electric, Inc.	31 Mar 2005	https://www.fda.gov/iceci/enforcementactions/warningletters/2005/ucm075346.htm

14 APPENDIX C – FDA WARNING LETTERS FOR STERILIZATION PROBLEMS

Company	Date of Issue	FDA URL for the Warning Letter (Sterilization failures)
C World KSG, Corp.	18 Feb. 2016	https://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm515524.htm
Aros Surgical Instruments, Corp.	25 Sept. 2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm468225.htm
9mm Special Effects	19 May 2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm448437.htm
BioLab-St. Joseph Corp.	18 Mar 2015	https://www.fda.gov/iceci/enforcementactions/warningletters/2015/ucm450839.htm
Customed, Inc.	09 Dec 2014	https://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm433090.htm
CareFusion Corporation	06 June 2014	https://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm405356.htm
Cytophil, Inc.	01 Apr 2014	https://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm393126.htm
ConMed Corp.	29 Jan 2014	https://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm384602.htm
Baxter Healthcare Corporation	19 Dec 2013	https://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm385262.htm
CryoLife, Inc.	29 Jan 2013	https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm341423.htm
Epflex Feinwerktechnik GmbH.	16 Sept 2013	https://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm369266.htm
Arrow International, Inc.	03 Aug 2005	https://web.archive.org/web/20090710133029/https://www.fda.gov/iceci/enforcementactions/warningletters/2005/ucm075510.htm

15 APPENDIX D – DEVICES THAT REQUIRE VALIDATED REPROCESSING METHODS

NEW

The devices identified by FDA as requiring a validated reprocessing method, including their product codes (“procodes”) [248]:

Device description	Relevant product codes
Bronchoscopes and accessories	EOQ, KTI, BTG, JEI, JEL, BST, BWH, JEK, ENZ, KTR, JEJ
Ear, Nose, and Throat endoscopes and accessories	EOX, GCL, FDW, EOB, EQN, EWY
Gastroenterology and Urology Endoscopes with elevator channels, such as duodenoscopes used for endoscopic retrograde cholangiopancreatography	FDT, FAK, FTK, ODF, FBN, ODG
Automated Endoscope Reprocessors	FEB, NZA, KOG, OUI
Colonoscopes	FDF, FDA
Neurological endoscopes	GWG
Arthroscopes	HRX
Laparoscopic instruments	GCJ, GEI

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17 EIDESSTATTLICHE VERSICHERUNG

Eidesstattliche Versicherung:

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Rottenburg, den 27.09.2017

Anna Reifschneider

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