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DEVELOPMENT OF A BIOLOGICAL HANDBOOK: A REFERENCE GUIDE FOR REGULATORY CONSIDERATIONS OF BIOLOGICAL PRODUCTS

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A capstone project submitted to the
Krieger School of Arts and Sciences
Advance Academic Programs
Johns Hopkins University
in partial fulfillment of the Degree of
Master of Science in Research Administration

Baltimore, Maryland
December 2019

Abstract

The broad range of chemical and biological compliance standards has resulted in a complex, multifaceted regulatory environment for the development and distribution of biological products. Due to this complexity, company processes are challenged with the task of developing procedures to meet the technical regulatory requirements, but still allow personnel to consider cross-functional business applications. The conceptualization of this regulatory model can be increasingly difficult for new or less experienced personnel for the reason of a lacking foundation of fundamental regulatory elements. Thus, the purpose of this Capstone Project was to create a biological handbook that can be used as a reference guide for regulatory considerations of biological product. This handbook was designed to bridge the knowledge gap between developing procedures and providing appropriate resources and basic information for key personnel.

The development of this handbook required the compilation of current regulations and Company processes, to then delineate, to use as a reference tool specific to the Texas logistic center. Guidance documents published by regulatory agencies were reviewed and provided useful interpretations of otherwise dense regulations. A search for other broad reference documents related to biological substance organization was unsuccessful. Each chapter provides a different regulatory aspect of biological products, some of which would require trigger collaboration between business functions. The project resulted in the creation of handbook, intended to provide basic information that may apply to biological operations conducted at the current logistics center and internationally transported, especially to Germany and South Korea.

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Glossary

Code of Federal Regulations: A collection of rules and regulations promulgated by Federal executive agencies. Published in the Federal Registrar, the CFR is divided into 50 titles, each then subdivided by a broad range of subject matter. An editorial compilation of CFR material is available online as the Electronic Code of Federal Regulations (e-CFR).

For Research Use Only: A Research Use Only (RUO) label is designated for products that are intended only for research laboratory use. The FDA defines RUO products as "in the laboratory research phase of development and not represented as an effective in vitro diagnostic product."[1]

In Vitro Diagnostics: Any device, reagent, material or system that is designed for laboratory diagnostics. [2]

Recombinant DNA/RNA: Commonly referred to as rDNA or rRNA, refers to the process of which the biologic genome being artificially created. Molecules of DNA/ RNA are formed in laboratory and purposefully bring genetic material together, sometimes from multiple sources to create a specific sequence of genome.

[1] Medical Devices, U.S. Code of Federal Regulations, 2019, Title 21, sec. 809.10.5 (i)
[2] *Medical Dictionary. s.v.* "in vitro diagnostic." accessed November 03, 2019, https://medical-dictionary.thefreedictionary.com/in+vitro+diagnostic

List of Abbreviations

FDA	Food and Drug Administration
CFR	Code of Federal Regulation
ATCC	American Type Culture Collection
CBER	Center for Biologics Evaluation and Research
CDER	Center for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CoA	Certificate of Analysis
cGMP	Current Good Manufacturing Practices
cGLP	Current Good Laboratory Practices
IVD	In Vitro Diagnostic
ISO	International Standard Organization
OVRR	Office of Vaccine Research and Review
PCR	Polymerase Chain Reaction
PCB	Production Cell Bank
EU	European Union
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid

Chapter 1. Introduction

1.1. Background

Biotechnology is a synonymous term used to describe a vast array of scientific innovations developed around the use of cellular and biomolecular processes to improve the quality of life.[3] As there becomes a broader range of applications and market demand biotechnology continues to offer promising advancements for the future; with the potential of improving medical, pharmaceutical, agriculture and environmental challenges. The use of biotechnology is not a new concept; it is safe to say we have far surpassed the basic concepts of fermentation and vaccinations that have evolved into our current modern biotechnology market. The production and quality process of biologic products focus on the nature of the product and its relevant discipline.[4]

By statute, a biological product includes a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."[5] By this definition, biological products differ from synthesized small molecular chemical drugs because chemicals are well-defined structures and thoroughly categorized using a Chemical Abstract Service (CAS) registry. Biological products are originated from natural living material such as human, animals, and microorganisms, making them

[3] "What Is Biotechnology?," Biotechnology Innovation Organization, Last modified 2019, https://www.bio.org/what-biotechnology.
[4] "Biological Safety," National Institute of Health, Last modified 2019, https://www.ors.od.nih.gov/sr/dohs/safety/laboratory/BioSafety/Pages/bio_chem_safety.aspx.
[5] 42 USC § 262 (i)(1)

difficult to categorize and track in the same methods as chemicals. Implementation of quality systems such as good manufacturing practices (GMP) offers biological product quality and insurance to consumers of acceptable, well- recognize policies and procedures.

Domestic oversight of biological products is provided by the Food and Drug Administration (FDA), organized by various centers and offices to focus on specific types of products and their marketed use. Biologic and medical device regulations are statute to Part 21 of the Code of Federal Regulation (CFR). Generally, regulated biological products respectively fall into the jurisdiction of the following FDA centers: Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), or Center for Devices and Radiological Health (CDRH).[6] International compliance authority and applicable regulations are dependent on the importing country and region. Each country with its own set of subject matter needed to successfully ship and import/export products without delay, product seizures, and potential for noncompliance citations, and subject to civil or criminal penalties.[7]

There is a need for a cohesive relationship across scientific, regulatory, business and logistical operations to create successful global importing/exporting outcomes. Coordination of this level builds a complex matrix that can be overwhelming and difficult to navigate without a clear point of origin that is needed to relay information in an organized manner across business functions.

[6] U.S. Food and Drug Administration, *FDA Overview Organization Chart*, image, 2019, https://www.fda.gov/about-fda/fda-organization-charts/fda-overview-organization-chart.
[7] Biological Safety, National Institute of Health

1.2. Statement of the Problem

There are a large variability and range of use for biologics; each has its own subplot of highly technical, regulated and complex operational activities. This requires a collective diversity of skills and background from many people to meet the broad scope of needs for product development and planning throughout the product lifecycle. This means that while scientists and product developers may be an integral element of a successful biotech company, not all personnel share the same specific experience for all marketed types of biological product manufacturing needs. Without a thorough understanding of applicable regulatory requirements and regulations, a company or institution may be left at risk of product quality, noncompliance, shipment holds, and loss of revenue.

In addition to the central personnel, there should be a resource of fundamental material of biological product requirements/elements when introducing new or less experienced employees the principle and practices related to the specific nature of a product. To the inexperienced, the macro-level of biotechnology can appear as a vast multi-dimensional environment, causing one to be left overwhelmed in the operations and lacking rationale. Thus, the author has designed a handbook for research administrators with the emphasis on easy access and readability. Access and readability are imperative to further understand the complex organizational structure and the methodology behind any company's policies and procedures, focusing on the regulatory and project management considerations.

Additionally, the author's current company encompasses multiple regulatory departments, each focused within the product, accompanied use and location of

manufacturing. Their business continues to expand by way of merger and acquisitions or through the development of products by their current research and development teams. In turn, the company growth results in operational changes that must be acknowledged for proper restructuring.

1.3. Project Questions

FDA provides oversight and regulations to a vast array of consumer products, many of which can be classified under biologic products. Regulatory authority is determined by its classification or type and its intended use. To create a handbook that includes an exhaustive review of regulatory content is not practical. Therefore, the primary project question for this Capstone Project was:

What elements should be included in this handbook to provide an effective overview of biologic product resources and considerations?

If the handbook is to provide information for key personnel as well with varying backgrounds:

What level of readability and complexity should the content be formatted?

1.4. Project Objectives

The primary objective of this project is to generate a handbook for use by the author's current place of employment as a centralized resource of essential biological information and considerations for researchers, regulatory administrators, or other applicable professionals. This handbook provides a centralized resource which is approached from a regulatory and operational perspective.

1.5. Significance

This project is significant to the author and research administrators because it documents and presents the challenges met over the past year during the author's career transition into the biotechnology industry. Despite the wealth of knowledge spread across the Company, there is not a single fundamental guide in biological product considerations for the use of diagnostic and life science products which a research administrator can access. While for some, relying on technical process documents as the foundation of further organizational roadmaps is not productive. Thus, there was a need for a biological handbook.

This biological handbook was designed to fill the gap of meeting the need to integrate applicable biologic product regulations with other functional areas in order to effectively collaborate during the manufacturing and disbursement of RUO and IVD biological products. This handbook is designed to be utilized as an onboarding training tool, reference tool, and guide for research administrators working in biotechnology.

1.6. Exclusions and Limitations.

The inherent complexity of biological products does not allow a handbook to include all biological regulatory references and operational considerations. Therefore, in an effort to build a handbook that can be used with the author's current Company needs biological product information will be limited to biologics labeled as:

- Research for Use Only (RUO), Not to be Used in Diagnostics Testing
- In Vitro Diagnostic (IVD) labeled as RUO

Although products manufactured at the current location include a limited number of IVD, ASR and GPR products that contain biologic substances; each product type could respectively need its own handbook. To credit these product types general information regarding IVD, ASR and GPR products was included.

- Vitro diagnostic (IVD) products (*limited information*)
- Analyte Specific Reagents (ASR)
- General Purpose Reagents (GPR)

Limiting the biological product by type allowed the Handbook to provide examples of international shipping elements and other bodies of regulatory oversight. Accordingly, this handbook provides information for biological products while importing essentials relating to the European Union (EU), specifically Germany, and South Korea.

Chapter 2. Literature Review

2.1. Overview of literature review.

A preliminary review of literature for this project focused on methods to understand fundamentals of biological products, bodies of regulatory oversight and management skills of bio-manufacturing in effort to provide information and best practices for specific biological products. FDA guidance documents regarding labeling applicable to Company products. These publications were reviewed against current Company process documents or standard operating procedures (SOPs) found to ensure relevance. The result of this review supplied a framework of basic information to be referenced or later built-upon as experience and knowledge develop.

An additional review was completed in effort to locate similar guidance material. This was completed to ensure inclusion of additional elements that may not have initially been identified or provide the author with a preconceived structure for relying the information in a clear and concise manner.

