A PROSPECTIVE STUDY OF CURRENT AND ALTERNATIVE REGULATORY REPORTING REQUIREMENTS REGARDING SECTION 361 HUMAN CELL, CELLULAR AND TISSUE-BASED PRODUCTS

by

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(Under the Direction of Grace Gowda)

ABSTRACT

The Food and Drug Administration oversees the regulation of drugs, biologics, medical devices, and Section 361 human cell, cellular and tissue-based products (HCT/Ps), a product classification regulated by Section 361 of the Public Health Service Act. FDA applies different mandatory safety event reporting requirements from manufacturers for HCT/P (adverse reaction reporting) s than non-HCT/P products (adverse event reporting). This prospective study reviews and compares reporting, and other regulatory considerations and requirements, of HCT/Ps and non-HCT/Ps and compares available data to identify safety gaps in mandatory reporting and the FDA's oversight of product safety. Potential gaps are identified regarding the reporting framework of HCT/Ps, the FDA's HCT/P oversight strategy, and the FDA's ability to inform and protect the general public health; the study is recommended for repetition to achieve statistical significance.

INDEX WORDS: Adverse Event; Adverse Reaction; Section 361; HCT/P; Human Cell, Cellular and Tissue-Based Product; Regulatory Affairs; Mandatory Reporting; FDA; Regenerative Medicine. 21 CFR 1271

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B.S., Auburn University, 2017

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2021

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December 2021

DEDICATION

This thesis is written and submitted in dedication to my family. To my wife whom I love tremendously, Jada, your continued confidence in me, willingness to stand by me, and ability to encourage me has been paramount to my success getting to this point; I am eternally thankful and grateful for all that you are and will become. To my mother and brother, Jana and Jesse Mayhall, along with my late-grandparents, Bill and Ina Greene, your willingness to give so generously and invest in my character, my profession, and my life is priceless; I do this all in your honor and memory. You inspired my sense of intrigue and my desire to help others with the skills and knowledge I have been given; I think of you all when I think of what has brought me to this point in my life. To the Starks and Burkeholders, your welcoming spirit and continued support is cherished and has catapulted me to the place that I am today.

ACKNOWLEDGEMENT

There are numerous other families to acknowledge for their support, encouragement, and inspiration through this phase of my professional and educational career.

To my professional family, first at Thermo Fisher Scientific – MBD Norcross (Jim, Kathy, Susan, Donny, Chuck, Sanda, et al.), thank you for welcoming a bright-eyed Auburn graduate into the workplace culture and for catalyzing my passion for Regulatory Affairs.

To my StimLabs colleagues, serving in this regulatory role has been a dream come true, working at StimLabs has allowed me so much that I cannot take for granted. I am grateful to work aside you as we accomplish our mission to innovate the industry and, most importantly, help those in need. Thank you for continued support and help as I navigated this journey and for my topic field of interest. To Melissa O'Connor, working at StimLabs is an opportunity of a lifetime; thank you for affording it to me and for your leadership at a company I dearly love.

To my University of Georgia family, you never shied away from a jab at my alma mater but accepted, welcomed, and molded me regardless of football rivalries. To Johnna Hodges, your positive attitude and determination to be a helper, a resource, and answer countless questions has quite literally gotten me to this moment. To Al Jacks, your kindness and mentorship is thoroughly appreciated. To Dr. Grace Gowda, thank you for accepting a moldable clay and for continuous support and patience; I am grateful this is a journey we embarked on together. To Dr. Michael Bartlett and Dr. Robert Geiger, thank you for your time and for serving on my committee.

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CHAPTER 1

INTRODUCTION

Medical standard-of-care has improved in parallel with the continued development of novel and innovative treatment options throughout the progressions of science, technology, and society. What was once unknown and recorded as the miraculous work of gods and deities, witch doctors, shaman, or magic is now more understood, characterized, repeatable, and is more available than ever before. Antibiotics, vaccines, and medical devices can propagate the human population through medically challenging experiences unlike before when bubonic plague, Poliovirus, and undiagnosed cardiovascular irregularity were exclusively considered to be morbidities throughout history. Significant scientific discovery and development was necessary to bring forth these life-saving and revolutionary molecules, materials, and devices; these discoveries have directed significant attention from the scientific and medical communities to utilizing renewable and regenerative native cells and tissues from the human body, or from the bodies of other humans, to further the availability of medicinal options by sustainable means.

Human tissue transplantation for medical purposes dates back as early as 3,000 years ago when ancient Hindu texts described early skin grafting procedures.[1] The earliest successfully documented tissue transplantation occurred in 1869 when Reverdin grafted skin from a patient's arm to treat a wound of a different location. Scientific methods were identified to harvest and utilize other tissues to transplant for medicinal purposes as when Davis, who utilized placental membrane to treat wounds in 1913, noted improved outcomes.[2] As general understanding of the microscopic elements of the human body became clearer, special attention turned to the

applications of cells; Thomas performed hematopoietic stem cell transplantation in 1957 to attempt to treat acute myeloid leukemia, treatment that would need refinement and improvement prior to 1979 when 50% success was observed in first remission patients. Similarly, improved fertility outcomes were identified when the harvesting of semen and oocytes brought forth breakthroughs in the methodology of *in vitro* fertilization. Today, there is tremendous interest in further characterizing and harnessing the capabilities of stem cells for suitability as treatment of complex diseases and disorders with high demand for safe and effective treatment options.

The Food and Drug Administration (FDA) oversees, regulates, and monitors compliance and enforcement activities over industry and processors responsible for a broad spectrum of necessary goods, such as drugs, biologics, and medical devices, to assure that safe and effective products are placed on the United States Market. This is accomplished by the rigorous review of pre-market submission, such as the new drug application (NDA), biologics license application (BLA), or pre-market approval (PMA) and pre-market notification (510(k)). Such product marketing applications require clinical evidence purporting product safety and efficacy, or an evaluation of substantial equivalence to a predicate device which raises no concerns of product safety and efficacy, prior to being deemed appropriate for intended uses. Additionally, quality must be incorporated into the manufacturing process and the product such that it meets quality and performance-based specifications. The requirements necessary for successfully marketing, and maintaining the lawful marketability, of each classification of product regulated by the FDA is described in Title 21 of the United States Code of Federal Regulations.

Human cells, cellular and tissue-based products (HCT/Ps) are human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient for health care related purposes and are subject to the FDA's oversight and regulation.[4] HCT/Ps can be

derived from a variety of tissue types such as skin, bone, amniotic membrane, tendon, hematopoietic progenitor cells from cord blood, oocyte, semen, and more; HCT/Ps can be suitable alternatives for myriad medical procedures or treatments in accordance to the labeled intended use. Organ components, such as heart valves, are regulated as HCT/Ps as the tissue alone provides structural functions; however, vascular or whole organs intended for transplantation do not meet the criteria of HCT/Ps and are not regulated by the Food and Drug Administration. Many HCT/P processors operate as tissue banks and receive additional and voluntary accreditation from the American Association of Tissue Banks, an institution that has promoted tissue donation, standards development, and ethical practice since its founding by chartering members of the first American Tissue Bank, the U.S. Navy Tissue Bank.[5]

Cells and tissues regulated as HCT/Ps, rather than HCT/Ps and a drug, medical device, or biologic, are unlike many of the medicinal products regulated by the Food and Drug Administration; no pre-market submission is necessary for the legal marketing of HCT/Ps. Cells and Tissues that meet the four regulatory criteria described in 21 CFR 1271.10(a) are regulated by Section 361 of the Public Health Service Act, along with regulations found in 21 CFR 1271. Instead, a self-designation of "361 status" is made by a tissue processer regarding a finished tissue product, against the codified criteria, to determine if the tissue is suitable to be solely regulated as a Section 361 HCT/P. According to the Code of Federal Regulations, to be classified as a Section 361 HCT/P, the following criteria must be met:

> "(1) The HCT/P is minimally manipulated;
> (2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the processor's objective intent;
> (3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(a) Is for autologous use;

(b) Is for allogeneic use in a first-degree or second-degree blood relative; or

(c) Is for reproductive use."[6]

An affirmative designation is not satisfactory to market a tissue product as a Section 361 HCT/P, processors of must obtain Tissue Establishment Registration from the Center for Biologics Evaluation and Research (CBER), must list the tissue products manufactured, and must be in compliance with the other regulations found in 21 CFR 1271.[6] 21 CFR 1271 details the requirements necessary to lawfully market an HCT/P in the United States and is broken down into sections which establish definitions and registration procedures, define the requirements for donor screening and eligibility determinations, depict the Good Tissue Practices, identify other requirements necessary for compliance, and describe how FDA oversees HCT/P industry enforcement activities; all of which are intended to prevent and mitigate risk associated with the spread of communicable disease from processed donor tissue to the recipient.[7] The Good Tissue Practices (GTP) are analogous to the current Good Manufacturing Practices for drugs, the Quality System Regulations for medical devices, and the Biologics regulations intended for biologicals; industry members responsible for the realization of HCT/Ps and non-HCT/P products are expected and required by the FDA to ensure safety of the public health. Donor screening and eligibility determination regulations are integral to determining processed tissue's suitability for transplantation purposes; the FDA requires that all tissues intended for transplantation be tested for "relative communicable disease agents and diseases", to prevent the transplantation of tissue loaded with dangerous, viral pathogens; additionally, the FDA sets

special criteria for test methods and laboratories performing said tests. Additional requirements described for members of industry regarding complaints and mandatory FDA reporting.

When a complaint or other quality event has been identified, reported, or received that meets the criteria of an adverse reaction, a processer has 15 days from becoming aware to submit Form FDA-3500A to the Center for Biologics Evaluation and Research (CBER) and must initiate investigation, obtain additional information necessary, follow-up with the FDA as necessary, and determine what corrective actions, field safety corrections, and other activities are necessary to prevent the further occurrence or repetition of the adverse reaction.[8] Complaints can be derived from negative biological experiences, such as the development of a rash or swelling in association with a product, or may product related and may involve physical damage, improper packaging, or labeling issues.

Not all complaints meet the HCT/P mandatory reporting criteria; only severe complaints involving communicable disease transmission resulting in death, permanent harm, or requiring surgical intervention and/or hospitalization are required to be reported. The timeliness of reporting assists the FDA in determining if its intervention is necessary to protect the general public health and prevent further occurrence of the adverse reaction.

Drugs, biologics, and medical devices are subjected to different mandatory reporting requirements than HCT/Ps; these non-HCT/P products require pre-market submissions such as new drug applications, biologics licenses applications, and pre-market approval or notification to be lawfully marketed. As such, the FDA performs a thorough review of presented clinical data, or data suggesting substantial equivalence to a predicate in the case of Class I and II medical devices, which supports the sponsor's safety and efficacy claims for the prospective non-HCT/P. Upon submission approval or clearance, non-HCT/P sponsors are required to participate in post-

marketing surveillance activities and are required to submit reports when complaints or detected quality events meet the criteria of an adverse event. The FDA applies the term “adverse drug experience", which is interchangeable to "adverse event" to non-HCT/P products for reporting purposes and defines such in 21 CFR 314.80 as:

> “Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action."[9]

Industry, importers, and certain healthcare providers and facilities are required to submit adverse event information to the respective adverse event reporting system according to product type. The Manufacturer and User Facility Device Experience (MAUDE) database, FDA Adverse Event Reporting System (FAERS), Vaccine Adverse Event Reporting System (VAERS), and MedWatch are electronic systems utilized by the FDA to receive adverse event reports from non-HCT/Ps from detected, observed, or experienced by industry, medical professionals and facilities, and the general public.