2.2. Regulations that Apply to IVD-RUO Products

The FDA Guidance document *Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only* outlines the statutes for IVD exemptions for RUO labeling. Generally, IVDs are subject to medical devices federal regulations 21 CFR 862, 21 CFR 864 and 21 CFR 866. Each IVD categorized as a Class I, II or III according to the level of control necessary to ensure safety and the efficacy of the product. Each classification determines the appropriate premarket approval process.[8,9]

[8] "Overview of IVD Regulations," U.S. Food and Drug Administration, last modified September 16, 2019, https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation#2
[9] 21 CFR § 826

In vitro diagnostics can be reagents, instruments, or systems intended for the use in diagnosis of diseases by collection, preparation, and examination of specimens taken from patients in the human body.[10]

The exemption requirements for an RUO IVD are much more extensive than the intended use labeling, 21 USC 360j(g) and section 520(g) of the FD&C Act provide the necessary requirements for a device exemption. Not all devices are eligible for exemption, device exemption applications must be submitted and granted by the Health and Human Services (HHS).

By classifying a product as RUO, it implies the product and its application is only intended in the use in discovering or developing knowledge related to diseases or other human conditions as long as the product and its use support the research instead of produce results for clinical or diagnostic use. There are various types of products that may be labeled as RUO, such as: reagents, instruments, and systems.[11] If in accordance with 21 CFR § 809.10(c)(2)(i) an IVD may be labeled as RUO if "a product in the laboratory phase of development, and not represented as an effective in vitro diagnostic product."

What is important to note about RUO products is that they are exempt from most regulatory controls and do not related to any mandatory standards for product quality and validation or good manufacturing practices. Even so, the lack of FDA jurisdiction does not exempt RUO products from abiding by chemical and biological transport regulations, global trade classification or possible foreign country restrictions (e.g. EU Directives).

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[10] 21 CFR § 809.3

[11] U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. *Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Guidance for Industry and Food and Drug Administration Staff.* (2013). https://www.fda.gov/media/87374/download

2.3. Review of Similar Documents and Details

The author was unsuccessful in locating guidance documents with a similar objective of the project handbook. However, academic institutional manuals regarding biological shipping processes were discovered and used in the development of biological consideration because similar standards apply.

Biological Shipping Manuals:

- Desert Research Institute (DRI): Guideline on Classification of Biological Materials for Shipment
- Dartmouth: Guide to Shipping Biological Materials
- University of Pennsylvania: Shipping Manual for Infectious Substances, Biological Materials
- Augusta University: Guide to Shipping Biological Substances and Materials

2.3.1. Guidelines on Classification of Biological Materials[12]

Biological guidelines provided by DRI highlights the general overview of biological material categorization as it relates to domestic transportation regulations. The scope of information was limited to information, no instructions were included. The simplicity of the guidance document allowed for a clear review of shipping categorization for domestic needs. Documentation was published in 2015, with no reference citing for biological shipping classifications steps. Additionally, review of manual verse current regulations was conducted to ensure it is it still current with federal regulations.

[12] "DRI Guideline On Classification Of Biological Materials For Shipment," Dri.Edu, Last modified 2015, https://www.dri.edu/Classifying_a_Biological_Shipment.pdf.

2.3.2. Guide to Shipping Biological Materials[13]

Guidance document provided by Dartmouth included a thorough review of information related to labeling and packaging details. The documentation provided visual aids for proper packing needs for each type of biological material to emphasis the impact on the safety of the human, animals, and environment for any regulated substances.

2.3.3. Shipping Manual for Infectious Substances, Biological Materials[14]

Building upon Dartmouth's *Guide to Shipping Biological Materials,* the shipping manual provided by the University of Pennsylvania concentrates information around the relationship of infectious substances and dangerous goods. In addition, it considers the best practices for shipping restrictions and emergency response steps for improper packing.

2.3.4. Guide to Shipping Biological Substances and Materials[15]

The largest of the reviewed guidance documents, the Augusta University manual is a process manual that may be used for extramural shipping needs. The guidance expands on environment and health safety considerations and penalties of noncompliance.

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[13] "Guide to Shipping Biological Materials," Dartmouth.Edu, accessed November 1, 2019, https://www.dartmouth.edu/~ehs/biological/biosafety_docs/shipping_guide.pdf.
[14] "University Of Pennsylvania Shipping Manual For Infectious Substances, Biological Materials," Ehrs.Upenn.Edu, Last modified 2017, https://ehrs.upenn.edu/sites/default/files/2018-02/Shipping%20October%202017r_0.pdf.
[15] "Guide To Shipping Biological Material Substances And Support Materials (Section 10-AU Biosafety Guide)," Augusta.Edu, Last modified 2013, https://www.augusta.edu/services/ehs/biosafe/documents/guide-for-shipping-biological-substance-and-support-materials.pdf.

2.4. Applicability of Literature Review.

All documents supplied the basis of product stewardship and presented a similar outline of information. However, each guidance document review builds upon the last, allowing a steady flow of learning when developing a method to organize these processes. It should be noted, the perspective of all documentation is provided from an academic institution. As an industry company that manufactures biologics products for marketability the need to continuously define the regulations would provide a more beneficial impact.

Given the amount of regulatory content applicable to RUO and IVD biological products, not including international regulations, it is clear that a handbook would benefit the Company by reducing time spent on searching through various governing websites for applicable regulatory content.

Chapter 3. Need(s) Assessment

3.1. Establishing the Need

The Company offers biological process documents, many of which stay in draft mode due to the ever-changing regulatory environment. Because of this, new projects are frequently started to restructure product import and exporting needs in an effort to find more efficient methods of bringing products to market. The Company's regulatory department(s) are compartmentalized across location and product application barriers. In turn, this results in a lack of standardization in procedures and training tools and has shown significant overlap in efforts across the organization. It is the author's hope that the need for this handbook with centralized information may create the basis of standardization because it only contains the framework of operational requirements.

3.2. Metrics.

Specific metrics were not used to determine the need for a handbook. Instead, this project is meant to serve as a reference of information applicable to RUO and IVD-RUO biological product regulatory and operational considerations during the planning throughout the product lifecycle. After continued use, metrics can be established to determine the impact of the handbook by providing data relating to the frequency of use, ease of access, and readability by use of end-user satisfaction surveys.

3.3. Sources Consulted.

The handbook is formatted to provide information to both experienced and new personnel. It is designed to provide specialized information to fill in any gaps in knowledge that a research administrator may have regarding fundamental biologic operations. The Company's Director of Regulatory Affairs and Quality Assurance as well

as the Product Regulatory Affairs Manager of Genomics Solutions Biomolecular Analysis Divisions (BAD) were consulted during the conception of this project. Both individuals have extensive experience in the area of regulatory affairs and quality assurance of medical devices.

3.4. Committees.

No official committees were used for this Capstone Project.

Chapter 4. Project Description

4.1. Discussion of Project Elements

The elements of this project included the creation of a Handbook made up of a compilation of definitions and regulatory resources that apply specifically to RUO and IVD-RUO biological products. The Handbook organizes the information from applicable basic definitions to regulatory considerations that may impact product shipments. Because of the vast array of biological products, intended use, export/import regulations, the Handbook will only account for the European Union/Germany and South Korea's international regulations. The Handbook focuses on sources and material that the author has found beneficial in developing an understanding of biological product concepts. The objective of this project is to develop a Handbook that could serve as a valuable reference guide for others.

A secondary element of this project was to provide the content in a clear, concise and easily readable format. The information was presented with flow-charts and examples when applicable in hope of by offering the information in a different form may provide additional clarity or easy identification.

Chapter 5. Methodology

5.1. Methodology Overview

The development of this Handbook required a thorough review of company policies and procedures, both federal and international regulations and other previously published biological guidance documents and manuals. Upon completion of review, it was determined that even by narrowing the scope by a product's intended use, there were still far too many elements for the Handbook to be considered an exhaustive compilation of regulatory needs. This is because operational, regulatory affairs activities touch every aspect of the product lifecycle. It was determined that the Handbook was to be developed with consideration of specific workplace applications that would benefit from such a guide, as such the handbook should not be considered exhaustive to all biological regulatory functions. Upon completion of the first draft, the previously listed consulting sources reviewed and provided feedback to ensure the appropriate coverage of relevant elements. The final draft version of the Handbook was disbursed to author's colleges for additional review and to determine the functional use for end-users.

5.2. Discussion of Handbook

The Handbook includes a total of nine chapters that are intended to provide definitions, references, and operational considerations when shipping RUO and IVD biological products; emphasis on South Korea and the EU (specifically Germany) import examples. The introduction to the Handbook is meant to express the intent of the assimilated material and provide the topics available for reference. Because the material differs from a manual or process document it does not require to be read in succession and instead end-users may only need to refer to individual chapters. The intent is for end-

users to access topics of interest easily for general guidance. Even so, the layout of the chapters is provided with fundamental information in the beginning that is built-upon to interpret the information in later chapters.

Chapter 1 supplies basic and broad definitions that may be useful for new or less experienced employees. The terms are focused around common chemical, biological, and manufacturing terms that the author has compiled throughout their own continuous training within the Company. For example, asking "what is a biologic" can be provided with a direct response that the Company has defined as well as reference that to help understand the product type descriptions provided in Chapter 2.

Chapter 3 supplies information and references on the identification of biologics and organized into their respective classifications for regulatory oversight. Classifications may differ from the US, EU, and South Korea, resulting in different documentation required to stay compliant with both domestic and international requirements. For example, biologics are derived from microorganisms, plants, or animals, many of which are produced using recombinant DNA/RNA. The variation between the biological origin and if its synthetic may dictate a classification.

The FDA functions as a basis for established US regulations of many products, but product compliance may also need to consider non-FDA issues that can impact operations. Chapter 4 brings awareness to domestic agency oversight by identifying both FDA regulations by its respective centers in addition to national transportation compliance aspects. It should be noted that state-level regulations are not included in the Handbook but should still be considered.

The company supports 32 countries, of which only two are acknowledged and given a high-level overview. The capabilities to effectively evaluate the risk for new biological and chemical products requires a specific scope of capabilities and workforce that the company chooses to outsource to third-parties. Chapter 5 identifies consulting companies the Company contracts to support chemical and biological product needs.