The U.S. Food and Drug Administration applies different mandatory reporting criteria and requirements for products that undergo premarket submission approval or clearance when compared to products marketed by a self-determination according to a risk-based regulatory framework. It is possible that the safety profile of Section 361 HCT/Ps as interpreted by the FDA per received adverse reaction reports does not adequately portray the safety of products of these non-reviewed medicinal products. The published guidance documents associated with the revised regulatory framework did not address product safety or mandatory reporting requirements regardless of the possibility that communicable disease be transmitted resulting from transplantation of a tissue product which has not undergone safety and efficacy review,

such as the Tuberculosis outbreak from Ayzio Biologics' FiberCel bone graft.[10,21] Limiting the criteria of mandatory reporting of product safety events related to HCT/Ps limits the scope of safety information received for this rapidly growing class of diverse products, often bringing only the most serious and severe safety events to the FDA's attention through mandatory adverse reaction reporting.

This study is intended to engage members of the Section 361 HCT/P industry for critical information necessary to identify a gap in safety surveillance, if such exists, in HCT/Ps as compared to non-HCT/P products based on the mandatory reporting requirements set forth when applying the regulations regarding the definition "adverse reaction" when compared to "adverse event" as is currently required. This study shall include recommendations for the Food and Drug Administration to improve its oversight of HCT/P safety data as a result of the evaluation and identification of a gap.

CHAPTER 2

LITERATURE REVIEW

Published Literature Review

A thorough literature review was conducted to identify previously conducted research comparing adverse reaction reporting rates to that of adverse event submissions; however, the niche topic and believed novelty of topic limited applicable previous research, and similar research, identifiable as suitable primary publication in the literary review process. Similarly, HCT/P regulation as is young and possibly under-studied in comparison to other regulatory topics of interest. As such, numerous publications, data sets, and FDA sources were thoroughly reviewed to establish a knowledge of prior contextual research and information made previously available regarding HCT/P adverse reactions, adverse events for drugs, biologics, and medical devices (non-HCT/Ps), and their respective reporting requirements and tendencies.

Regulatory Review

The identification of unsuitable tissue made available for transplantation as the cause of increased reports and instances of HIV and Hepatitis infection in tissue recipients caused significant alarm to the Centers for Disease Control and Prevention in the early 1990's.[1] This identified failure of protecting the general public health the Food and Drug Administration initiated the establishment of the human cell and tissue regulatory pathway by publishing the "Human Tissue for Transplantation interim rule" which identified disease testing, donor screening, and documentation of such records as immediate interventions to combat the concern of communicable disease associated with tissue transplant. The interim rule was succeeded with

the 1997 publication of former Vice-President Al Gore's National Performance Review titled "Reinventing the Regulation of Human Tissue" along with "A Proposed Approach to Regulation of Cellular and Tissue-Based Products".[2] These documents identified the necessity to regulate cells and tissues, in part due to the concern that uncontrolled cells and tissue presented due to risk of communicable disease transmission. The FDA's "Proposed Approach" document admitted that previous control and regulation efforts of these products was incomplete and ineffective; a risk-based, tiered framework was recommended with focus on preventing disease transmission, preventing handling-related contamination, and ensuring that tissue that didn't meet what would become the "core tissue rules" were subjected to clinical safety and efficacy review.[3] The interim rule was finalized in 1997 in 21 CFR 1270, requiring HCT/P processers of allogeneic cells and tissues to conduct donor screening based on eligibility criteria such as laboratory testing for viral and bacterial agents, whose transmission from donor would cause life-altering or life-threating effects in the recipient, along with taking the donor's medical history into account when determining eligibility to identify patterns of behavior that pose risks of HIV and Hepatitis transmission or may have familial history or exposure to Creutzfeldt-Jakob Disease or Tuberculosis.[3,4] Additionally, HCT/P processers were subject to increased documentation and recordkeeping requirements brought forth by the activities intended to reduce the risk of disease transmission.[4] FDA described and documented its intention to continue to develop regulations and requirements such as adverse event reporting requirements, good manufacturing practices, and other requirements in the "Proposed Approach" document to further mitigate product-associated risk and inform the FDA of certain safety events of concern for Section 361 HCT/Ps following the implementation of 21 CFR 1270.[3] The FDA's continued effort of regulation development occurred between 1999 and 2001 with the release of three proposed rules, the

"registration rule", the "donor suitability" rule, and the "current good tissue practices" rule, which would later be codified as 21 CFR 1271.[1] The issuance of final rule provided industry with only 90 days to comply with establish registration requirements; however, a three-year grace period was granted to comply with other finalized rules after postponement due to delay in rule establishment. In May 2005, the Current Good Tissue Practice Rule was finalized and became effective; requiring all tissue recovered on the day of, or any day after implementation which fit the criteria of a Section 361 HCT/P to be regulated per 21 CFR 1271; allowing tissue recovered prior to implementation of 21 CFR 1271 to be regulated under 21 CFR 1270.[5] In 2020, the FDA announced the revocation of 21 CFR Part 1270 in accordance with the "Enforcing the Regulatory Reform Agenda" Executive Order, number 13777 in 2017, due to its outdatedness, as it solely applied to tissues recovered prior to May 25, 2005, and its ineffectiveness .[6] The implementation of the FDA's vision of robust tissue regulation by the establishment and enforcement of 21 CFR 1271, along with the highly unlikely possibility that tissue processed prior to May 25, 2005 was still in circulation, distribution, or inventory, allowed the FDA to reduce the quantity of regulations associated with cells and tissues.

21 CFR 1271 is comprised of six subparts which provide industry with the entire regulatory pathway for the lawful marketing of Section 361 HCT/Ps.[7] Compliance with all subparts is required for all Section 361 HCT/Ps; however, HCT/Ps also regulated as drugs, biologics, or medical devices need only comply with subparts C and D which describe the donor-eligibility regulations and the Good Tissue Practices, respectively. The other subparts describe general information such as definitions and applicability of regulations; procedural information necessary to perform mandatory registration activities; mandatory reporting and labeling requirements; and FDA's rights and capabilities when performing inspection or enforcement-

related activities. Each subpart of Part 1271 described is intended to prevent and mitigate risk associated with the spread of communicable disease from processed donor tissue to the recipient.

Donor screening and eligibility determination regulations play a forefront role to mitigating the risk of communicable disease transmission from a donor to a recipient. A determination of donor eligibility based on the results of donor screening is mandatory for every processed tissue to ensure suitability for transplantation purposes. The FDA requires that all tissues intended for transplantation be tested for "relative communicable disease agents and diseases", known as "RCDADs", to prevent the transplantation of tissue loaded with dangerous, viral pathogens; relevant communicable disease agents and diseases consist of HIV-1 and 2, HTLV-I and II, Hepatitis B, Hepatitis C, Cytomegalovirus, human transmissible spongiform encephalopathy, Creutzfeldt-Jakob Disease, *Treponema pallidum*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and other communicable risks related to xenotransplantation.[8] Compliant donor screening consists of evaluating clinical and lifestyle risk factors through donor testing and a thorough review of a donor's medical history for RCDADs or lifestyle choices that place the donor at a higher risk of transmitting RCDADs. The FDA mandates that donor testing be conducted utilizing FDA-licensed, approved, or cleared screening tests by qualified and certified laboratories capable of testing human samples per the Clinical Laboratory Improvement Amendments of 1988, in accordance with 42 CFR 493, or otherwise qualified by the Centers for Medicare and Medicaid Services. The donor screening and eligibility regulations set forth specific specimen testing requirements such as proximity to gathering sample in relation to conducting tissue recovery, plasma dilution factor, and situational factors such as proximity to receiving blood or other product transfusion or lapsed time post-death. Generally, donor samples are not retested to determine if positive results are false or not; however, confirmatory testing

may be permissible depending on the reactivity and specificity of syphilis testing. Tissues which yield positive results for donor screening are not immediately deemed ineligible for transplantation; rather, tissue processors are allowed to label RCDAD-positive product with written warnings and directions to physicians or point of care to delineate the risk of transplanting an RCDAD-positive cell or tissue product. The FDA requires the risks associated with Section 361 HCT/Ps that are distributed under exceptional use to be clearly labeled and that recipients and point-of-care physicians alike are informed and educated regarding the risk, and other safety-related concerns regarding transplantation, of accepting HCT/Ps.

Fishman et al. reviewed the implications of preventing the transmission of infection associated with human allografts.[9] A single donor's tissue may be processed to over 100 HCT/P units able to be transplanted in as many different individuals; over 2 million tissue allografts are transplanted each year for the repair, reconstruction, replacement, or supplementation of recipient tissue which supports the necessity of rigorous donor screening testing. The mandatory testing RCDADs are not intended to be the only factors taken into consideration to determine donor eligibility. Fishman describes a myriad of risk factors such as same-sex activities; sexual activity in exchange for money and drugs; claiming intravenous, intramuscular, or subcutaneous non-medicinal drug use; and recent incarceration as being high-risk behavioral factors for rejecting donation. Certain clinical factors may be identifiable through codified donor testing; however, rejecting donation from donors with questionable medical or social histories limit potential for transmission of communicable disease and likelihood of reportable events upstream of processing activities.

The Good Tissue Practices (GTP) are analogous to the current Good Manufacturing Practices for drugs, the Quality System Regulations for medical devices, and the Biologics

regulations intended for biologicals. A manufacturing environment in compliance with the Good Tissue Practices is intended to purport safer product with lower risk of transmitting communicable disease introducible in post-recovery handling, processing, or distribution activities. The GTPs direct tissue processors to establish myriad processes and controls related to finished product realization and outline the requirements for tissue processing, labeling, packaging, distribution, and more.[10] Tissue processors are obligated to meet or exceed these requirements and are subject to the FDA's regulatory enforcement consequences should the obligation not be met. Tissue processing facilities must incorporate control into the facility layout and design ensuring that garbage, sewage, and other wastes are controlled and disposed of appropriately, and that cleaning and sanitization methods are appropriate, to reduce the likeliness that environmental factors cause cross-contamination of communicable disease for in-process or finished tissue products; environmental monitoring and controls are utilized to assure the suitability of environmental and facility-related controls. Similarly, facility equipment must have established cleaning, sanitization, and maintenance schedules with routine inspections and documentation and recording of associated activities to prevent cross-contamination or exposure to communicable disease; additionally, reagents and solutions used in tissue processing must be separated or quarantined until a verification against specifications has been met that considers the reduction of risk of disease transmission. The GMPs require the integration of quality into tissue manufacturing like establishing processes for tissue manufacturing activities that prevent transmission of disease and ensure that finished product specifications are met; activities such as the investigations, corrective actions, and audits meant to control and improve product, process, or system quality; competency and training requirements for personnel; and activities necessary to ensure changes to processes are adequately documented, reviewed, and provide consistent and

repeatable outputs prior to implementation. Elements of product traceability are required to be implemented into the quality system of tissue processers; tissue must be assigned a unique donor identifier that is not linked to medical or government-based identifiers and must be used through processing and distribution in a manner that tracks the donor's tissue to an individual recipient, and from the recipient back to the donor. The GTP also describe the requirements for product labeling storage and distribution. The prevention of contamination and introduction of communicable disease in product realization for industry that must comply with 21 CFR 1271 is a focal point to increase product safety within the regulatory framework established by the part.

Subpart E illustrates labeling criteria for HCT/Ps. HCT/Ps have special labeling requirements that assist in mitigating risk to tissue recipients; certain tissues, such as those suitable for certain subsets of recipients sharing a like condition with a donor that would generally preclude tissue donation, must bear adequate warning and be labeled for exceptional use as permissible according to Part 1271. Tissue labeling must support tracking efforts and establish traceability from the donor to the recipient as well as from the recipient back to the donor; this assists with investigations, field corrections, and recall activities.[11] Additionally, processors must include the name and physical address of the entity responsible for determining donor eligibility and product release; instructions for use must account for further prevention of introduction, transmission, or spread of communicable disease.

Subpart E also describes FDA reporting requirements and post-market surveillance activities that tissue processers must perform to remain in compliance with the FDA to keep tissue products lawfully marketed. Tissue manufacturers are required by 21 CFR 1271.350(b) to report deviations to the core GTP requirements as described in 21 CFR 1271.150(b).[11] Deviations from standard procedures in relation to facilities, environmental control, equipment, supplies and

reagents, tissue recovery, processing and process controls, labeling, storage, and receipt, and distribution activities must be reported to the FDA within 45 days with deviation event descriptions and details along with corrective actions taken to address the situation.[10,11] Additionally, tissue processers must establish procedures to monitor, receive, evaluate, document, and investigate complaints. 21 CFR 1271.3(aa) defines a complaint, in HCT/P terms, as a written, oral, or electronic complaint which purports that a tissue has or is capable of transmitting communicable disease or that a problem exists where communicable disease transmission is a possibility or where the processer is out of compliance with core GTP.[11] 21 CFR 1271.320 details the requirements processers must satisfy regarding complaints; complaints must be thoroughly documented with significant information recorded and maintained to allow for the identification of trends or determination of isolated events along with adequate review, investigation, evaluation, and disposition of activity necessary to address the complaint, such as corrective action, recall, field safety correction, etc. All complaints must be reviewed, evaluated, and investigated; a strong and sound justification is necessary to justify that certain complaints may be of little concern of safety, and thus do not require investigation.

Complaint review activities assist processers in determining if a complaint event meets the definition of an adverse reaction and necessitates a reporting to FDA. The FDA defines an adverse reaction in 21 CFR 1271.350(a) as "an adverse reaction involving a communicable disease if it:

> (i) Is fatal;
> (ii) Is life- threatening;
> (iii) Results in permanent impairment of a body function or permanent damage to a body structure; or
> (iv) Necessitates medical or surgical intervention, including hospitalization."[11]

Part 1271's implementation brought forth different requirements than that of the Final Tissue Rule in 1997 or the "Proposed Approach" document released the same year; adverse event reports have not been applicable to the HCT/P industry since prior to May 25th, 2005. Rather, the HCT/P industry is required to submit adverse reaction reports when instances of transmission of communicable disease are confirmed and fatal, life threatening, causes permanent impact to body function or permanent damage to body structure, or requires medical or surgical intervention, including hospitalization.[7]

Adverse reaction reporting is a rare regulatory requirement codified only for HCT/Ps and prospective drugs or biologics distributable across state lines for clinical purposes under an investigational new drug (IND) application. 21 CFR 312.32 defines "serious suspected adverse reaction" in the same manner of which HCT/P adverse reactions are defined; however, IND adverse reactions can be further classified as "suspected" or "unexpected" based on the possibility the IND product is the root cause of an adverse reaction or if an event was not listed in an investigator's brochure.[12]

Finished biologics are subject to postmarket surveillance activities which inform the FDA of quality events of concern identified by, or reported to, a manufacturer. Recipients of a Biologics License are required to report serious and unexpected adverse experiences as "Postmarketing 15-day 'Alert Reports'" in accordance with the information required per 21 CFR 600.80.[13] An adverse experience is considered unexpected if it is not listed in current labeling. Serious adverse experiences share contextual characteristics of HCT/P adverse reactions in that events resulting in death or life-threating outcomes, hospitalization, significant disability, or incapacity or impairment require mandatory reporting; however, no such requirement exists for HCT/P processers to list possible effects or events in product labeling to which adverse reactions

are compared to determine mandatory reportability like that of unexpected adverse experience monitoring conducted by biologics manufacturers. Such a list of possible adverse reactions for biologics labeling would likely result from clinical trials, biocompatibility testing, and other measures of product safety; none of which are necessary for the marketing of Section 361 HCT/Ps. Vaccines, a prominent subset of product classified and regulated as biologics, have a public-facing, web-based portal which can be accessed by medical professionals and the general public, to submit adverse occurrence information data to the FDA and the Centers for Disease Control and Prevention.[14] The biologics industry can detect and investigate adverse experience signals by postmarket surveillance activities; however, a potential disconnect appears between the regulatory requirements of mandatory adverse reporting for biologics and the name of this electronic system is observed in that biologics regulations call for the reporting of adverse reactions whereas the system has been named the Vaccine Adverse Event Reporting System.

Medical device manufacturers must inform the FDA of reportable events as described in 21 CFR 803.50(a), the Medical Device Reporting (MDR) regulations require manufacturers and device user facilities to report "MDR reportable events" where an event resulting in death or serious injury, could be attributed to a device that caused, contributed, or would cause or contribute to such an event, in the case of a malfunction's recurrence.[15] The MDR regulations define serious injury using synonymous language to that of HCT/P adverse reaction in that serious injury, as defined in 21 CFR 803.3(w), as being life threatening, resulting in permanent impairment or damage to body structure or function, or requiring medical or surgical intervention to prevent permanent effect. HCT/Ps do not establish different adverse reaction reporting criteria to the different facets of tissue processing such as tissue bank, tissue recovery center, tissue storage facility, or tissue distributor; Part 803 describes separate MDR reporting criteria for

device user facilities, device manufacturers, and device importers.[15] Medical device importers and user facilities must report to both the FDA and the manufacturer when mandatory reporting is necessary; however, tissue processors are not required to submit mandatory reports to tissue recovery affiliates, regardless of the possibility of recovery activities contributing to reaction root cause. Similarly, to HCT/Ps, MDR reporting activities are submitted utilizing FDA Form 3500A when submitting individual adverse event reports.

Mandatory reporting activities for drugs and generics are defined in 21 CFR 314.80; investigational counterparts follow the regulations for mandatory reporting described in the investigational new drug regulations of 21 CF 312.[12,16] Drug manufacturers are given two separate adverse event reporting avenues based on regulatory definition and event severity. The term "adverse drug experience" is synonymous with "adverse event", the terms concern events associated with use of a drug in humans regardless or not if the root cause is drug related, including events from professional practice, drug overdose, drug abuse, drug withdrawal, or drug failure. Adverse events are further classified as being serious, resulting in death, life-threatening experience, hospitalization, disability and incapacity, anomaly, or birth defect, and can also be unexpected, which regards events not previously described in product labeling., 21 CFR 314.80(c)(1)(i) directs drug manufacturers to report each serious and unexpected adverse event within 15 days of becoming aware; this is frequently referred to as the "15-Day Report".[16] Additionally, drug manufacturers must abide with 21 CFR 314.80(c)(2) which requires the submission of a report detailing all other adverse events; analysis of any "15-Day Reports", actions taken in response of such events, and patient identification code and adverse reaction terms describing all individual case safety reports on a quarterly basis for the first three years post-application approval and on an annual basis thereafter.[16] This allows the FDA to prioritize

serious and unexpected adverse events while still maintaining adequate observation and surveillance of all other adverse events should FDA intervention be necessary to correct or control patterns of threatening danger to the general public health.

In 2007, Wang et al. conducted the first review of reports regarding human cells and tissues adverse event reports submitted to FDA's Medwatch system between years 2001 and 2004.[17] Prior to Part 1271's establishment and implementation, HCT/P processers reported safety events in accordance with reporting criteria of adverse events rather than adverse reactions; adverse reaction reporting did not become the mandatory reporting subject matter until the implementation of 21 CFR 1271.[3] Wang's timeframe for report reviewing aligned between the final proposed rule for tissue regulation and the year prior to the conglomeration of additional proposed rule's effective date; providing an interested perspective to the frequency of adverse event reports made with regard to human cells and tissues prior to the requirement of adverse reaction reporting.[17] Wang identified 83 tissue-based adverse events during the time frame of interest while conducting research in the MedWatch database, which has now been replaced by the FDA Adverse Event Report System (FAERS). Wang noted that the primary event described was bacterial or fungal infection; however, nine of the eleven deaths connected with HCT/Ps between 2001 and 2004, according to MedWatch, were in association with a heart valve graft which was recalled in 2002. 62 of 83 (74.6%) of identified HCT/P adverse events were attributed to bacterial and yeast infections, combined, only one case of Creutzfeldt-Jakob Disease was identified and no viral infections were detected.[8] This lack of viral transmission in association with transplantation suggest that the donor eligibility and screening requirements are effective with the codifying of 21 CFR 1271 displayed effectiveness at mitigating the risk of disease transmission resulting from tissue transplantation.

The Food and Drug Administration uses the FDA Adverse Event Reporting System (FAERS) dashboard as its public-facing adverse event data analysis tool which displays publicly-reported adverse events ("direct"), events which require a "15-day report" ("expedited"), and non-serious or expected adverse events ("non-expedited") subject to annual reporting.[18] One shortcoming of the public dashboard is that FDA does not have a way to discern separate reports of one kind from multiple submissions of the same report; thus the FDA does not purport such data to be entirely accurate nor causation or correlation of a confirmed report and disclaims the data available to the public.

The Medical device reporting database is equally limiting in the conclusiveness of its respective data in that reports may be incomplete, misleading, or may be biased; in 2019 a study reported the FDA's estimate of participation in medical device reporting by non-manufacturer sources, such as user facilities, distributors, physicians, and the public, to also be approximately 0.5%.[20] The MAUDE is further limited in its user interface and output capabilities due to older or outdated technology or data presentation as compared to FAERS. MAUDE's output capacity is 500 reports in any searchable range; this limits the ability to which industry, or the FDA, can monitor MAUDE data as any date can have over 500 reported events, causing a tremendous burden of data to filter through given the database's user limitations. A single medical device can be attributed thousands of medical device reports such as Essure, a contraceptive device which was the subject of 16,086 medical device reports in 2020.[21]

The Vaccine Adverse Event Reporting System is accessible through the Centers for Disease Control and Prevention's "CDC Wonder" system for ease of use and public interaction, while the FDA makes raw data available for industrial uses.[22] While its subject is only applicable to a subset of the biologics product classification, the database is easily manipulatable with clear

outputs and legible data. In 2020, 49,968 vaccine-related events were reported using VAERS; however, the database output total is 180,891 given that reports may present more than one symptom (e.g., injection site soreness and localized rash).