Shipping products internationally requires its own set of regulatory compliance hurdles. Chapter 6 identifies the international and foreign regulatory authorities in the EU and South Korea with their appropriate customs, regulations, and standards needed to import from the US. This is not easily determined though some countries attempt to harmonize their regulatory processes in hopes that by standardization, there leaves less room for varied interpretations and noncompliance. The severity of noncompliance differs for various countries; Chapter 7 outlines the legal considerations of importing products with noncompliance.

Some biological products require licensing or specific permits because of their intended use or content. This is to ensure the safety and quality of products during their shipment and end-use process. Chapter 8&9 provides manufacturing and product information and resources on quality controls and risks that must be considered during their production and before shipping with biological content regardless of a domestic or international destination.

As previously stated, due to the nature of biologics, they are not as easily categorized as a chemical for regulatory purposes. Chapter 9 discusses some of these issues and offers possible options to organize the information needed for proper data reporting.

Chapter 6. Project Results and Discussion

This project resulted in the creation of a handbook to help new or less experienced research administrators in navigating biological products regulatory elements. The handbook is a compilation of statutory references and guidelines that are meant to be quickly utilized for biochemical product areas within a question. Throughout the authors career transition into the biotechnology industry from clinical research provided many challenges in navigating appropriate resources when assimilating to the new regulatory environment. All the literature and information reviewed during the development of this project only further acknowledged the complexity of the biological product lifecycle. It was identified early on in the project that the handbook could not include information for all types of biologics or even all stages of the biological lifecycle, instead it is focused from the perspective of the author and fellow coworkers to utilize for general resources.

Through discussions and feedback provided by the consulting sources, it was also acknowledged that the intellectual property of the Company's compliance processes being publicly available is not within the best interest because of a competitive marketplace. This concern resulted in a need to keep the Company unidentified and attempt to generalize business strategies or management concepts that would otherwise be specific to the Company but still allow a useful handbook for further utilization.

Chapter 7. Recommendations

All recommendation is based on the research, personal challenges, and source feedback that the handbook presented itself with during development. The recommendations are largely based around the need to define and establish processes surrounding the health of this documentation and methods of ensuring its usefulness for the future. The desire of a handbook to be utilized as a central means of information began with the Company's current challenge of keeping relevant information available and accessible to everyone.

7.1. Recommendation 1: Establish Ownership of Handbook and Assign Updating of Handbook to a Single Entity

The regulatory landscape is continuously changing; the challenge to stay compliant is at constant risk. Although the Company chooses to use third-party providers in tracking and navigating global regulations, internal controls must be reviewed to ensure they are covered. For the Handbook to be a useful resource, it must be mapped into the internal review process during applicable regulatory updates. There is not a document management platform at this current company, all processes are updated manually. By establishing genomics regulatory team ownership, given in recommendation one, the team governs the process performance of the handbook and will be reviewed on a bi-annual basis.

It would not be ideal to include this documentation with formal change controls since that would allow it be part of the auditing system. Instead this document should remain informal but still must maintain some sort of quality checks.

There are various regulatory departments within the Company, each with its own processes. By producing a reference tool that sources key contact information for other departments, it must be agreed upon they each take responsibility of actionable items that may result from referencing this handbook. However, the accuracy and updating of this handbook must be assigned to a single entity. Assigning responsibility allows for changes, updates or questions to be addressed in an organized manner. The recommendation to establish departmental ownership allows them process governance for the relevancy of the handbook.

If the Company decides to break their current, siloed approach to product development the Handbook may then be valued as a central resource of information in order to integrate other department process or considerations.

7.2. Recommendation 2: Future Development of the Handbook

As a means to be a valuable resource for varying levels of experienced staff, there was a strong emphasis on providing the information in a manner that allowed for quick access to crucial elements and ease of readability. The handbook needs to be kept up to date. The Company must enable the handbook to grow within other applicable areas of regulatory concerns, for example, supporting new countries with entirely new regulations that can be added into the current handbook with ease because the information does not directly relate to specific process. The handbook outlines information in a meta-data form that will allow for straightforward navigation, even if more information is added or changed.

This recommendation is a real scenario that the Company faces regularly. As product regulations change, the manufacturing and shipping processes must be updated to

include new variables. Adding one new element may require a complete restructuring because of its downstream impact but this requires the rework of multiple documents across multiple platforms.

7.3. Recommendation 3: Company Needs to Develop a Process for End-User Feedback into the Content of the Handbook

Once available as a finalized document, a larger pool of end-user feedback is possible and should be encouraged. This element was important to the author because the opportunity to allow feedback invites collaboration with more experienced counterparts. As the author noted, this project resulted in identifying gaps and challenges the author's current knowledge of biological product concepts. Providing a culture of continuous learning would support further growth, and development for all included.

Chapter 8. Conclusion

The development of biological products requires a multifaceted approach to stay in compliance with the many regulatory aspects. As one of many biotechnology companies that develop and distribute some variation of products that contain biologic, it is critical to understand applicable regulations that lead to its specific operational activities. Given the complexity and variability, it may be difficult to distinguish a starting point and only then navigate to applicable regulatory requirements. While biotech companies generally contain professionals with a scientific background, the degree of knowledge and understanding can be diverse. Understanding the regulatory to operational aspects help individuals understand the larger company goal. The handbook offers the opportunity to communicate with personnel beyond their current department that may resulting more efficient workflow management because the awareness of cross-functional impact is more likely to be acknowledged.

For some, the need of a handbook would serve as a valuable onboarding tool if newer to the specific product or industry needs or may also provide as useful as a general reference tool. The author hopes that the results of this Biological Handbook serve as a useful resource to research administrators. The Handbook seeks to serve as an onboarding training tool, regulatory and reference guide for biological products.

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Appendix 1: Biological Handbook

BIOLOGICAL HANDBOOK: A REFERENCE GUIDE FOR REGULATORY CONSIDERATIONS

Introduction

This biological handbook is intended to serve as localized resource of fundamental information and regulations applicable to Product Regulatory Affairs (PRA), Genomics Division at the Company, specifically products manufactured and shipped from the Texas logistics center (TX-LC). The documentation provides an overview of product information and processes that comply with appropriate required quality management standards and regulations.

The Company conducts business on a global level. The PRA division is aimed at aiding in the global market assessment by coordinating regulatory information that impact the Company. A basic workflow was developed to provide high-level overview of regulatory responsibility for the PRA team (Appendix I).

The Genomics product portfolio of products manufactured and focuses in reagents, buffers, kits, accessories and their associated software.[1] Due to the complexity and the objective of keeping this handbook as a basic reference guide, there may be regulatory elements not covered. Instead, references and key contact are offered as starting points for further review. Refer to Company standard operating procedures or work instruction for specific company processes.

[1] Agilent, Genomics

Table of Content

Chapter 1. Key Terms and Definitions

5-Bill of Material - A sales BOM in SAP. A BOM that includes one or more parts each with their own 3-BOM. It represents a sellable product. A 5-BOM may be configurable at the time of quotation (have variable elements selected during the sales process).

Analyte Specific Reagents (ASRs) – Analyte Specific Reagents (ASRs) are defined as "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens (21CFR864.4020(a))."[1]

Biohazard – Defined as "any biological or chemical substance that has the potential of infection and considered dangerous to humans, animals or the environment. Management and control of biohazards are divided into four level of risk, also known as biosafety levels."[2]

Biosafety Levels – The Center for Disease Control defines and organizes biosafety levels based on "the severity of infection, risks of containment, severity of infection, transmissibility, origin of microbe, agent in question and route of exposure."[3] There are four biosafety levels, refer to chapter 3 for more information.

Blood Products - whole blood, plasma, serum, antibody, antiserum, coagulation factor, red blood cell, albumin), cell lines, hybridoma, monoclonal antibody, tissue culture, ascitic fluid, extract, feces, fluids, hormones, peptides, tissue, urine.

Comparative Genomic Hybridization – Commonly abbreviated as CGH, refers to a "a molecular cytogenetic method for analyzing copy number variations (CNVs) relative to ploidy level in the DNA of a test sample compared to a reference sample."[4]

Component – "Any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device (21CFR820.3)."[5]

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[1] "§ 864.4020 Analyte Specific Reagents," Code of Federal Regulations, accessed August 1, 2019, https://www.law.cornell.edu/cfr/text/21/864.4020

[2] "Biohazards Definition," Aftermath.Com, Last modified 2017, https://www.aftermath.com/content/biohazards-definition/.

[3] "Biosafety Levels 1, 2, 3 & 4 | What's the Difference?," Consolidated Sterilizer Systems, Last modified 2019, https://consteril.com/biosafety-levels-difference.

[4] "Karyotyping And CGH," Institute For Cancer Genetics And Informatics, Last modified 2017, https://icgi.net/Diagnostics/kariotyping-and-CGH.

[5] "§ 820.30 Design Control," Code of Federal Regulations, accessed August 1, 2019, https://www.law.cornell.edu/cfr/text/21/part-820

Failure modes and effects analysis (FMEA) – Is a step-by-step approach for identifying all possible failures in a design, a manufacturing or assembly process, or a product or service.[6]

Foreseeable Misuse - Unintended conduct that may result from readily predictable human behavior. Foreseeable misuse includes mistakes, lapses, slips or use of a product or system in a way not intended but which can result from readily predictable human behavior including well-meant optimization or readily available shortcuts.

General Purpose Reagent (GPR) – "Chemical reagent that has general laboratory application, is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and is not labeled or otherwise intended for a specific diagnostic application (21CFR864.4010)." [7]

In vitro diagnostic medical device IVD – "A medical device intended by the manufacturer for the examination of specimens derived from the human body to provide information for diagnostic, monitoring or compatibility purposes."[8]

In vitro diagnostic products – Defined as "chemical reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body (21CFR809)."[9]

Indications for Use - The clinical conditions intended to be diagnosed or treated by the product.

Intended Use – A key regulatory concept for all products. The intended use is demonstrated through labeling. The use for which a product, process or service is intended according to the specifications, instructions, and information provided by the manufacturer.[10]

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[6] "What Is FMEA? Failure Mode & Effects Analysis | ASQ," Asq.Org, Last modified 2019, https://asq.org/quality-resources/fmea.

[7] "§ 864.4010 General Purpose Reagent," Code of Federal Regulations, accessed August 1, 2019, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=864.4010

[8] Kazunari Asanuma, *Definition Of The Terms 'Medical Device' And 'In Vitro Diagnostic (IVD) Medical Device'*, ebook Global Harmonization Task Force, 2012, http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf.

[9] "§ 809 In Vitro Diagnostic Products for Human Use," Code of Federal Regulations, accessed August 1, 2019, https://www.law.cornell.edu/cfr/text/21/part-809

[10] Kazunari Asanuma, *Principles Of Medical Devices Classification*, ebook Global Harmonization Task Force, 2012, http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwiPmNPl_5rmAhVSbKwKHdP-BVoQFjAAegQIBBAC&url=http%3A%2F%2Fwww.imdrf.org%2Fdocs%2Fghtf%2Ffinal%2Fsg1%2Ftechnical-docs%2Fghtf-sg1-n77-2012-principles-medical-devices-classification-121102.docx&usg=AOvVaw2VJBF0eiSU0-OR7gqz59k7.

Labeling – Refers to any **"**written, printed or graphic matter affixed to a medical device or any of its containers or wrappers, or accompanying a medical device, related to identification, technical description, and use of the medical device, but excluding shipping documents.[11]

Manufacturer – Defined as "any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions (CFR820.3)."[12]

Manufacturing material – Defined as "any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer (21CFR820.3) ."[13]

Medical Device – Defined by the WHO, **"**Any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material, or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices,
- providing information for medical purposes by means of in vitro examination of specimens derived from the human body, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means,
- aids for disabled/handicapped people,
- devices for the treatment/diagnosis of diseases and injuries in animals,
- accessories for medical devices,
- disinfection substances, and,
- devices incorporating animal and human tissues which can meet the requirements of the above definition but are subject to different controls."[14]

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[11] Abraao Carvalho, *Labelling For Medical Devices*, ebook Global Harmonization Task Force, 2005, http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n43-2005-labelling-medical-devices-050603.pdf.

[12] 21CFR820.3

[13] 21CFR820.3

[14] Gary Syring, "Overview: FDA Regulation of Medical Devices," Qrasupport, Last modified 2003, http://www.qrasupport.com/FDA_MED_DEVICE.html.

Material Safety Data Sheet – Defined by OSHA**, "**A Material Safety Data Sheet (MSDS) is a safety document required by the Occupational Safety and Health Administration (OSHA) that contains data about the physical properties of a particular hazardous substance."[15]

Original Equipment Manufacturer: A company that uses product components from one or more other companies to build a product that it sells under its own company name and brand.

Product Regulatory Affairs (PRA) – Company team that supports timely market access for products by requiring that products are compliant with appropriate regulations and meet customers' stated expectations in terms of safety and environmental requirements.

Product class – Defined as "those products intended for use for a particular determination or for a related group of determinations or products with common or related characteristics or those intended for common or related uses. A class may be further divided into subclasses when appropriate (21CFR809)."[16]

Quality Management System (QMS) – the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management (21CFR820.3).[17]

Quality – The totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance (21CFR820.3).[18]

Reagents- A substance used to carry out a laboratory test. Reagents may be used in chemical reaction to detect, measure, or make other substances.[19]

Risk - Combination of the probability of occurrence of harm and the severity of that harm. ISO14971

Risk Assessment - The overall process comprising a risk analysis and a risk evaluation. ISO14971

Risk Control - The process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels. ISO14971

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[15] "OSHA MSDS Rules | MSDS Authoring Services Inc.," MSDS Authoring, accessed 2 September 2019, https://msdsauthoring.com/msds-safety-data-sheet-chemicals-osha-msds-rules.
[16] "§ 809 In Vitro Diagnostic Products for Human Use," Code of Federal Regulations, accessed August 1, 2019, https://www.law.cornell.edu/cfr/text/21/part-809
[17] "§ 820.3 Quality System Regulation," Code of Federal Regulations, accessed August 1, 2019, https://www.law.cornell.edu/cfr/text/21/part-820
[18] 21CFR820.3
[19] *NCI Dictionary of Cancer Terms. s.v.* "reagent" accessed November 03, 2019, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/reagent

Specification – Defined as **"**Any requirement with which a product, process, service, or other activity must conform (21CFR820.3)."[20]

Substance – A substance refers to a "chemical and any associated compounds regardless of natural occurrence, any additives for preservation, but excluding any diluter that would change its composition (e.g. any constant chemical or pure substance that cannot be separated into different components)."[21]

[20] 21CFR820.3

[21] "Substances And Mixtures | Introduction To Chemistry," Introduction To Chemistry, accessed 3 November 2019, https://courses.lumenlearning.com/introchem/chapter/substances-and-mixtures/.

Chapter 2. Product Types and Description

This section outlines the current products applicable to the guidelines presents in later chapters. Biologics apply to the reagents, or a component in a kit that is used for a broad range of research applications. ***Sellable names of product lines will not be included for initial intent of this handbook.***

2.1 Microarray Reagents

Microarrays are a tool used to help detect RNA or DNA to determine if an individual's DNA contain an alteration in their genes.[22] Also known as biochips, microarrays are glass slides with a specific DNA or RNA oligonucleotide sequence bound to the surface that detect the presence or changes in nucleotide or protein sequences. By accompanying different bioreagent, researchers are enabled to prepare samples and label targeted RNA, gDNA, or miRNA in order to utilize the slides with the microarray hardware.

Bioreagent for processing microarrays: *A link will be provided for Company Use Only*

2.2 Next Generation Sequencing

Next Generation Sequencing (NGS) relates to DNA sequencing technology used in genomics research.[23] Sequencing can be processed in parallel, resulting in thousands or millions of sequences in a much shorter timeframe. Through target-enrichment or

[22] "DNA Microarray Technology Fact Sheet," Genome.Gov, accessed 9 September 2019, https://www.genome.gov/about-genomics/fact-sheets/DNA-Microarray-Technology.
[23] Sam Behjati and Patrick S. Tarpey, "What Is Next Generation Sequencing," *Archives of Disease in Childhood - Education & Practice Edition* 98, no. 6 (2013): 236-238, doi:10.1136/archdischild-2013-304340.

amplicon methods, genomics regions can be selectively captured prior to sequencing; resulting in an increase in sample throughput and opportunity of cost reduction.

Bioreagents used for NGS are mainly used to promote the amplification of targeted sequences for the Illumina platform.[24]

2.3 Mutagenesis and Cloning

The process of purposefully changing the genetic information in a controlled method of a gene or organism that results in a mutation is known as mutagenesis. In vitro site-directed mutagenesis methods allow researchers to study the fundamentals of the protein-function relationship through gene expression and vector modification.[25,26]The molecular cloning, or creation of DNA copies allows for further exploration of protein functioning.

Both site-directed and random mutagenesis kits may be used for various application. Reagents necessary to support targeted mutagenesis are included in the kits.

2.4 Polymerase Chain Reaction (PCR) & Quantitative PCR (qPCR)

Techniques and its associated reagents needed for PCR are fundamental in amplifying segments of DNA in a wide range of clinical research applications

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[24] "NGS Tutorials | Bioinformatics Tutorials And More," Illumina.Com, accessed 10 September 2019, https://www.illumina.com/science/technology/next-generation-sequencing/beginners/tutorials.html.
[25] Fanli Zeng et al., "Multiple-Site Fragment Deletion, Insertion and Substitution Mutagenesis by Modified Overlap Extension PCR," *Biotechnology & Biotechnological Equipment* 31, no. 2 (2017): 339-348, doi:10.1080/13102818.2017.1279033.
[26]Ziad J. Sahab, Suzan M. Semaan and Qing-Xiang Amy Sang, "Methodology and Applications of Disease Biomarker Identification in Human Serum," *Biomarker Insights* 2 (2007): 117727190700200, doi:10.1177/117727190700200034.

such as: cloning, mutagenesis and NGS.[27] With engineered proteins and animal origin additive used for the stabilization of enzymes, these components must be assessed for risks. Refer to chapter 8 for more animal origin country specific information.

2.5 Antibodies

Products that contain antibodies are mainly used to purify serums to help identify and isolate individual proteins that server as markers that help identify mutations, infections or disease. If recombinant, antibodies tested in vitro have the advantage of creating large libraries that have binding properties for in vitro testing.[28] The intended use of the antibodies will determine the appropriate labeling classification below. For example, if the antibody is the active ingredient in a reagent, but does not constitute as the complete kit, then this makes antibody ineligible to be labeled as an IVD.

[27] Eric M Farell and Gladys Alexandre, "Bovine Serum Albumin Further Enhances The Effects Of Organic Solvents On Increased Yield Of Polymerase Chain Reaction Of GC-Rich Templates," *BMC Research Notes* 5, no. 1 (2012): 257, doi:10.1186/1756-0500-5-257.
[28] Weinberg, Wendy, Michelle Frazier-Jessen, Wen Wu, Andrea Weir, Melanie Hartsough, Patricia Keegan, and Chana Fuchs. "Development and Regulation of Monoclonal Antibody Products: Challenges and Opportunities." Cancer and Metastasis Reviews 24, no. 4 (Dec, 2005): 569-84, https://www.ncbi.nlm.nih.gov/pubmed/16408162.

Chapter 3. Classification and Identification

Similar to chemicals, not all biological material is regulated the same. The classification of biological substances is related to the corresponding hazard classification of laboratories and industrial processes. Even products with the same intent may differ in classification based on the country of origin. Shipping regulations are developed and monitored to create an ideal workflow of potential harmful products while ensuring the safety to humans, animals and the environment during transport. Proper labeling and packaging is an essential step in ensuring safety and avoiding exposure. The classifications below are basic biological material standards and should not be considered exhaustive.

Dependent on the host regulations, the accurate identification of a substance in a product allows the company to determine which substance may be included in a product if the objective is market targeted countries. Full compositional data must be identified for the purpose of meeting registration requirements for importing into countries. Refer to Section 8.1.1 for substance tracking requirements.

3.1 Biologic Shipping Classification List

Before products are transported, they must be properly classified in order to determine the correct type of packaging and labeling.