The FDA's databases for drugs, biologics, and medical device safety reporting make critical information regarding product safety available and accessible for the public, allowing increased transparency in product safety should such information be sought out by the general public or medical professionals and allowing non-industrial voices an avenue to be heard regarding negative product interactions in real-life scenarios. These databases are limited by the conclusions that can be drawn from their respective data for establishing a rate of adverse event occurrence or assigning correlation between a product and a submitted report; however, the existence of each database creates additional tools by which postmarket surveillance for adverse events are monitored, which has an assumed improvement of product safety by raising awareness of safety events potentially attributed to a manufacturer's product line. No such resource is available to Section 361 HCT/P manufacturers. HCT/P manufacturers are reliant on the compliance of transplant recipients, medical professionals, and other external sources to report adverse reactions as complaints or quality events; otherwise, processers use word-of-mouth, social media outlets, and other networks as input systems for gauging the safety of product. Manufacturers also receive word of adverse reaction reports directly received by the FDA through its communication line from CBER's MedWatch observing office, the Office of Biostatistics and Epidemiology, who notifies the Tissue Safety Team of a received adverse reaction report regarding an HCT/P prior to collaborating with the Office of Compliance and Biologics Quality, who notifies the HCT/P manufacturer in accordance with SOPP 8508.[23] Additionally, HCT/P adverse reactions submitted to the FDA are not accessible by average

public avenues; an individual must submit a Freedom of Information Act request to the FDA asking for information, such as how many adverse reaction reports have been received over specific time durations, regarding HCT/Ps and their mandatory reports. CBER does not publicize the number of mandatory reports it receives, or that are submitted on MedWatch; this lack of available data makes comparing other reporting frequencies difficult, regardless of all database limitations. There is no true public metric available to gauge the reporting frequency of HCT/P adverse reactions; one may extrapolate that the occurrence of death, life-altering injury, and/or medical intervention associated with HCT/P transplantation would justify issuing field safety corrective actions or recall preventing further recurrence of such adverse reaction. CBER reported 22 tissue recalls in 2019 with 16, 14, and 25 being reported in accordance with the FDA's recall postings in 2018, 2016, and 2014, respectively. [24, 25, 26, 27] The average number of recalls posted in these four years (19.3) is reasonably comparable to the average number of adverse events per year as observed by Wang et al. between 2001 and 2004 (27.7) when extrapolating that the finalization and codifying of 21 CFR 1271 likely improved general HCT/P safety.[17] Regardless of product volume compared to non-HCT/Ps, CBER has shifted regulation and control to the regenerative medicine space to enforce the new regenerative medicine regulatory framework which provided clarity on self-designations regarding the minimal manipulation and homologous use "core rules" and directed industry to begin IND and BLA activities if product did not meet the clarified and elaborated definitions as provided. For example, adipose tissue could not be ground into a powder and used to treat tendonitis; grounding adipose tissue destroys the tissue's original relevant characteristics and treating inflammation is not homologous to the tissue's function in the donor. CBER's last warning letter,

and 13 of 18 untitled letters issued by the center in 2021, have been centric to HCT/Ps and regenerative medicine.[28]

A literature review of the regulations which for HCT/Ps compared to non-HCT/Ps, such as drugs, devices, and biologics, identifies a regulatory gap in safety monitoring caused by the differences of regulatory requirement for adverse reaction reporting of a product classification not subject to safety and efficacy review compared to reviewed product classifications which require adverse event reporting scenarios. The FDA's strategy for protecting the public health from negative product safety events associated with Section 361 HCT/P use is accomplished by limiting tissue product processing and use by the "four core rules" of 21 CFR 1271.10(a) to prevent product from being used for indications which would require product effectiveness data, by requiring quality tissue manufacturing practices that prevent the overprocessing and handling of product as to not introduce or transmit communicable disease, and by performing robust donor eligibility testing and screening procedures to mitigate and prevent the transmission of RCDADs from HCT/P to recipient. The FDA has numerous databases and tools intended to inform the general public's decision making and assist non-HCT/P industry's effort of postmarket surveillance, but information for this subset of regulated product is difficult or impossible to access without navigating legal hoops for the purposes of gaining information. CBER has carried out significant enforcement activity over the rapidly evolving category of HCT/Ps but has not supplemented its oversight and safety surveillance with improved HCT/P reporting requirements. HCT/P regulation contains a gap whose addressing would improve the depth of which safety can be purported in accordance with its regulatory pathway at the cost of little resource given estimated annual HCT/P transplantation volume, regardless of the potent dangers potentially hidden in HCT/Ps.

CHAPTER 3

METHODS

Research Hypothesis

The mandatory reporting of safety events caused by Section 361 HCT/Ps is less than that of non-HCT/P products because of establishment "adverse reaction" reporting in HCT/Ps compared to non-HCT/P "adverse event" reporting.

Study Design

The conducted research was two-folded. First, comprehensive literature research was conducted regarding the reporting of adverse events for drugs and adverse reactions for drugs utilizing publicly available means, such as google.com and information made available by the Food and Drug Administration Website (fda.gov), to acquire an advanced and in-depth understanding of current findings related to the topic.

Second, a qualitative and quantitative online survey was deployed to gather data to address research questions of interest to identify the approximate number of complaints reported to the FDA when using adverse reaction reporting requirements and identify the difference in reporting rate, if any, when using the definition of "adverse event" to evaluate complaint reportability. An additional area of research interest involved the opinions of members of the Section 361 HCT/P industry and their perception of tissue product safety and the adequacy of the current reporting framework. No identifiable information, trade secrets, or other private or proprietary information was requested or recorded in the surveying process; responses were anonymized, and information raw data was not distributed. To prevent any questions from not

being recorded in the surveying process, the survey required input for each answer prior to proceeding to the next question or page; however, the completion of the survey was entirely voluntary, and participants could exit the survey by closing the browser window without difficulty. Participants who abandoned the survey were included in the dataset with all answers provided up to the point of abandoning the survey; no information was requested if the participant abandoned the survey and participants were not contacted to inquire about completing the survey after abandonment as no traceability system was implemented to purport survey response anonymity.

Subject Recruitment

The implemented survey was intended for members employed in the regulated industry processing human cell, cellular and tissue-based products, in accordance with Section 361 of the Public Health Services Act, or who were employed in the HCT/P industry after January 1st, 2018. The desired sample size was 45 responses. Inclusion criteria was implemented through anonymous self-identification prior to beginning the survey; participants were twice asked to confirm that they met the inclusion criteria, once during the informed consent stage and again prior to proceeding to the first survey question. Responses that did not provide consent or that were not confirmatory to the second asking of the inclusion criteria were directed to a screen thanking the participant for their time and were not permitted to continue the survey. Individuals excluded from the survey by not providing informed consent or indicating that they did not meet the inclusion criteria were documented and reported. The exclusion criteria are described below:

Exclusion Criteria

- Employer does not manufacture HCT/Ps per Section 361 of the PHS Act
- Individual has not been employed in the HCT/P industry since January 1st, 2018

The survey was distributed through professional networks via LinkedIn, email, and by word-of-mouth and in-person recruitment; the survey was intended to be distributed by the American Association of Tissue Banks through its accredited tissue banking network. The Survey was built using the Qualtrics system and request information from the population regarding the handling of received complaints and reporting of adverse reactions between January 1st, 2020, to December 31st, 2020, along with a series of opinion-based questions (Appendix B).

IRB Approval

Acquiring approval from the University of Georgia Institutional Review Board (IRB) was necessary to conduct this research per institutional and federal regulations for conducting research with human subjects found in 45 CFR 46.[11] The research proposal, a copy of the survey to be distributed, and the research application were submitted to the IRB on August 10th, 2021. The research protocol provided necessary detail regarding the safeguarding of personal information and the methods by which anonymity were maintained through the survey process. The review board provided approval on August 27th, 2021, with "Not Human Subject Research" status given that the research protocol did not involve clinical procedures as defined by the FDA and Department of Human Health Services.

Statistical Rationale

A population of at least 45 respondents was desired to establish statistical significance for the proposed research method. A significance level of $p = 0.1$ (90% confidence) was utilized to perform a two-tailed T-test to challenge the null hypothesis that the reporting frequency of Section 361 HCT/P products is equal to that of non-Section 361 HCT/P products when applying the adverse event reporting requirements to HCT/Ps.

Data Analysis

The primary statistical analysis tools utilized was descriptive statistics to characterize the data gathered of the sample population's reception and handling of complaints and adverse reaction reporting to the Food and Drug Administration over the timespan of interest. Descriptive statistics were used to evaluate quantitative data gathered for comparative purposes to assist in drawing conclusions relating to the research question.

Three Chi-squared tests of independence were conducted to evaluate the relationships between data gathered from the survey. The first Chi-squared test was conducted to evaluate the perception of HCT/P safety from industry members regarding their mandatory reporting history according to survey inputs to determine if a relationship exists between the reportability of complaints when applying the adverse event definition, compared to the adverse reaction reporting regulations, and the opinion of how adequate the current HCT/P reporting framework is at informing the general public of HCT/P safety. A second Chi-squared test was conducted to evaluate the relationship of perceived mandatory reporting frequency for HCT/Ps and non-HCT/Ps as compared to the adequacy of the current HCT/P reporting framework in informing the FDA of safety related events. A final Chi-squared test was conducted to identify a relationship between an HCT/P industry member's willingness to accept an HCT/P from another firm, given their awareness and knowledge of safety and reporting tendencies, and the participant's belief regarding the likelihood that the general public's opinion would be negatively affected by subjecting the HCT/P industry to the adverse event mandatory reporting requirements. Data analysis was performed utilizing the MiniTab Statistical Software package and Microsoft Excel.

CHAPTER 4

RESULTS

The purpose of this research was to acquire critical information necessary to identify a gap in safety surveillance, if such exists, in HCT/Ps as compared to non-HCT/P products based on the mandatory reporting requirements set forth when applying the regulations regarding the definition "adverse reaction" when compared to "adverse event" as is currently required. The desired population of 45 survey participants was not achieved and only ten (10) surveys were completed; two (2) surveys were completed partially before being abandoned and left incomplete. Fourteen (14) individuals provided informed consent and confirmed their employment in the HCT/P industry; however, these individuals abandoned the survey prior to being shown the first question.

Survey participants were asked to provide the number of complaints received between January 1st, 2020, and December 31st, 2020, and were then directed to apply the codified definition of adverse reaction and adverse event to their received complaints. Given that receiving zero complaints during a calendar year is a possibility, the data received from respondents who received no complaints were kept for analytical purposes. An average of 18.3±23.7 complaints were received by tissue processers representing the surveyed population; the standard deviation is larger than the received complaint mean as a result of numerous respondents reporting zero (0) complaints and one individual who reported 75 complaints. Respondents reported that 1.18±0.902 complaints received that met the requirements for mandatory adverse reaction reporting as described in 21 CFR 1271.320 while 5.36 ± 4.50

complaints received met the definition of an adverse event for reporting purposes as described in 21 CFR 314.80. The total disclosed complaints, complaints fitting adverse reaction requirements, and complaints fitting the adverse event requirements displayed sample variance of σ_2 =563.82, σ_2 =8.96, and σ_2 =222.85, respectively (Table 1). This may be the result from an outlier response which reported 75 total complaints, 10 adverse reaction results, and 50 adverse event results. Four members of the surveyed population indicated that zero (0) complaints were received between January 1st, 2020, and December 31st, 2020.

Table 1. Descriptive Statistics of Complaints Provided

Descriptive Statistic	Total Complaints	Complaints as Adverse Reactions	Complaints as Adverse Events
Mean	18.27272727	1.18181818	5.36363636
Standard Error	7.15934343	0.90270484	4.50105589
Standard Deviation	23.7448559	2.99393326	14.9283136
Sample Variance	563.8181818	8.96363636	222.854545
Skewness	1.555681293	3.06524759	3.22143837
Minimum	0	0	0
Maximum	75	10	50
Confidence Level (95.0%)	15.95201125	2.01135173	10.0289775

Complaint data presented by survey participants was used to perform a two-tailed t test with equal variance to test the null hypothesis that the reporting frequency of Section 361 HCT/P products is equal to that of non-Section 361 HCT/P products when applying the adverse event reporting requirements to HCT/Ps. Table 2 describes two (2) two-sided t-tests which were performed. The first t-test conducted included all data gathered from the survey. The second t-test conducted threw out the potential data outlier, which was previously described, as a data response. The null hypothesis fails to be rejected as there was no statistically significant difference in the reportability of received complaints provided by respondents $t(22) = 1.05$, $p = 0.304$ despite respondents providing information suggesting that more complaints were reportable as adverse events (5.36±4.50) than as adverse reactions (1.182±0.902).