3.1.1 Infectious Substances

Infectious substances are those that contain pathogens. Per IATA (§ 3.6.2) infectious microorganisms are categorized by the following categories and definitions:

Category A – Infectious Substance: Any microorganism that has the ability to cause "permanent disability, life threatening or fatal disease in otherwise healthy humans or animals."[29] Infectious substances must be packed in accordance with IATA Dangerous Goods (DG) regulations. Refer to Section 3.2.3 for DG information.

- UN Assignment(s): UN2814 & UN2900
- *Examples:* Escherichia coli, verotoxigenic (cultures only), Ebola virus. Refer to IATA (3.6.2.2.2.1) for indicative examples

Category B – Biological Substance: Other substances that contain infectious pathogens that does not meet the definition of Category A.

- UN Assignment(s): UN3373
- *Examples:* A blood sample containing Escherichia coli, instead of a culture

3.1.2 Genetically Modified Organisms (GMO) or Genetically Modified Micro-Organisms (GMMO)

GMO/GMMOs are regulated similar to infectious disease categories but even though they do not meet the definition of an infectious disease. These modified organisms are still capable of altering its environment or animals.[30]

- UN Assignment(s): UN3245

[29] IATA,"Dangerous Goods Regulations. Classification of Infectious Substances," 3.6.2.2.2.1 § (2017).
[30] IATA, "Genetically Modified Micro-Organisms (GMMOs) or Genetically Modified Organisms (GMO)," 3.9.2.5.1 § (2017).

3.1.3 Exempt Specimen

Human or animal specimen that was collected directly from the subject and transports for medical use (e.g. diagnosis) or has a very low risk of containing infectious pathogens are exempt from these IATA shipping regulations.

This classification is not applicable to company products. Information included for correctness.

3.1.4 Biologic Product

A common classification for Company products, but are capable of infectious specimen category; biological products are those "manufactured and distributed in accordance national government and authorities….this may include but not limited to unfinished/finished products such as vaccines and diagnostic products."[31]

UN Assignment(s): UN3733, UN2900 or UN2814

3.2 International Goods Classification

To adhere to trade policies and procedures control codes must properly be assigned to import and export products/items when they are meant to be shipped across international borders in order to control appropriate duty rates and obligations, set quotas and gather trade statistics. Governments require imports and exports to be assigned a classification in order to track types of substances that are shipped into and out of countries. Correct classification allows for faster turnaround times, minimize duty cost and eliminate one potential source of shipment delays.

[31] IATA 3.6.2.1.2

All legal responsibility and compliance adherence are owned by our highly trained global trade team.

3.2.1 Harmonized Tariff Schedule (HTS)[32]

- A code required by importing authority to assess the duties and taxes on the products or items.
- Used to determine trade compliance statistics

3.2.2 Export Control Classification Number (ECCN)

- Alphanumeric commodity code used to identify a product/items export licensing requirement.
    - All domestic companies are required to provide an ECCN to the US Government

Please use the web-based interface trade automation tool to locate technical information about our products classification logic: *A link will be provided for Company Use Only*

Corporate compliance policy: *A link will be provided for Company Use Only*

3.2.3 Dangerous Goods

Dangerous Goods (DG) are defined by IATA as "any solid, liquid, gas that may endanger a person or transport carrier during the shipment via air transport."[33] DG classification in conjunction with GHS is an integral component of the hazard

[32] "A Harmonized System for Intended Use Codes," Customsinfo.Com, accessed 1 October 2019, https://www.customsinfo.com/A-Harmonized-System-for-Intended-Use-Codes.
[33] "Frequently Asked Questions," IATA.Org, Last modified 2019, https://www.iata.org/whatwedo/cargo/dgr/Pages/faq.aspx.

substance/dangerous goods framework. Guided by GHS, DG classifications are managed and maintained by the Company's logistics center.

- DG via aircraft, refer to IATA- *DG Global Reference Manual*
- DG via ground, refer to 49 CFR 171-180 – DOT Ground Transport

DG Classification is required to ensure the following:

- Safe Transport of hazardous materials per the trade requirements
- Safety for all individuals involved in handling of the cargo
- Ensure proper handling and packaging for loading/unloading of all goods

3.2.4 Hazard Communication Standard (HCS)

The identification of hazardous chemicals is crucial to workplace safety. Similar to GHS this accomplished through standardizing labeling, SDSs and training requirements as stated in 29CFR1910.1200.[34] It is important to note that HSC has been aligned with GHS safety standards but inclusion of articles results in more hazard chemical classification that dangerous goods.

3.2.5 Toxic Substance Control Act (TSCA)

Under the management of the dangerous good program, the Company is responsible for the procurement of biological and chemical mixtures and substances information to provide to the US Environmental Protection Agency. Refer to 15 U.S.C. §§ 2601-2629 for detailed information about TSCA.

In addition, 40 C.F.R. §§ 704.3 may provide definitions applicable to TSCA requirements.

[34] "Hazard Communication | Occupational Safety and Health Administration," Osha.Gov, accessed 25 November 2019, https://www.osha.gov/dsg/hazcom/index.html.

Chapter 4. Domestic Regulatory Oversight

Genomics regulatory affairs complies with a number of regulations, standards, guidance and quality systems throughout different phases of a products lifecycle. A high-level of domestic oversight and their functions are provided in this section. Reference to specific regulations or guidance documents are presented in other chapters applicable to the topic. Refer to chapter 6 for international agencies overview. This list may not be exhaustive, as regulatory jurisdiction and requirements can come from state, regional, and national entities and be further regulated by postal, carrier and import/export controls depending on the product scope. For example, a large number of biological products manufactured at TX-LC are labeled as Research Use Only (RUO). Because RUO products are not used in diagnostic like medical devices, they do not fall within the jurisdiction of FDA and quality system regulation oversight. Even so, FDA information is provided to allow a foundational understanding of biological product oversight outside of this niche classification of RUO.

4.1 Food and Drug Administration (FDA)

The FDA is one of eleven agencies within the Department of Health & Human Services (HHS). The responsibilities of the FDA is two-fold, the primary mission to "protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation" and secondly to aid

in the innovation of medications and foods for further public advancement.[35] Biologic regulation, in addition to food, drug and medical devices are codified in 21 CFR by their associated functional areas. As a prominent regulatory agency responsible for such a wide range of consumer products, they are composed of various centers and organizations to take on the large scale of potential advancements. Refer to Appendix II for the current organizational structure of the FDA.

Because of the diversity of biologics there are three centers that regulate biological products: (1) Center for Drug Evaluation and Research (CDER), (2) Center for Biologics Evaluation and Research (CBER), and (3) Center for Devices and Radiological Health (CDRH).

This handbook outlines the three main centers and their responsibilities but the degree of applicable regulations for biological products will vary by individual classes and nature of products. Refer to Table 4.1 for centers responsible for biological products review and regulations.

[35] "FDA Organization," U.S. Food And Drug Administration, Last modified 2019, https://www.fda.gov/about-fda/fda-organization.

Table 4.1. FDA Centers with Biological Oversight

Center for Drug Evaluation and Research (CDER)	Center for Biologics Evaluation and Research (CBER)	Center for Devices and Radiological Health (CDRH)
• Monoclonal antibodies (mAbs) • Enzymes • Small molecule (organic chemicals) • Oligonucleotide therapies • Therapeutic proteins and peptides • Therapeutic immune therapies • Combination products with biologic primary *Center is **not** applicable	• Vaccines • Plasma/serum products* • Blood products* • IVD for blood • Gene therapies • Somatic human cells or tissue • Somatic animal cells or tissue • Gene therapies • Antivenoms • Combination products with biologic primary	• IVD* • ASR* • GPR* • Medical device • Radiation-emitting devices • Medical imaging agent • Diagnostic and Radiopharmaceuticals • Surgical and therapeutic • Combination products with biologic primary

Source: Data adapted Centanni, John M., and Michael J. Roy. *Biotechnology Operations : Principles and Practices, Second Edition*, CRC Press LLC, 2016. 70
(*) applicable to department

4.1.1 Center for Drug Evaluation and Research

The CDER regulates biological therapeutics and generic drugs that are distributed as over the counter and prescription drugs. This means all the biologically derived cells, molecules, tissues or other biologics listed in Chart 4.1 are intended to be used for the treatment, diagnosis, or prevention of diseases and are generally based by their therapeutic category.[36] The CDER is concentrated in human safety, thus rely more on ICH guidelines. It should be noted that bio-therapeutics may be regulated under both CDER and CBER.

The CBER regulates a large number of biological products intended for human use, this includes but is not limited to tissue-based products, blood products, vaccines,

[36] "Center For Drug Evaluation And Research | CDER," U.S. Food And Drug Administration, Last modified 2019, https://www.fda.gov/about-fda/office-medical-products-and-tobacco/center-drug-evaluation-and-research-cder.

cellular & gene therapies and select IVDs.[37] Review of products is focused on the type of molecule, thus rely more on FDA regulations and guidelines.

4.1.2 Center for Devices and Radiological Health (CDRH)

The CDRH regulates the use of medical devices and safe radiation emitting product by monitoring the safety, efficacy and quality of products for human use.[38] Products regulated by the CDRH must be registered with the FDA.

4.2 U.S. Department of Agriculture (USDA)

The USDA regulates biological products with animal derived materials.

4.2.1 Animal and Plant Health Inspection Service (APHIS), Veterinary Service (VS)

USDA-APHIS is a supplementary federal department that regulates and manages importing and exporting controls products that contain animal derived materials while supporting the facilitation of international trade.[39] Many model organisms used in marketed kits contain an animal origin source because of genome similarities and ease of availability.

The USDA-APHIS, Center of Veterinary Biologics (CVB) supports exporting controls for licensed biological products. The CVB facilitates exporting permits, licenses and inspection forms and guidance needed for international shipping. For example,

[37] "CBER Product Jurisdiction," U.S. Food And Drug Administration, Last modified 2019, https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/cber-product-jurisdiction.
[38] "Center For Devices And Radiological Health," U.S. Food And Drug Administration, Last modified 2019, https://www.fda.gov/about-fda/office-medical-products-and-tobacco/center-devices-and-radiological-health.
[39] "USDA APHIS | Imports: Animal And Animal Products," Aphis.Usda.Gov, Last modified 2019, https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-and-animal-product-import-information.

veterinary biologic export certificate requirements are supported under EC 142/2011; the CVB offers guidelines for proper preparation prior to request.[40]

The process of importing animal products may include multiple requirements. Licensing, permitting or certification authorization must be granted prior to importing. Shipping documentation with associated permit types may be found in APHIS Animal Product Manual, refer to website to ensure capture of latest version.[41]

4.3 Federal Transport

Manufacturing and logistics must comply with applicable domestic and international transport regulations. The method(s) of transport dictate the regulatory oversight.

- **International Air Transport Association (IATA):** Applies to air transport /regulates dangerous goods (e.g. infectious substances)
- **Postal Service Dangerous Goods:** Applies to products/specimen shipped by mail
- **US Department of Transportation (DOT):** Applies if product/specimen is sent via ground carrier
- **Federal Aviation Administration (FAA):** Applies to hazardous materials

4.4 International Organization for Standards (ISO)

International standards are utilized in international trade, setting a quality and safety standard for industry products and services. Regardless of a country's primary language, the organization uses the standardized acronym 'ISO,' to maintain international recognition instead of each country having their own based on their foreign language

[40] *Guidelines For Preparation Of Regulation (EU) 142/2011 Export Certificates*, ebook APHIS, 2019, https://www.aphis.usda.gov/regulations/vs/iregs/products/downloads/ee-guide-ex-cert.pdf.
[41] *Animal Product Manual*, ebook, 2nd ed., 2014, https://www.aphis.usda.gov/import_export/plants/manuals/ports/downloads/apm

structures. The organization identifies itself as independent, separating itself from government oversight to develop standards for international market needs.[42] Refer to Chapter 9 for Company specific ISO certifications.

[42] "About Us," ISO, Last modified 2019, https://www.iso.org/about-us.html.

Chapter 5. Consulting Business Partners

Regulatory business processes, specific to Genomics PRA are provided additional third-party consulting services to support chemical and biological compliance efforts.

5.1 ARCARDIS

A contracting company, that is utilized to assist in international chemical and biological governing regulations during the product development phase. As a global consulting firm with an active presence in over 70 countries and large-scale operation size. ARCARDS has the support structure to continuously monitor new and changing regulations proactively.[43] Services include the review of product information to determine the workflow of the regulatory requirements needed to ship into targeted countries, if even applicable.

This may include but not limited to:

- Risk and Compliance Assessments
- Compliance Assessment
- ChemAdvisor Reviews
- Biological Implications

ARCADIS website: https://www.arcadis.com/en/global/

Contact GSD Manager specific SOW information via email at: *A link will be provided for Company Use Only*

[43] "Arcadis Environmental Health And Safety," Arcadis, accessed 17 September 2019, https://www.arcadis.com/en/global/our-perspectives/2019/arcadis-environmental-health-and-safety/#.

5.2 Sphera Solutions

The generation of Safety Data Sheets (SDS) documents for country specific product releases are contracted through Sphera Solutions. This is to include required language translations for all targeted countries.

Sphera Solutions website: https://sphera.com

Refer to respective Supplier Program Manager for process information: *A link will be provided for Company Use Only*

Chapter 6. International Oversight

Regulations and requirements for international product compliance are developed with the same objective as the US, to ensure the safety of the public by reducing risks and improving the quality of life through new innovations. Meeting the standards of foreign agencies can pose challenges if the Company lacks tools or resources for proper awareness and compliance. To meet the basic objective of compliance requires recognizing foreign agencies that impact the importation and marketability of Company products.

6.1 European Union (EU)

The European Union (EU), comprised of 28 countries, is a union meant to serve as a single source for policies that relate to economic and/or political views. Germany falls under the jurisdiction of the EU. A large portion of regulations or laws that implicate importation and standards of Company products marketed for Germany used may be referenced under EU legislation. EU legislation is meant to harmonize product safety standards for all EU member states, resulting in directive(s) for a "single market."[44]

[44] "Export.Gov - Trade Regulations, Customs and Standards," Export.Gov, Last modified 2016, https://2016.export.gov/germany/MarketResearchonGermany/CountryCommercialGuide/TradeReg

6.1.1 European Commission (EC)

The EC is a subgroup appointed by the EU organized to develop and enforce harmonized EU standards. With 53 executive agencies, the EC websites holds a repository of EC directives.

- Refer to Section 8.3.1.1 for labeling and packaging EC legislation
- Refer to Section 8.1.1. for REACH regulation overview

6.2 South Korea Oversight

Similar to other countries, there are various agencies that provide oversight for goods exported to South Korea. Navigating the importing requirements and meeting industry standards can present itself as challenging without proper subject matter expert, this is due to differing business models.

6.2.1 Ministry of Environment (MoE)

The MoE supports chemical substance registration and evaluation under 'K-REACH' Act.[45]

[45] "Revised K-REACH - The Act On The Registration And Evaluation Of Chemicals - News And Articles - Chemical Inspection And Regulation Service | Enabling Chemical Compliance For A Safer World | CIRS," CIRS-Reach, Last modified 2019, http://www.cirs-reach.com/news-and-articles/revised-korea-reach---the-act-on-the-registration-and-evaluation-of-chemicals.html.

Chapter 7. Legal Consideration

The many phases of the product lifecycle and its output require layering compliance roles that must be met by the Company. There are many government and non-government agencies, in additional to international agencies with noncompliant punitive actions. Significant penalties can be a result of noncompliance, with the possibility of criminal and/or civil sanctions.

7.1 Environmental Noncompliance

The most important aspect of non-compliance is the consideration of elevated risk. Both chemical and biological can pose a great threat to humans, animals and the environment if not handled with care. The safety aspects of non-compliance begin in the product development phase and should be thoroughly considered if all aspects of safety are not properly planned and executed.

7.2 Impact of Wrong Classification

Proper classification is a critical element of product development because of its downstream impact on the global trade environment.

Inaccurate information may result in higher duty levitation including:

- Incorrect duty assessment
- Shipment delays such as a delay in customs clearance
- Additional licensing requirements
- Fines/penalties

7.3 Misbranding and Adulteration

The FDA enforces false or misleading product labeling is a serious violation in all countries. Misbranding normally occurs as a result of following improper procedures or

an individual neglecting the proper procedures. Adulteration or misbranding may leave an individual in addition to the company liable to penalties.

7.4 Shipping Penalties

Enforced by the Pipeline and Hazardous Safety Administration shipping biological hazard products that are not in compliance with shipping regulations can result in public safety repercussions civil penalties. Per 49CFR107.329, 171.1 civil penalties include the following:[46]

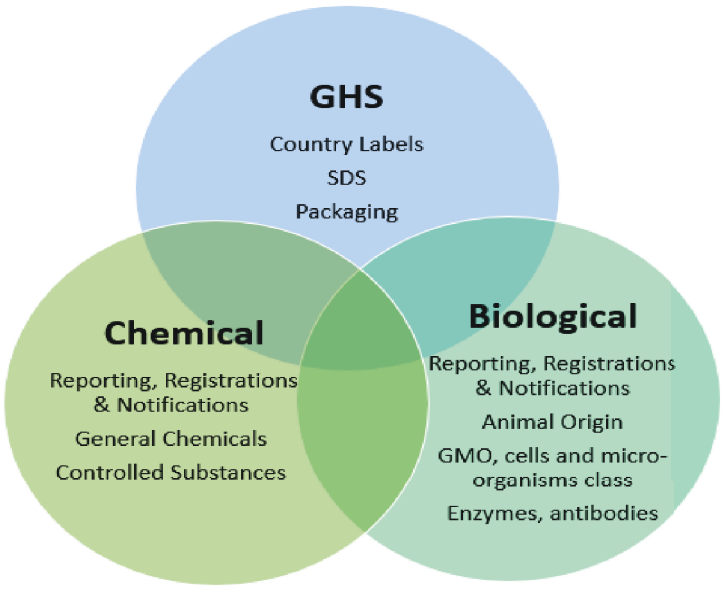
- Up to a $75,000 penalty for knowingly violating Federal hazard material transportation law
- Up to $175,000 penalty for knowingly violating Federal hazard material transportation law or violating a special permit law that results in server injury or death, or substantial destruction to property.

[46] Federal hazardous material transportation law, U.S Code of Federal Regulation, Chapter 49, sec.107

Chapter 8. Shipping Consideration

The shipping of both biological and chemical products can create a complicated down-stream compliance workflow due to multi-layered regulations and classifications across internal and external factors. This means that our Company must ensure the compliance of any host country. For example, chemical and biological regulations are closely related to trade regulations and export licenses, if there is a gap in the relationship between transport code and permit license manufacturers elevate their risks of non-compliance. Additionally, product compliance elements must be met for host country. Overlapping challenges between chemical, biological and product regulations and restrictions are represented in Figure 8.1.

Figure 8.1. Product Compliance Challenges



8.1.1 Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)

Prior to EU REACH regulation (EC 1907/2006), substances manufactured and marketed within various products were not tracked and reviewed to adequately assess risks of substances. Through REACH, a process was developed to provide proactive measures of assessing chemical properties for risk management.[47]

REACH regulations must be considered during the early stages of product development. Early data compilation is used to assess a cost-benefit analysis to help the R&D project team with potential marketability.

8.1.2 Act on the Registration and Evaluation of Chemicals (K-REACH)

Similar to objective and process as EU REACH regulations. Through an organized registration process, chemicals can be managed for hazard and risk elements. An overview of the K-REACH framework is provided by ChemLinked is provided in Figure 8.1.

South Korea, PRA Contact: *A link will be provided for Company Use Only*

8.2 Packaging Requirements

Packaging should comply, at minimum, with IATA biological materials classification requirements and GHS labeling.

[47] "Understanding REACH - ECHA," ECHA.Europa, Last modified 2019, https://echa.europa.eu/regulations/reach/understanding-reach.

8.3 Labeling:

A product classification triggers the development of product labeling by identifying the basic requirements for any product to be market released. Correct labeling is an integral element the regulatory classification because the Intended Use is demonstrated through labeling requirements. Labeling requirements do not just apply to its primary container/box but also apply to any secondary container and packing inserts (e.g. user manual, certificate of analysis, SDS).