Table 2. Two-Tailed T Test for Complaints Provided as Adverse Events and Reactions

Whole Data Set			*Outlier Removed*	
Complaints as Adverse Events	Complaints as Adverse Reactions		Complaints as Adverse Reactions	*Complaints as Adverse Events*
5.5	1.08333333	Mean	0.27272727	1.45454545
202.818182	8.26515152	Variance	0.41818182	7.07272727
12	12	Observations	11	11
	105.541667	Pooled Variance	3.74545455	
	0	Hypothesized Mean Difference	0	
	22	df	20	
	-1.0530725	t Stat	-1.4321211	
	0.30373712	P(T<=t) two-tail	0.16755359	

Survey participants were asked to select the percentage range which best described the occurrence of their company's received complaints against six sets of criteria describing the reportability of complaints, the percent of complaints fitting the adverse reaction definition, the percentage of complaints fitting the adverse event definition, and common causes of complaints such as if the complaint was reported from human use, handling characteristics, or product use. A Chi-squared (x^2) test of independence was conducted comparing the inputs from the six criteria questions and were compared to the participant's response when asked to prove a supportive or disinclined opinion on the HCT/P reporting framework's adequacy in providing the general public with an accurate product safety profile. The null hypothesis was that there is no relationship between the way that complaint handling and mandatory reporting rates changed, when utilizing different regulatory definitions, and the belief that the current mandatory reporting framework for HCT/Ps adequately informs the public of tissue product safety profiles. The null hypothesis failed to be rejected as the Chi-squared test did not show a significant relationship $x^2(5, N=160) = 6.791$, $p = 0.237$ between the items of interest. Figure 3 describes the Chi square test of independence results from comparing complaint frequencies to perceptions of the reporting framework's adequacy in informing the general public.

	Q1	Q2	Q3	Q4	Q5	Q6	All
YES	10	9	6	12	14	8	59
	9.59	5.90	4.06	11.06	16.59	11.80	
	0.0177	1.6288	0.9314	0.0794	0.4054	1.2237	
NO	16	7	5	18	31	24	101
	16.41	10.10	6.94	18.94	28.41	20.20	
	0.0104	0.9515	0.5441	0.0464	0.2368	0.7149	
All	26	16	11	30	45	32	160

Cell Contents
Count
Expected count
Contribution to Chi-square

Chi-Square Test

	Chi-Square	DF	P-Value
Pearson	6.791	5	0.237
Likelihood Ratio	6.748	5	0.240

1 cell(s) with expected counts less than 5.

Figure 1. Independence for Complaints and Adequacy for Informing General Public

A second Chi Square test of independence test was conducted to evaluate the relationship between respondents' opinions of frequency of adverse reactions and adverse events reported to the FDA by the HCT/P and non-HCT/P industries, respectively, and the supportive or disinclined opinion that the current mandatory reporting framework for HCT/Ps is adequate in informing the FDA of HCT/P safety events. The null hypothesis was that there is no relationship between the perceived mandatory reporting frequency and the opinion of the mandatory reporting framework's adequacy in informing the FDA of HCT/P safety events. The null hypothesis failed to be rejected as no relationship was identified between opinion of adequacy and opinion of

frequency of mandatory reporting activities $x^2(1, N=58) = 0.368$, $p = 0.544$. Figure 2 describes the results of the performed Chi-squared test.

	Q1	Q2	All
YES	16	20	36
	14.90	21.10	
	0.08174	0.05770	
NO	8	14	22
	9.10	12.90	
	0.13375	0.09441	
All	24	34	58

Cell Contents
Count
Expected count
Contribution to Chi-square

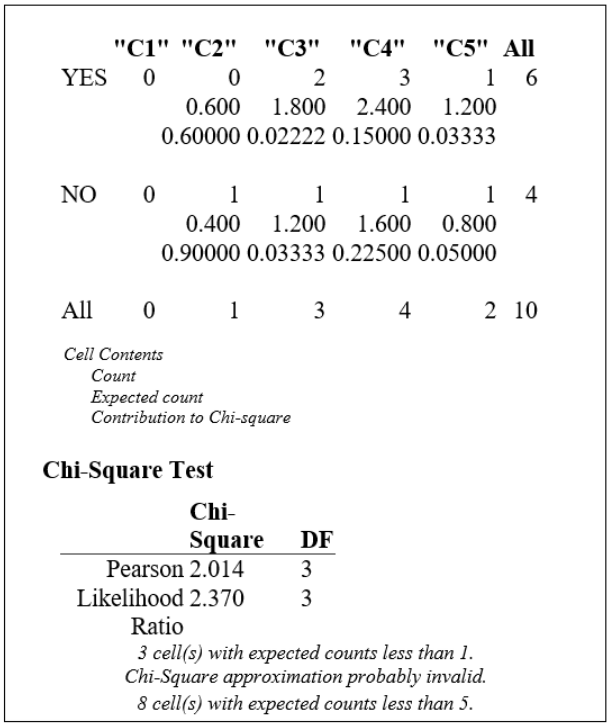
Chi-Square Test

	Chi-Square	DF	P-Value
Pearson	0.368	1	0.544
Likelihood Ratio	0.370	1	0.543

Figure 2. Independence of Reporting Frequency Belief and Adequacy of Informing FDA

Finally, respondents were presented with an increasing scale, where the lowest response indicated strong unwillingness and the high response indicated absolute willingness, describing the likeliness of accepting an HCT/P transplant from another tissue processer. Respondents were also asked to provide their opinion as to if changing the adverse reaction reporting framework would negatively affect the general public's opinion of HCT/Ps. A final Chi-squared test of independence was performed to determine any relationship between an industry member's willingness to accept a different processer's HCT/P for transplant and the potential for the

general public to develop a negative opinion of HCT/Ps as a result of adopting the adverse event-based mandatory reporting framework. The null hypothesis was that no relationship exists between the willingness to accept a competitor's HCT/P and the belief that the general public would develop a negative opinion if the adverse event reporting framework was implemented. The null hypothesis failed to be rejected as no significant relationship was identified between the two points of interest. Figure 3 describes the results of the final Chi-squared test of independence.



	"C1"	"C2"	"C3"	"C4"	"C5"	All
YES	0	0	2	3	1	6
		0.600	1.800	2.400	1.200	
		0.60000	0.02222	0.15000	0.03333	
NO	0	1	1	1	1	4
		0.400	1.200	1.600	0.800	
		0.90000	0.03333	0.22500	0.05000	
All	0	1	3	4	2	10

Cell Contents
Count
Expected count
Contribution to Chi-square

Chi-Square Test

	Chi-Square	DF
Pearson	2.014	3
Likelihood Ratio	2.370	3

3 cell(s) with expected counts less than 1.
Chi-Square approximation probably invalid.
8 cell(s) with expected counts less than 5.

Figure 3. Independence of HCT/P Treatment Openness and Potential Public Opinion

CHAPTER 5

DISCUSSION

Results Discussion

This purpose of this study was to engage members of the Section 361 HCT/P industry for critical information necessary to identify a gap in safety surveillance, if such exists, in HCT/Ps as compared to non-HCT/P products based on the mandatory reporting requirements set forth when applying the currently required definition of "adverse reaction" compared to "adverse event". Study recruitment through described means failed; therefore, the results of this study should be viewed as inconclusive until repeated with a population appropriately sized to achieve significance. Instead, this study should be utilized as a pilot study establishing a contextual and data baseline for previously unexplored comparative analysis, according to the best of the researcher's knowledge.

An increase in complaints meeting the definition of adverse event was observed when participants reviewed the 2020 calendar year complaints from the perspective of adverse event driven reporting as compared to adverse reaction mandatory reporting. The data is inconclusive and may be misrepresentative of a statistically significant population; however, the observed increase of complaints meeting the definition of an adverse event as compared to complaints which meet the definition of an adverse reaction may be indicative of the presence of a gap in the FDA's oversight of HCT/P safety. Only serious and unexpected adverse reactions are required for mandatory reporting per 21 CFR 314.80; but the phenomenon of more complaints meeting classification of an adverse event as compared to that of an adverse reaction is indicative that

further investigation is necessary before disregarding such an observation. Mirroring the mandatory reporting regulations required of drug manufacturers would not significantly alter the burden of complaint monitoring for HCT/P manufacturers, as the severity of an adverse reaction is similar to that of a serious adverse event. Instead, HCT/P processors would maintain a more descriptive account of events meeting this broader regulatory definition which could be presented to the FDA at the FDA's discretion dependent upon risk and product classification. The two-tailed t test did not support the alternative hypothesis, that there is a statistically significant difference in the reporting of HCT/Ps and non-HCT/Ps when utilizing the regulatory definition of adverse event. The same limitations apply to the applicability of the t-test calculation based in this research project, and that no true conclusions are drawable as a result of the insignificant sample size; however, the similarity of respondents reporting zero (0) complaints as meeting the adverse event or reaction definition, according to raw data, when using similar reporting criteria may indicate that amending adverse reaction criteria would not change the regulatory burden for the HCT/P industry. The value and validity of this statement is supported when comparing available HCT/P recall data from the FDA and its archives to the observation of adverse events reported in 2001 to 2004, prior to the implementation of adverse reaction reporting requirements stated in 21 CFR 1271, as described by Wang.[12] Figure 4 displays a two-tailed t test conducted to evaluate the similarity of the data observed by Wang in 2001 to 2004 to the recall data, believed to be associated with adverse reaction reporting, as made public by the Center for Biologics Evaluation and Research on the FDA's website and its archive. As noted, this comparison considers the likeliness of a tissue recall being associated with an event meeting the criteria for adverse reaction reporting by involving transmission of disease with death, debilitation or impairment, and hospitalization or medical intervention.

Results of the t test indicate there is significant similarity in the number of adverse events identified prior to the implementation of adverse reaction reporting to that of perceived adverse reaction reports submitted to FDA as indicated by tissue recalls reported. Such data does not conclude that no significant regulatory burden would be placed on tissue processers as a result from adopting adverse event reporting requirements as the data for comparative purposes may be incomplete or misrepresentative of the true reporting frequency for the tissue industry; however, a baseline is established to provide greater clarification and context should more representative data be released for public use.

Table 3. Two-Tailed T Test for Early Adverse Event Reports and Available Recall Data

	CBER Recalls[13,14,15,16]	Tissue AEs identified 2001-2004[12]
Total Identified Events	77	83
Mean	19.25	27.67
Variance	26.25	0
Observations	4	3
Pooled Variance	15.75	
df	5	
t Stat	-2.78	
P(T<=t) two-tail	0.0389	
t Critical two-tail	1.49	

The first Chi-squared test evaluated the relationship between complaint analysis against three criteria centric to complaint reportability and three criteria involving the characteristics to the responder's opinion of the adequacy of the adverse reaction reporting framework in informing the general public of product safety. Respondents who selected lower percentage ranges to best describe the complaints analyzed against the three reportability criteria also acknowledged that a higher number of their complaints occurred regarding human us; these individuals answered that the adverse reaction reporting framework is adequate in informing the

public of HCT/P safety information. Likewise, individuals who selected increased percentage ranges to best describe their complaints as being involved with product characteristics such as handling or packaging or product use causing irritation, rash, or hives. The relationship observed was not statistically significant, but a pattern exists where individuals who reported higher product use and characteristic-related complaints believe that the current reporting system is inadequate in informing the public; meanwhile, individuals who reported low percentage answers as described are trusting of the adverse reaction reporting system and believe an adequately informed public exists as a result of the current reporting framework. While the data did not show a significant relationship; it is important to note that individuals whose inputs reflected a low percentage of meeting a reportability threshold indicated their belief that the general public is adequately aware of tissue safety under the current mandatory reporting framework. This pattern, albeit insignificant from a numeric standpoint, is of particular interest in that a hypothetical bias may exist when an employer receives a lesser number of product complaints, or of product complaints that require reporting, that an assumption is made for the entire HCT/P industry given the observed experience as a member of the employer's Quality system. Coincidentally, such a bias could be overcome with increased efforts to make the public aware of HCT/Ps and instances of adverse event. The same may be true for employees of Quality systems who receive high numbers of HCT/P complaints related to product characteristics or use. A participant's experience in a high-complaint volume quality system could lead the participant to believe that the public may be "blind to the truth of HCT/Ps" or assume that the public is naïve to the dangers of tissue given that tissue is not as prominent as other regulated products, such as drugs, devices, and biologics. A similar pattern is observed for second Chi-squared test

which evaluated perceived reporting frequency compared to adequacy in informing the FDA of tissue safety matters.

The final Chi-squared test asked industry members to share, on a descriptive scale from one to five, how likely they would be to receive a competitor's HCT/P followed by their thoughts on the directionality of the public opinion of HCT/Ps should the reporting framework be revised. 60% of the participating population believed the public opinion of HCT/Ps would be negatively impacted if adverse reaction reporting was replaced with adverse event reporting requirements; however, 66% of the subset reported they would likely accept an HCT/P transplant from a competitor while 33% we impartial to the notion of receiving a competitor HCT/P transplantation. A peculiar observation should be noted in that the most significant differences in expected and actual outcome as observed in Figure 3 comes from individuals suggesting that the public opinion of HCT/Ps would decrease with the changing reporting requirements; however, these individuals did not allow different reporting requirements to affect their likelihood to accept an HCT/P from a competitor. The logic utilized by this subset may be misconstrued by the data's lack of variety and sample significance or may result from the manner in which responses were weighted for data analysis purposes; this weighting of answers may have further misconstrued the results of the Chi-squared test by allowing inputs of less than five (5) or by accepting zeros (0) in Chi-squared data analysis. The context of the logic behind this surprising stray from expectation was not under the scope of he of the research as described but could be important in gauging public support and feasibility prior to the implementation of any changes.

Regulatory Discussion

The Section 361 HCT/P industry represents a significantly smaller product category by market volume and annual use in comparison to the plethora of drugs, medical devices, and

biologics that are manufactured or used each year; however, it is the Food and Drug Administration's mission to protect the public health includes ensuring the safety of biological products, such as Section 361 HCT/P events.[17] The Food and Drug Administration's regulation of HCT/Ps appears adequate in accomplishing its overarching goal of preventing the introduction or transmission of communicable disease by requiring donor eligibility determinations based on laboratory testing and risk factor identification while limiting processing, handling, and product use to maintain regulatory status as a Section 361 HCT/P. The FDA requires quality-driven tissue processing similar to the environments derived by compliance with the Good Manufacturing Practices and Quality System Regulations for drugs and medical devices. HCT/P deviation reporting helps inform the FDA of manufacturing-quality integration status when these core regulations have direct implications on product quality or safety and further mitigate risk of cross-contamination or introduction of communicable disease by increasing or mandating the control of environmental, processing, and handling activities.

Similarly, the adverse reaction mandatory reporting regulations inform the FDA of serious product-related outcomes involving communicable disease and resulting in death, severe illness, debilitation, impairment, or require medical intervention or hospitalization to resolve the outcome. The defining factor of reportability for HCT/Ps is the involvement of communicable disease; certain adverse reactions such as pain, redness, itchiness, allergic reaction, and swelling do not meet the mandatory reporting threshold outright unless communicable disease is implicated in determining a root cause for the questioned event. Tissue processors may be in an adventitious position, over the wellbeing of the general public health, by not being required to report reactions where medical intervention, or hospitalization, was necessary to resolve the reaction unless there is a confirmation of communicated disease. A strong, hypothetical

justification by industry could prevent the FDA from being notified of localized bacterial infection and associated symptoms could be exempt from the mandatory reporting requirements if a convincing argument differentiating between a in localized infection caused by bacteria compared to infection with systemic symptoms in comparison to the definition of communicable disease in 21 CFR 1271.3(r).[7] The underreporting of adverse reactions due to the stipulation requiring communicable disease involvement may hide other agency concerns regarding compliance with 21 CFR 1271; the stipulation that HCT/P reportable events involve communicable disease prevents the FDA from receiving valuable information, that would otherwise be detected at routine inspection intervals, to potentially indicate a tissue processor's loss of control over processing and product.

The Center for Biologics Evaluation and Research makes the availability of HCT/P adverse reaction and deviation reporting data difficult to obtain. The FDA's stance on mandatory reporting rates is that report rate may be inconclusive of significance and report data may not accurately describe causation; nevertheless, the FDA makes large amounts of data on reportable events associated with drug, medical device, and biologic product use available for industry and public interest. HCT/P data is limited in volume and is difficult to find unless a Freedom of Information Act request is made. The increased transparency provided in making HCT/P deviation reports and adverse reaction reports publicized, in a manner protecting any sensitive donor identifying information, could result in increased societal awareness of HCT/Ps as treatment options and equip medical professionals with additional information necessary to adequately treat patients if the use of an HCT/P is requested, required, or preferred for any reason. A public record of reported adverse reactions and HCT/P deviations may also increase the quality of information presented to the FDA in these reports by providing tissue processors

an industry-driven resource with which a processor could compare events and deviations to those previously reported to justify necessity to issue an adverse reaction or HCT/P deviation report.

Historically, the Food and Drug Administration has been a reactionary agency, allowing disaster and tragedy to drive federal policy and direct Agency regulation and enforcement activity. One of the early food and drug legislations outgrew its relevance only 31 years after its congressional approval; the Food and Drugs Act of 1906 was quickly replaced with the Food, Drug, and Cosmetic Act of 1938 after the death of over 100 people, including children, at the hands of the sulfanilamide tragedy.[18] Similarly, the Kefauver-Harris Amendments, which improved the safety and efficacy requirements for drugs, were inspired by the European thalidomide tragedy in which thousands of infants were born with developmental birth defects after pregnant women used thalidomide for nausea and pregnancy-related symptoms.[19] The HCT/P regulations have been codified since 2005 and have undergone very little change from a regulatory perspective. In 2017, a series of four guidance documents were released which shifted the regenerative medicine regulatory framework. The Final Guidance for HCT/P minimal manipulation and homologous use brought clarity and explanation of previously difficult to understand regulatory jargon to assist industry in evaluating HCT/Ps against the four "core tissue rules" and instructed industry to begin exploring the necessity for premarket submission if self-made evaluations of tissue products did not align with the FDA's clarified explanations of minimal manipulation and homologous use.[10] This guidance was partially released in response to an increase in stems cells and other regenerative medicine products being marketed as Section 361 HCT/Ps but intended for non-homologous uses which would require safety and efficacy data, such as Parkinson's Disease, Cancer, and more. The FDA granted a three-year enforcement discretion period to allow the review and activities necessary for premarket submission.

CBER has placed emphasis on controlling the non-compliant marketing of stem cell clinic and stem cell processor products, as observed in the 13 issued untitled letters to regenerative medicine facilities and clinics in the 2021 calendar year; however, no further information has been provided regarding the latest outbreak of communicable disease resulting from a Section 361 HCT/P.[10,20] On June 2nd, 2021, Aziyo Biologics, Inc., a Richmond, California based regenerative medicine company, announced an urgent voluntary recall which was communicated by the FDA's channels, indicating that its FiberCel viable bone matrix product was being recalled upon identification of infection from one hospital; 7 of 23 recipients of lot NMDS211001 had reported infection, with four of seven testing positive with Tuberculosis.[21] On June 18th, 2021, the Washington Post reported that 113 individuals had received the cadaveric bone graft as a transplant; eight deaths were reported in association with the FiberCel product.[22] To date, the FDA has yet to announce any enforcement actions to be taken against Aziyo Biologics, make public the root cause of the Tuberculosis outbreak, or a regulation-based plan to prevent the recurrence of such an outbreak. The Food and Drug Administration should consider all aspects of HCT/P safety, from product processing and donor eligibility determination decisions to the criteria for safety event reporting and how that information is disseminated to the public, when determining its response to reshape and redirect the increased aspects of safety into HCT/Ps resulting from this tissue-based tragedy.

CHAPTER 6

LIMITATIONS

Numerous challenges and limitations were encountered during the execution of the study as initially designed and intended. Survey participation, despite aggressive circulation tactics, was not successful to meet the threshold to achieve appropriate power and statistical significance as intended. The survey was routed through numerous professional avenues including the "Stem Cell and Regenerative Medicine" interest group on LinkedIn, which consists of over 8,800 members. Additionally, the survey was posted on numerous messaging and discussion boards on the Regulatory Affairs Professional Society (RAPS) website which bolsters its membership of 27,000 regulatory professionals across the globe.[31] Countless members of the HCT/P industry were contacted directly through email, LinkedIn messaging, and by posting on LinkedIn using standard posting and category tagging measures. Numerous well-connected HCT/P industry members committed verbally or by email to aid in sharing the survey among their numerous tissue bank clients, coworkers, or fellow industry colleagues. This word-of-mouth style recruitment campaign proved to be unsuccessful in gathering the appropriate sample size for data collecting purposes.

Leadership from the American Association of Tissue Banks was consulted early in the survey distribution and recruitment process to gauge the association's interest and willingness to distribute the survey link to its 120+ tissue bank affiliate members.[30] The American Association of Tissue Bank's status and leverage was a critical component anticipated to be used during survey roll-out and population recruitment. The AATB was contacted numerous times with

acknowledgement of request; however, no progress came to fruition in allowing the AATB to lend its resources. Multiple representatives of the AATB's Staff were contacted with no distribution of the research survey through the association's system.

The continued effects of the Coronavirus "Covid-19" pandemic caused additional disruptions related to the survey recruitment opportunities. The increase of cases caused by the "Delta Variant" forced businesses, organizations, and societies to find alternatives to hosting gatherings, such as continuing education conferences, at which large quantities of members of the target population could be recruited or submit survey results in-person. The American Association of Tissue Banks postponed its Annual Meeting, scheduled initially for October 12th through 15th in Atlanta, Georgia, and opted to delay until December, choosing a virtual meeting rather than an in-person, conference-style event. This event's postponement and adaptation to a virtual format impeded a final opportunity to network with industry representatives in-person; further preventing high-quality recruitment opportunities within the industry in a presumed high-success recruitment environment.

Statistical significance was not met as anticipated regarding survey completion; more survey interactions resulted in the recording of incomplete surveys than complete surveys. Data and results of this study can only be viewed as a preliminary data trends; no conclusive statistical inferences nor determinations can be drawn as research concludes. Two root causes for this disparity in survey completion may be attributable to low survey completion rate. It is possible that industry representatives became hesitant of divulging information necessary to complete the survey out with concern that such information could be given to the FDA or an accreditation body such as the AATB; this risk was mitigated by making individuals aware that data was for research purposes only in survey link distribution emails and in informed consent agreement.