Regulatory Affairs at Company is responsible for ensuring the labeling information adheres to all applicable regulations and/or guidelines that could lead to misbranding or adulteration. Because our company offers "kits" through various items, labeling methods will depend on the country of origin. There are 4 areas/elements/job applicable GHS, CE Marking, SDS, and certificate of analysis.

8.3.1 GHS Labeling

The Globally Harmonized System (GHS) is used for the classification and labeling of chemicals. Its objective is to *harmonize* the way hazardous chemicals are communicated on an international level. In turn, simplifying the sale, transportation and safety of chemicals. It is important to note that while GHS is not a regulation but instead is a set of recommendations, the US has adopted the GHS process and should be supported.[48] The Department of Labor, Occupational Safety and Health Administration provides relevant oversight of GHS criteria. Published in the federal registrar and

[48] *Globally Harmonized System of Classification And Labelling Of Chemicals (GHS)*, ebook, 7th ed. New York and Geneva: United Nations, 2019, https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev07/English/ST_SG_AC10_30_Rev7e.pdf

effective in 2012, modification to the Hazard Communication Standards (HCS)[49] was finalized to conform to GHS standards.

Although GHS labeling is heavily concentrated on chemical information, it is still an important element of biological product considerations. Not only are biological components suspended in a chemical, but the biological risk should give proper warning by proper biosafety level identification.

There are 6 main elements of UN GHS Labeling[50]:

1. **Signal Word** - Indicates hazard level (Danger, Warning)
2. **GHS Symbols (Hazard Pictograms)** – Identify chemical/physical, health or environment risks.
    - Refer to Appendix III for commonly used hazardous symbols.
3. **Manufacturer Information** – Company name, address and telephone.
4. **Precautionary Statements/First Aid** - Safety Data Sheet identified by P-Code
5. **Hazard Statements** - Hazard and degree of hazards identified by H-Code
6. **Product Identifier:** Manufacturer product number and name

[49] Chapter 29, Parts 1910, 1915, and 1926," Code of Federal Regulations, accessed October 27, 2019, https://www.osha.gov/laws-regs/federalregister/2012-03-26

[50] "Globally Harmonized System (GHS) Labeling Requirement," BRADY, Last modified 2019, https://www.bradyid.com/applications/ghs-labeling-requirements.

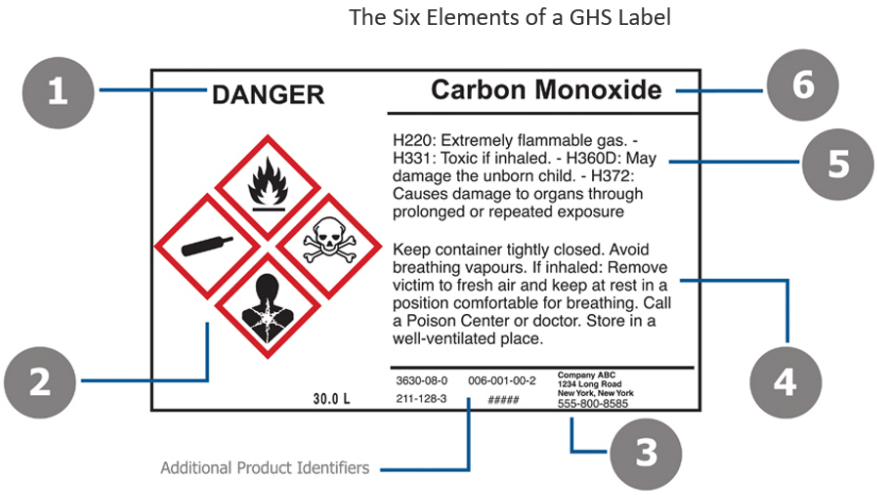


Figure 8.2 Elements of a GHS Label
Source: "Globally Harmonized System (GHS) Labeling Requirements," BRADY, accessed November 01, 2019, https://www.bradyid.com/applications/ghs-labeling-requirements

There are a large number of countries that have adopted the GHS process. Even so, many countries or their respective authorities have published their GHS guidelines due to their varying regulatory frameworks. Per GHS ver7 1.1.3.1.5, countries are to use a building block approach, allowing them to freely determine which elements of the GHS system they are willing to apply within their framework.

Genomics specific product labeling requirements SOP: *A link will be provided for Company Use Only*

8.3.2 Labeling in European Union

Mandated by the European Parliament and the Council, GHS has slowly been implemented in the EU since the year 2004 by the European Chemical Agency (ECHA). Relevant legislation regarding labeling and its resources have been provided for reference.

(EC) No1272/2008: Regulation that refers to EU "classification, labeling and packaging of substances and mixtures" requirements into regulation." [51] The regulation is commonly referred to as 'CLP.'

The bio-chemical composition is required for all final products.

(EC) No 1272/2008: Click Here

Annex VIII – The cataloguing of classifications of hazardous substances, per the EU, is published in Annex VIII. Recent guidance to help determine the criteria CLP sets forth for hazardous mixtures and its relationship identified hazardous materials in Annex VIII.[52]

Guidance on Annex VIII to CLP (Version 22/07/2019): ECHA Documents

8.3.3 Labeling in South Korea

Chemical verification must be completed for all reagents or mixtures to verify status as regulated/unregulated substance. Chemical substances need to be registered for products accumulating to shipping more and 1 ton annually of chemical.

Mandated by the National Institute for Environmental Research (NIER), the Republic of Korea has implemented some GHS requirements. Labeling products for South Korea exporting must include both the GHS labeling and the specific South Korea labeling. Relevant legislation regarding labeling and its resources have been provided for reference.

[51] GHS Labeling Requirement, BRADY
[52] "Guidance On CLP - ECHA", Echa.Europa, accessed 21 September 2019, https://echa.europa.eu/guidance-documents/guidance-on-clp.

Toxic Chemical Control Act- exempt for laboratory reagents used for scientific analysis

8.4 Safety Data Sheet (SDS)

Safety Data Sheets are utilized as a regulatory compliance document for communicating chemical/biological product information. These documents provide end-users with information for safe handling by outlining hazardous ingredients and appropriate safety instructions. Sphera and PRA is responsible for the proper generation and maintenance of SDSs.

Logistics reviewer is responsible for the proper transport classification provided on all SDSs.

SDS Generation Process SOP: *A link will be provided for Company Use Only*

8.4.1 South Korea SDS

Currently South Korean SDSs are not mandatory for laboratory reagents for scientific analysis. However, process concerning SDS generation are in-review to update processes on new OSHA regulation.

Industrial Safety and Health Act (ISHA) – Effective January 16, 2020 the Ministry of Employment and Labor (MOEL) has been amended to comply with GHS requirements relating to safety data sheets. Highlight of applicable amendments provided by ChemWatch include:[53]

[53] Sunny Lee, "South Korea's Osha SDS Submission Rules Approaching Legislature," Chemical Watch, Last modified 2019, https://chemicalwatch.com/71638/south-koreas-osha-sds-submission-rules-approaching-legislature.

- Company must submit all product SDS to the MOEL 30 days before importation to be registered, and must include the following elements:
    - Name of Product
    - Name and content of any controlled substances
    - Handling instructions
    - Hazards
    - 100% composition information
        - As a possible intellectual property issue, exemptions may be granted for substances that comply with K-REACH

Occupational Safety and Health Act information: Click Here
Domestic Representative regarding regulation changes: *A link will be provided for Company Use Only*

8.5 Marking

All products must be marked with clear and legible writing, placed in a conspicuous location. Entities that are in possession of the goods before shipment are aware of best standards for ensuring correct markings.

A CE marking, implemented by the European Commission, is a required identification tag before products can be entered into the EU marketplace. The marking signifies that it has met all of the European Economic Area qualification.

Refer to link for CE marking information: Decision 768/2008

8.6 Documentation

A product declaration is utilized to outline all the applicable laws/regulations, allowing the Company to certify all the criteria has been met.

8.6.1 Declaration of Dangerous Goods

Shipments that hold hazardous material must submit a DG declaration in addition to other appliable safety labeling.

8.6.2 Animal Origin (AO) Declaration/Certificate

Products that contain animal derived substances require a separate inspection process when entering customs. This is because the importation of biological products within contained sources of animal origin may add additional risks to the public. Special import conditions must be met during the transportation of products with AO, for example, splitting the delivery and separating the non-animal origin products may reduce the risks of contamination. Refer to our Company's EHS database for specific information regarding the biological compositions of production.

AO Declaration elements:

- Product name: Trading name of product(s) that appear on packaging must match;
- Description: All imported products must list any raw material sourced with animal origin, species and concentration;
- Biological information: biological composition (w/v%), exact weight and CAS number if applicable;
- End Use: Statement for end use that must match their US FDA export certificate and,
- Country of Origin: States the country of origin.

8.6.2.1 Germany: EU Veterinary Regulations

Shipment requires supporting documentation for products that contain animal origin. Enforced by customs Veterinary authorities, AO products may only enter with the require AO documentation. Declarations are generated during the transfer order created by our logistics team.

Animal origin documentation may include:

- AO Declaration
- Certificate of Analysis
- Process Statement
- Product Specification Sheet

8.6.2.2 South Korea: AO Declaration per shipment

Biological products are subject to customs quarantine process enforced by the Animal and Plant Quarantine Agency (APQA).

The manufacturer (Company) must provide an export certificate and be endorsed **prior** to shipping products that contain animal derived materials or are classified as blood products. The US Department of Agriculture (USDA) provides guidance on the exportation of animal products.

Per the USDA[54] basic information required on all export certificates include:

- Product name and any species of origin
- Number of packages- packages are considered by the sellable part-number
- Total weight
- Shipping container number and seal
- Date of shipment
- Name of the vessel or aircraft used for transportation

[54] "USDA APHIS | Korea," Aphis.Usda.Gov, Last modified 2019, https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/export/iregs-for-animal-product-exports/sa_international_regulations/sa_by_country/sa_k/ct_product_korea.