The survey required participants to select an answer to all questions, including providing informed consent and confirming they work within the industry, prior to continuing to the next question. Alternatively, the high number of survey takers who responded with only informed consent and employment confirmation may have lost interest, become distracted, or changed their mind; the survey did not provide individuals with an opportunity to describe why the survey was not completed.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This purpose of this study was to engage members of the Section 361 HCT/P industry for critical information necessary to identify a gap in safety surveillance, if such exists, in HCT/Ps as compared to non-HCT/P products based on the mandatory reporting requirements set forth when applying the currently required definition of "adverse reaction" compared to "adverse event". The data gathered to evaluate the hypothesis is insufficient to statistically support or disprove any notion, theory, or conclusion drawn, observed, or discussed; however, preliminary data analysis may suggest that adopting the adverse event mandatory reporting framework may increase the quantity of events reported without placing further regulatory burden on the reporting entity and increase the quality of information provided to the FDA by implementing routine reporting of non-serious and expected adverse events of products which undergo no safety and efficacy review prior to marketing. The context of the data gathered, reviewed, and presented suggests that this study may have succeeded in establishing an information and data baseline for future repetition so that conclusions, patterns, and theories may be adequately dispositioned, with statistical relevance and support to confirm the believed gap in the oversight of HCT/P safety as conducted by the Food and Drug Administration. The FDA may be limiting its ability to surveille the American market by requiring only the most severe HCT/P safety events that involve the transmission of communicable disease be reported to the Agency. This alleged gap could be closed by adopting less specific mandatory reporting requirements to

broaden the range of what can be classified as an HCT/P safety event, alert the FDA of high-priority and severe safety events with a prioritized reporting deadline, and maintain data of less serious HCT/P safety events for annual or periodical reporting at appropriate intervals determined by the FDA. The FDA's current practice may be insufficient in publicizing HCT/P related safety data. The FDA must adapt its regulatory enforcement strategy to ensure continued effectiveness of the regenerative medicine framework's requirements and controls; increased safety reporting standards should be considered for review and optimization as the regenerative medicine field continues to expand.

Recommendations

It is recommended that this study serve as a preliminary pilot study and that it be repeated in the future so that statistically significant conclusions can be drawn from data gathered from the study. When repeated, this study should be amended in a manner that addresses the limitations experienced as described; specifically, collaboration with the American Association of Tissue Banks should be secured to increase the likelihood of surveying a statistically significant population. A Freedom of Information Act request should be submitted to the FDA for the release of the number of HCT/P adverse reaction reports the FDA received in the desired timeframe to improve the robustness of data collection; though it was not a significant point of interest in this study, the number of HCT/P deviations submitted to the FDA may also be of interest in further defining a GTP-related safety gap. If such a gap exists, it is unclear what the significance of the gap could be; this may be of interest for investigation

It is recommended that the Food and Drug Administration consider amending the adverse reaction reporting regulations found in 21 CFR 1271.350(a) to mirror the adverse event reporting requirements as described in 21 CFR 314.80(c) which requires that serious and unexpected

adverse events be reported within 15 days of awareness while compiling a list of non-serious or expected adverse events to be provided at FDA-determined intervals. Implementing this change would remove the stipulation that the only HCT/P events necessary for reporting are safety events associated with the transmission of communicable disease; the FDA would benefit by receiving more descriptive sets of safety event data without jeopardizing the necessity to make "15-Day Reports" when events previously meeting the criteria of an adverse reaction. Given the significance of preventing the introduction or transmission of communicable disease; a requirement could be added to this proposed HCT/P adverse event reporting framework that requires the notification of communicable disease transmission independent of death, life threatening illness, debilitation or impairment, or medical intervention. Similarly, the adverse event report detailing non-serious and expected adverse events could become a requirement that follows annual registration and HCT/P product listing timeline. This action would close the gap believed to exist between the adequacy of the HCT/P reporting framework and the ability to inform the FDA of safety related events while also closing potential "loopholes" for adverse reaction reporting when events occur without the transmission of communicable disease.

Upon the implementation of the new HCT/P adverse event reporting framework, the FDA should consider implementing a publicly accessible database for the review and submission of HCT/P adverse events similar to that of FAERS, VAERS, or MAUDE for the drug, biologics, and medical device industries. A database or program of this nature would satisfy the believed gap that exists concerning the public's opinion of HCT/P safety and subtly show industry that a robust effort for surveilling product safety is a priority for all regulated products, regardless of product classification population size.

REFERENCES

1. Kohlhauser,M.;Luze,H.; Nischwitz, S.P.; Kamolz, L.P. Historical Evolution of Skin Grafting—A Journey through Time. Medicina2021,57,348. https://doi.org/10.3390/medicina57040348

2. Silini AR, Cargnoni A, Magatti M, Pianta S and Parolini O (2015) The long path of human placenta, and its derivatives, in regenerative medicine. Front. Bioeng. Biotechnol. 3:162. doi: 10.3389/fbioe.2015.00162

3. Henig I, Zuckerman T. Hematopoietic Stem Cell Transplantation—50 Years of Evolution and Future Perspectives. Rambam Maimonides Med J 2014;5 (4):e0028. doi:10.5041/RMMJ.10162

4. Tissue & Tissue Products. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products. January 27, 2021. Accessed October 25, 2021.

5. About the American Association of Tissue Banks. American Association of Tissue Banks. Aatb.org. https://www.aatb.org/about. Published 2021. Accessed October 25, 2021.

6. Code of Federal Regulations Title 21. Part 1271 - Human Cells, Tissues, And Cellular And Tissue-Based Products. Subpart A - General Provisions. U.S. Food and Drug Administration Accessdata.fda.gov.https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.10. October 01, 2021. Accessed October 25, 2021.

7. Code of Federal Regulations Title 21. Part 1271 - Human Cells, Tissues, And Cellular And Tissue-Based Products. U.S. Food and Drug Administration Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271&showFR=1. October 01, 2021. Accessed October 25, 2021.

8. CFR - Code of Federal Regulations Title 21. Part 1271 - Human Cells, Tissues, And Cellular and Tissue-Based Products. Subpart E - Additional Requirements for Establishments Described in § 1271.10. U.S. Food and Drug Administration Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.350. Published 2021. Accessed October 26, 2021.

9. Code of Federal Regulations Title 21. Part 314 - Applications For FDA Approval To Market A New Drug. Subpart B - Applications. U.S. Food and Drug Administration. Accessdata.fda.gov. 9. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs /cfcfr/cfrsearch.cfm?fr=314.80. October 01, 2021. Accessed October 26, 2021.

10. Guidance for Industry and Food and Drug Administration Staff. "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" Office of Communication, Outreach, and Development. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue- based-products-minimal. 2020. Accessed October 27, 2021.

11. Code of Federal Regulations Title 45. Part 46 – Protection of Human Subjects. National Archive and Records administration ecfr.gov. https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46?toc=1. October 25, 2021. Accessed October 29, 2021.

12. Wang S, Zinderman C, Wise R, Braun M. Infections and human tissue transplants: review of FDA MedWatch reports 2001-2004. Cell Tissue Bank. 2007;8(3):211-9. doi: 10.1007/s10561-007-9034-3. Epub 2007 Feb 3. PMID: 17278013.

13. Washington: CBER FY 2014 Recall Postings." US Official News, 14 Mar. 2015. Gale OneFile: News, link.gale.com/apps/doc/A405262818/STND?u=uga&sid=ebsco&xid= 65e86bd9. March 14, 2015. Accessed October 27, 2021.

14. CBER FY 2016 Recall Postings. U.S. Food and Drug Administration. Archive-it.org. http://wayback.archive-it.org/7993/20171101133049/https://www.fda.gov/ BiologicsBloodVaccines/SafetyAvailability/Recalls/ucm523840.htm. November 01, 2017. Accessed October 27. 2021.

15. CBER FY 2018 Recall Postings. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/recalls-biologics/cber-fy-2018-recall-postings. Published October 02, 2019. Accessed October 29, 2021.

16. CBER FY 2019 Recall Postings. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/recalls-biologics/cber-fy-2019-recall-postings. Published 2021. Accessed October 17, 2021.

17. Ballentine C. Sulfanilamide Disaster. *FDA Consumer.* U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/files/about%20fda/published/The-Sulfanilamide-Disaster.pdf. 1981. Accessed November 13, 2021.

18. What We Do. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/about-fda/what-we-do. March 28, 2018. Accessed November 13, 2021.

19. Laws Enforced by FDA. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/regulatory-information/laws-enforced-fda. April 09, 2021. Accessed November 13, 2021.

20. BIMO/Team Biologics/Internet Surveillance/Other. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/enforcement-actions-cber/bimoteam-biologicsinternet-surveillanceother. November 10, 2021. Accessed November 14, 2021.

21. Urgent Voluntary Notification: FiberCel Fiber Viable Bone Matrix ("FiberCel") - Lot Number: NMDS210011. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/recalls-biologics/urgent-voluntary-notification-fibercel-fiber-viable-bone-matrix-fibercel-lot-number-nmds210011. Published 2021. Accessed November 14, 2021.

22. Sun L, Bernstein L. CDC investigating TB cases linked to tainted bone repair product used in more than 100 patients. *The Washington Post*. https://www.washingtonpost.com /health/2021/06/18/tb-bone-product/. June 18, 2021. Accessed November 15, 2021.

APPENDIX A

LITERATURE REVIEW BIBLIOGRAPHY

1. Compliance Program Guidance Manual Inspection of Tissue Establishments (CBER) 7341.002A. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/media/79650/download. Accessed November 02, 2021.

2. Wells MA. Overview of FDA regulation of human cellular and tissue-based products. Food Drug Law J. 1997;52(4):401-8. PMID: 10346672.

3. Proposed Approach to Regulation of Cellular and Tissue-Based Products. Office of Communication, Training, and Manufacturers Assistance. Food and Drug Administration. Fda.gov. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/proposed-approach-regulation-cellular-and-tissue-based-products. September 27, 2018. Accessed November 02, 2021.

4. Code of Federal Regulations Title 21. Part 1270 - Human Tissue Intended for Transplantation. U.S. Food and Drug Administration. Accessdata.fda.gov.https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1270&showFR=1. October 01, 2021. Accessed November 02, 2021.

5. Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement; Final Rule. 69 *Federal Register* 68611. (24 Nov 2004) 68611-68688.

6. Revocation of the Regulations for Human Tissue Intended for Transplantation and Human Dura Mater; Proposed Rule. 85 *Federal Register* 82990. (21 Dec 2020) 82990-82994.

7. Code of Federal Regulations Title 21. Part 1271 - Human Cells, Tissues, and Cellular and Tissue-Based Products. U.S. Food and Drug Administration. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271&showFR=1. October 01, 2021. Accessed November 2, 2021.

8. CFR - Code of Federal Regulations Title 21. Part 1271 - Human Cells, Tissues, and Cellular and Tissue-Based Products. Subpart C - Donor Eligibility. U.S. Food and Drug Administration Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271&showFR=1&subpartNode.21:8.0.1.5.61.3. October 01, 2021. Accessed November 4, 2021.

9. Fishman JA, Greenwald MA, Grossi PA. Transmission of infection with human allografts: essential considerations in donor screening. Clin Infect Dis. 2012 Sep;55(5):720-7. doi: 10.1093/cid/cis519. Epub 2012 Jun 5. PMID: 22670038.

10. CFR - Code of Federal Regulations Title 21. Part 1271 - Human Cells, Tissues, and Cellular and Tissue-Based Products. Subpart D - Current Good Tissue Practice. U.S. Food and Drug Administration. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271&showFR=1&subpartNode=21:8.0.1.5.61.4. October 01, 2021. Accessed November 4, 2021.

11. CFR - Code of Federal Regulations Title 21. Part 1271 - Human Cells, Tissues, And Cellular and Tissue-Based Products. Subpart E - Additional Requirements for Establishments Described in § 1271.10. U.S. Food and Drug Administration Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.350. Published 2021. Accessed October 26, 2021.

12. Code of Federal Regulations Title 21. Part 312 - Investigational New Drug Application. Subpart B - Investigational New Drug Application (IND). U.S. Food and Drug Administration. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.2. October 01, 2021. Accessed November 5, 2021.

13. Code of Federal Regulations Title 21. Part 600 - Biological Products: General. Subpart D - Reporting of Adverse Experiences. U.S. Food and Drug Administration. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80. October 01, 2021. Accessed November 5, 2021.

14. Vaccine Adverse Events. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/vaccine-adverse-events January 27, 2017. Accessed November 5, 2021.

15. CFR - Code of Federal Regulations Title 21 Part 803. Medical Device Reporting. Subpart A - General Provisions.U.S. Food and Drug Administration. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=803&showFR=1. October 10, 2021. Accessed November 6, 2021.

16. Code of Federal Regulations Title 21. Part 314 - Applications For FDA Approval To Market A New Drug. Subpart B - Applications. U.S. Food and Drug Administration. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.80. October 01, 2021. Accessed October 26, 2021.

17. Wang S, Zinderman C, Wise R, Braun M. Infections and human tissue transplants: review of FDA MedWatch reports 2001-2004. Cell Tissue Bank. 2007;8(3):211-9. doi: 10.1007/s10561-007-9034-3. Epub 2007 Feb 3. PMID: 17278013.

18. FDA Adverse Events Reporting System (FAERS) Public Dashboard. U.S. Food and Drug Administration. Fis.fda.gov. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. June 30, 2021. Acccessed November 11, 2021.

19. Martin CB, Hales CM, Gu Q, Ogden CL. Prescription Drug Use in the United States, 2015-2016. NCHS Data Brief. 2019 May;(334):1-8. PMID: 31112126.

20. Craig et al. The Need for Greater Reporting of Medical Device Incidents. EMJ Innov. 2019;3[1]:56-63.

21. Problems Reported with Essure. U.S. Food and Drug Administration. U.S. Food and Drug Administration. Fda.gov. https://www.fda.gov/medical-devices/essure-permanent-birth-control/problems-reported-essure. September 29, 2021. Accessed November 07, 2021.

22. United States Department of Health and Human Services (DHHS), Public Health Service (PHS), Centers for Disease Control (CDC) / Food and Drug Administration (FDA), Vaccine Adverse Event Reporting System (VAERS) 2020., CDC WONDER On-line Database. Accessed at http://wonder.cdc.gov/vaers.html on Nov 13, 2021 10:49:23 PM

23. SOPP 8508: Procedures for Handling Adverse Reaction Reports Related to "361" Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). U.S. Food and Drug Administration. Fda.gov. https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/SOPP-8508--Procedures-for-Handling-Adverse-Reaction-Reports-Related-to-%22361%22-Human-Cells--Tissues--and-Cellular-and-Tissue-Based-Products-%28HCT-Ps%29.pdf. March 26, 2008. Accessed November 11, 2021.

24. Washington: CBER FY 2014 Recall Postings." US Official News, 14 Mar. 2015. Gale OneFile: News, link.gale.com/apps/doc/A405262818/STND?u=uga&sid=ebsco&xid=65e86bd9. March 14, 2015. Accessed October 27, 2021.

25. CBER FY 2016 Recall Postings. U.S. Food and Drug Administration. Archive-it.org. http://wayback.archive-it.org/7993/20171101133049/https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/ucm523840.htm. November 01, 2017. Accessed October 27. 2021.

26. CBER FY 2018 Recall Postings. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/recalls-biologics/cber-fy-2018-recall-postings. Published October 02, 2019. Accessed October 29, 2021.

27. CBER FY 2019 Recall Postings. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/recalls-biologics/cber-fy-2019-recall-postings. Published 2021. Accessed October 17, 2021.

28. BIMO/Team Biologics/Internet Surveillance/Other. U.S. Food and Drug Administration. fda.gov. https://www.fda.gov/vaccines-blood-biologics/enforcement-actions-cber/bimoteam-biologicsinternet-surveillanceother. November 10, 2021. Accessed November 14, 2021.

29. Guidance for Industry and Food and Drug Administration Staff. "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" Office of Communication, Outreach, and Development. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue- based-products-minimal. 2020. Accessed October 27, 2021.

30. About the American Association of Tissue Banks. American Association of Tissue Banks. Aatb.org. https://www.aatb.org/about. Published 2021. Accessed October 25, 2021.

31. Join RAPS | We are Regulatory. Regulatory Affairs Professional Society. https://www.raps.org/join-raps. Published 2021. Accessed October 12, 2021.

APPENDIX B

RESEARCH SURVEY

Read Carefully. You are invited to participate in a research study about the requirements and frequency of FDA reporting for Section 361 human cell, cellular and tissue-based products (HCT/Ps) compared to non-HCT/Ps (drugs, medical devices, biologics). The United States Food and Drug Administration (FDA) defines the following terms in the United States Code of Federal Regulations; these definitions are relevant to the area of interest for which this research study has been planned.

The FDA requires the following of HCT/P manufacturers regarding “adverse reactions” in 21 CFR 1271.350(a):
“[HCT/P firms] must investigate any adverse reaction involving a communicable disease related to an HCT/P that [the firm] made available for distribution. [The firm] must report to FDA an adverse reaction involving a communicable disease if it:
(i) Is fatal;
(ii) Is life-threatening;
(iii) Results in permanent impairment of a body function or permanent damage to body structure; or
(iv) Necessitates medical or surgical intervention, including hospitalization.”

The FDA applies the term “adverse drug experience", which is interchangeable to "adverse event" to non-HCT/P products for reporting purposes and defines such in 21 CFR 314.80 as: “Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action."

Participation in this study is entirely voluntary and requires only opinion-based questions; you will not be asked to provide any identifiable or confidential, proprietary, or trade secret information in the following survey. Your responses shall not be distributed, and anonymity shall be protected and maintained through the survey participation process.

By agreeing below, you are agreeing to be honest in your responses and affirm that your employer manufactures HCT/Ps per Section 361 of the Public Health Services Act or that you were employed by a manufacturer of Section 361 HCT/Ps after January 1st, 2018.

- I Consent and Agree
- I Do not Consent or Do Not Agree

Question One. Do you currently work, or were you employed for any time after January 1st, 2018, for a human cell, cellular and tissue based products (HCT/P) manufacturer?

- Yes
- No

Question Two. Approximately how many complaints did you or your employer receive between January 1st, 2020 and December 31st, 2020?

- Text box entry

Question Three. Approximately how many of these complaints involved communicable disease and were fatal, life-threatening, resulted in permanent impairment of a body function or permanent damage to a body structure, or necessitated medical or surgical intervention (including hospitalization), in accordance with 21 CFR 1271.350(a)?

- Text box entry

Question Three. Approximately how many of these complaints involved communicable disease and were fatal, life-threatening, resulted in permanent impairment of a body function or permanent damage to a body structure, or necessitated medical or surgical intervention (including hospitalization), in accordance with 21 CFR 1271.350(a)?

- Text box entry

Question Five. Utilize the following definitions to select your response:

Adverse Reaction (21 CFR 1271.350(a)): "[HCT/P firms] must investigate any adverse reaction involving a communicable disease related to an HCT/P that [the firm] made available for distribution. [The firm] must report to FDA an adverse reaction involving a communicable disease if it:
(i) Is fatal;
(ii) Is life-threatening;
(iii) Results in permanent impairment of a body function or permanent damage to body structure; or
(iv) Necessitates medical or surgical intervention, including hospitalization."

Adverse Drug Experience ("Adverse Event", 21 CFR 314.80): Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action."

Select the most accurate for each of the six conditions below regarding the following statement.

Approximately how many complaints received received by you or your employer...
1) Were determined to be reportable according to the FDA's HCT/P reporting requirement as found in 21 CFR 1271.350?

- 0-10%
- 0-20%
- 0-30%
- 0-40%
- 0-50%
- 0-60%
- 0-70%
- 0-80%
- 0-90%
- 90-100%

2) Were identified as involving a communicable disease upon investigation (infectious agent, relevant communicable disease agent or disease, etc)?

- 0-10%
- 0-20%
- 0-30%
- 0-40%
- 0-50%
- 0-60%
- 0-70%
- 0-80%
- 0-90%
- 90-100%

3)Were fatal, life threatening, resulted in permanent damage or impairment to body structure/function, or necessitated medical intervention/hospitalization?

- 0-10%
- 0-20%
- 0-30%
- 0-40%
- 0-50%
- 0-60%
- 0-70%
- 0-80%
- 0-90%
- 90-100%

4) Were associated with product use in humans, whether or not considered product related?

- 0-10%
- 0-20%
- 0-30%
- 0-40%
- 0-50%
- 0-60%
- 0-70%
- 0-80%
- 0-90%
- 90-100%

5) Were related to product Characteristics (Handling, packaging, appearance, labeling?

- 0-10%
- 0-20%
- 0-30%
- 0-40%
- 0-50%
- 0-60%
- 0-70%
- 0-80%
- 0-90%
- 90-100%

6) Were related to product use (irritation, hives, rash, fever, illness, disease, etc.)?

- 0-10%
- 0-20%
- 0-30%
- 0-40%
- 0-50%
- 0-60%
- 0-70%
- 0-80%
- 0-90%
- 90-100%

Question Six. Do you believe the reporting framework for HCT/Ps is adequate in informing the general public of an accurate product safety profile?

- Yes
- No

Question Six. Do you believe the reporting framework for HCT/Ps is adequate in informing the general public of an accurate product safety profile?

- Yes
- No

Question Eight. Based on your opinion and experience with HCT/P complaints, your opinion of complaints received by non-HCT/P (drug, medical device, biologic) manufacturers, and your knowledge of the current reporting framework...

Select the percentage that you believe most accurately represents the frequency of reporting adverse events to the FDA for non-HCT/P products as compared to the frequency of adverse reaction reporting for HCT/P products?

HCT/Ps

- 0-20%
- 20-40%
- 40-60%
- 60-80-%
- 80-100%

Non-HCT/Ps (drugs, medical devices, biologics)

- 0-20%
- 20-40%
- 40-60%
- 60-80-%
- 80-100%

Question Nine. Do you trust the safety of competitor HCT/Ps enough to accept a competitor product as treatment based on your knowledge of the adverse reaction reporting framework?

- I would never accept a competitor HCT/P as a treatment
- I would not likely accept a competitor HCT/P as a treatment
- I am indifferent about accepting a competitor HCT/P as a treatment
- I would likely accept a competitor HCT/P as a treatment
- I would absolutely accept a competitor HCT/P as a treatment

Question Ten. Do you think changing the mandatory reporting framework for HCT/Ps from adverse reaction to adverse events would negatively impact the general public's opinion of HCT/Ps?

- Yes
- No

We thank you for your time spent taking this survey.
Your response has been recorded.