Chapter 9. Safety and Quality

9.1 Biosafety Level

Due to the nature of biologics, they may be harmful to humans, animals or the environment. Laboratories that conduct research must be provided the identification and proper laboratory practices needed to conduct the handling, research and waste management for all associated chemicals and biologics. The Center for Disease Control has designated 4-levels of biosafety that refer to the risk of exposure.[55]

Ranked from lowest to highest biosafety levels are: BSL 1, BLS 2, BSL 3, BLS 4.

Refer to OSHA standard 29 CFR 1910.1030 for biosafety guidelines and requirements. Biosafety levels are guided by GHS and are integrated into the TX-LC facility manual, in conjunction with all agent safety data sheets.

9.2 Quality Management System (QMS)

The QMS framework is built on processes that safeguard quality, safety and compliance all products and services. The Environmental, Health and Safety Management System (EHSMS) supports operational efficiency related to training, product manufacturing, sales and distribution.

ISO Certificates current help Company-wide and TX-LC specific:

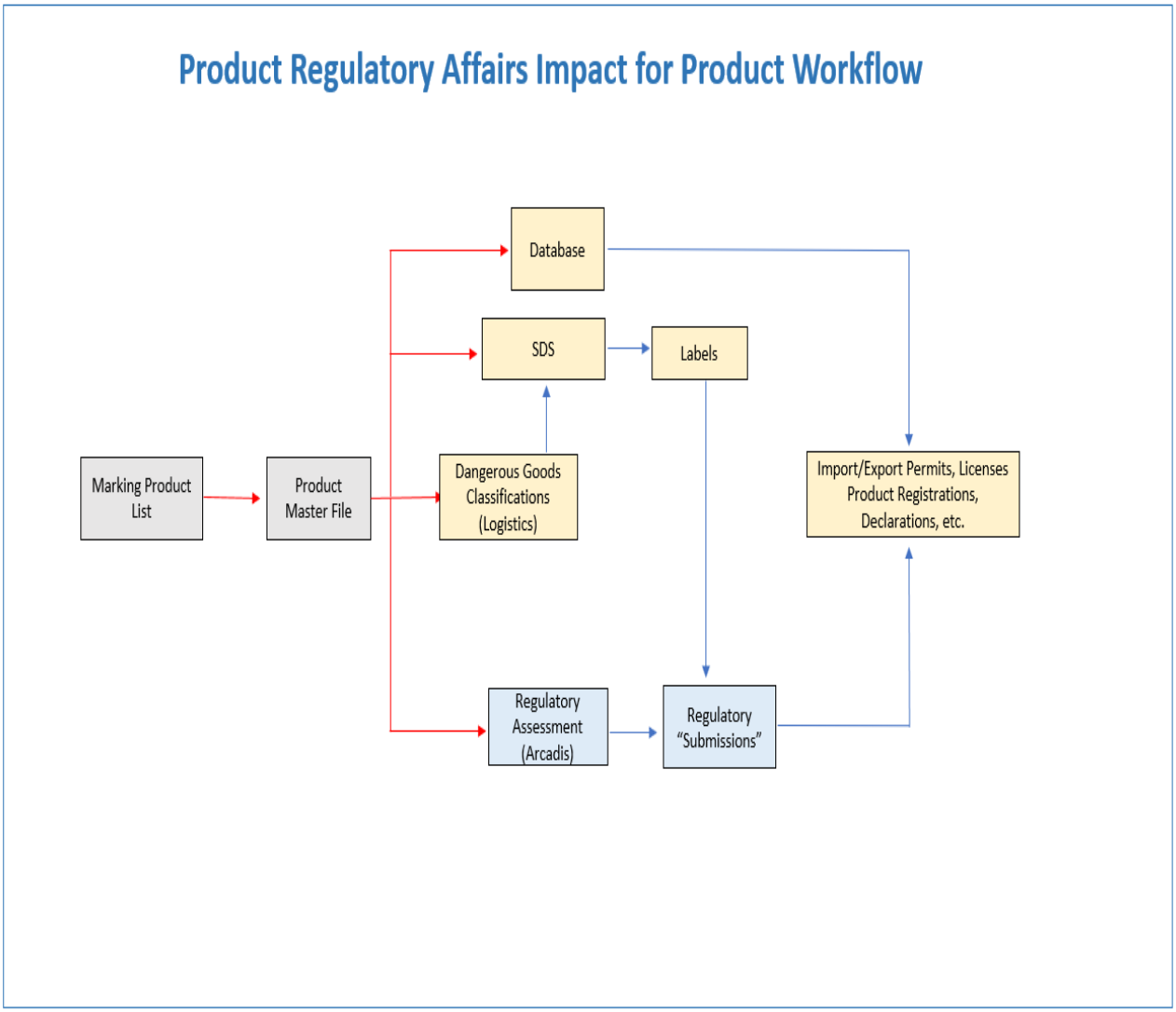
- ISO 9001- Quality Management System
- ISO 13485 – Medical Device Quality Management System
- ISO 14001 – Environment Management System

[55]"Guidelines for Biosafety Laboratory Competency
." https://stacks.cdc.gov/view/cdc/11597 (accessed September 30, 2019).

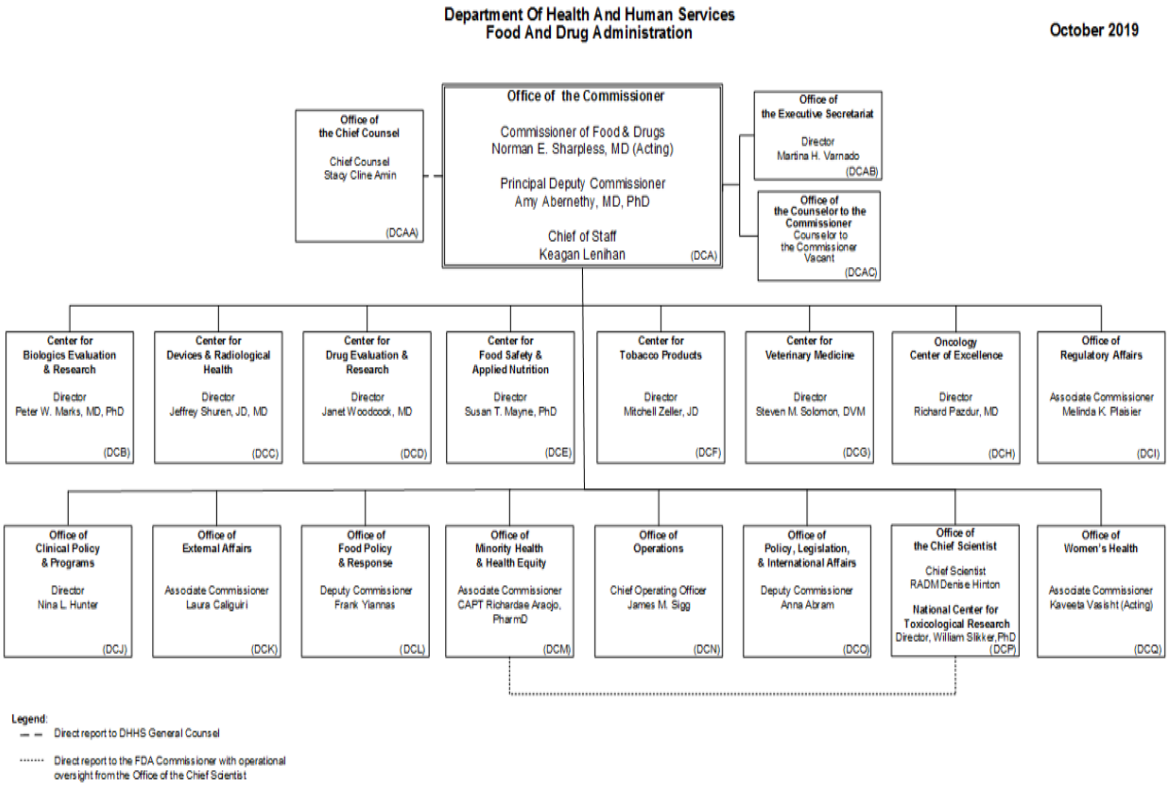
List of Abbreviations

BOM	Bill-Of-Material
CAPA	A Corrective and Preventative Action
CLP	Classification, Labeling and Packaging
DGG	Diagnostic and Genomics Group
Early Access / EA	Early customer access
FDA	United States Food and Drug Administration
GDP	Good Documentation Practices
GMP	Good Manufacturing Practices
GSD	Genomics Solutions Division
IDE	Investigational Device Exemption
ISO	International Organization for Standardization
LC	Logistics Center
MSDS/SDS	(Material) Safety Data Sheets
NGS	Next generation Sequencing
NIH	National Institutes of Health
QA	Quality Assurance
R&D	Research and Development
RA	Regulatory Affairs
RAMM	Risk Analysis and Mitigation Matrix.
RUO	Research Use Only
SAP	Systems, Applications and Products
SCM	Supply Chain Management
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
UN	United Nations

Appendix I: PRA Impact for Product Workflow



Appendix II: FDA Organizational Chart



Source: *Organizational Chat: Department of Human Service, Food and Drug Administration* . U.S. Food and Drug Administration "FDA Overview Organization Chart" https://www.fda.gov/about-fda/fda-organization-charts/fda-overview-organization-chart: Food and Drug Administration, 2019.

Appendix III: Common GHS Hazard Symbols

Common GHS Hazard Symbols	
Hazard	Pictogram
Corrosive	
Environment	
Flammable	
Toxic	
Irritant	
Carcinogen/Reproductive Hazard	
Gas Cylinder	
Explosive	
Oxidizing	

Source: "Hazard Pictograms." http://www.hse.gov.uk/chemical-classification/labelling-packaging/hazard-symbols-hazard-pictograms.htm, Health and Safety Executives. 2019

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Appendix 2: Biography

Sherilyn Garcia received her Bachelor of Science degree in Clinical Research from the University of North Carolina Wilmington. She has experience in a broad range of clinical research activities, largely based in roles in a Clinical Research Organization (CRO), focusing her efforts in project management and study-startups. Sherilyn earned her Master of Science in Research Administration from Johns Hopkins University with a focus in compliance, legal, and regulatory issues and administering and facilitating research programs. Currently, she works for a Biotechnology company, providing support in a Product Regulatory Affairs role. She is a Marine Corps veteran and proudly served during Operation Enduring Freedom/Operation Iraqi Freedom.