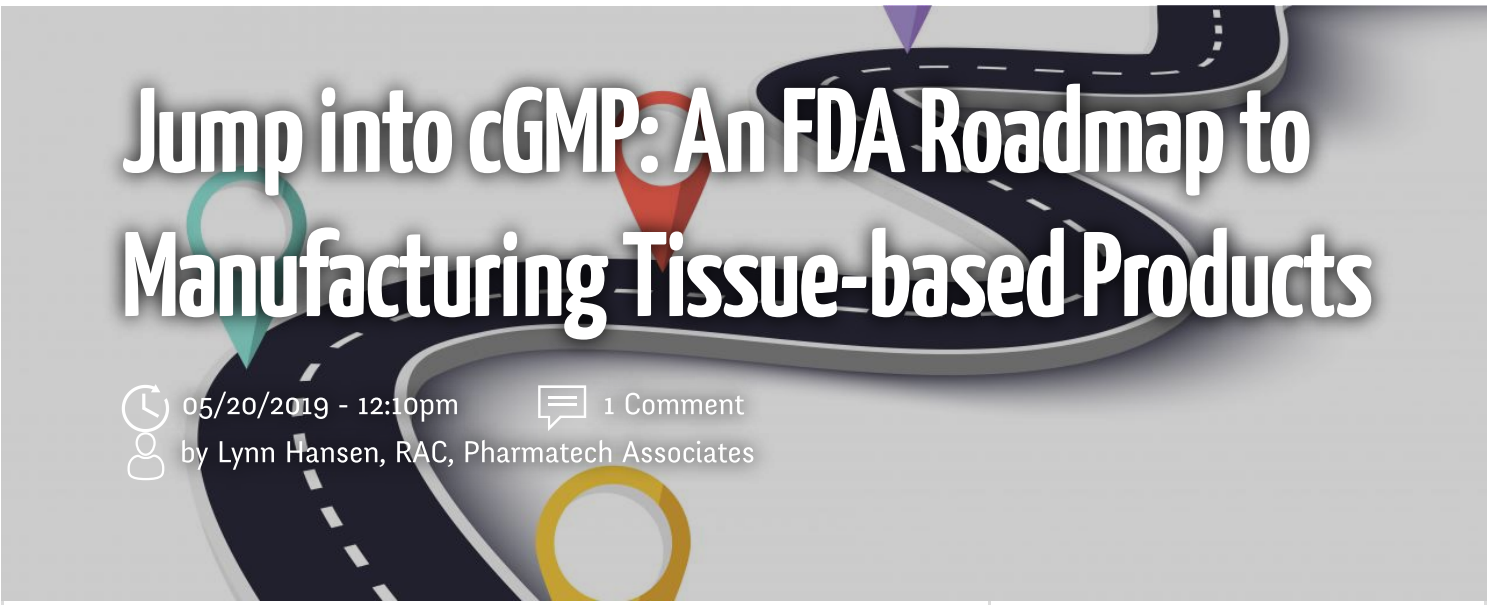

Jump into cGMP: An FDA Roadmap to Manufacturing Tissue-based Products

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Pharmaceutical Processing

Regulatory

Companies currently in the tissue-based regenerative medicine business need to understand and comply with the FDA's expectations for human cells, tissues and cellular and tissue-based product (HCT/P) under development in the next two years. HCT/P pertains to products containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

If we are to jump into cGMP, where is the line of converting from 361 to 351 Regulations and Practices for a manufacturing facility drawn? The present column explores a basic roadmap for the process of migration to the new regulatory environment, within the 36-month timetable mandated by the FDA and ending on November 16, 2020.

Let's start by examining the HCT/P products under Section 361 of the Public Health Services Act (PHSA) and 21 CFR 1271.

Historic framework

In March 1997, FDA announced plans for a more comprehensive, risked-based approach for regulating HCT/P products.

The FDA's regulatory framework goals were to: Prevent the unwitting use of contaminated tissues that carry the potential for transmitting infectious disease; Prevent any improper handling or processing that might contaminate or damage tissues; Ensure that clinical safety and effectiveness are demonstrated for cells and tissues that are highly processed, used for purposes other than replacement or combined with non-tissue components, or that have systemic effects.

Three different rules were implemented and are identified in Table 1.

Final Rule	**21 CFR 1271 Subpart(s)**	**Effective Date (Published Date)**	**Issues Addressed**
Establishment Registration and Listing	A,B	4 April 2001, 21 January 2003 (19 January 2001)	Applicability: types and uses of products that will be regulated by these rules; requirements for registering and listing HCT/Ps
Donor Eligibility	C	25 May 2005 (25 May 2004)	Requirements for donor screening and testing for relevant communicable disease agents and diseases
Current Good Tissue Practices (CGTP)	D, E, F	25 May 2005 (25 November 2004)	Manufacturing to ensure HCT/Ps do not contain communicable disease agents; Reporting: labeling and

			compliance inspections

Manufacturers will have to focus on transforming from good cellular and tissue practices to the characterization-intensive world of GMPs if the current HCT/P products are to move into the Investigational New Drug (IND) and Biologics Laboratory Applications (BLA), world. The challenge is in establishing a feasible approach to convert from 361 Good Tissue Practice (CGTP) to 351 Good Manufacturing Practice (CGMP) regulation.

Four criteria—Drugs, Biologics or Medical Devices

An HCT/P is regulated solely under Section 361 of the PHSA and (§1271.10(a)) if it meets all the following criteria—the product is:

- Minimally manipulated;
- Intended for homologous use only;
- Not combined with another article;
- Not dependent on metabolic activity of living cells, except for autologous use, use in a first-degree or seconddegree blood relative, or for reproductive use; and has no systemic effect.

HCT/Ps not meeting all four criteria above are regulated as drugs, devices, and/or biological products under Section 351 of the PHSA and the Federal Food, Drug and Cosmetic Act (FD&C Act). This means that the HCT/P requirements are subject to regulations specific to drugs, biological products (CGMPs) or medical devices (Quality Systems Regulation (QMS)), in addition to the applicable sections of Part 1271.

There can be a large number of analytical and manufacturing controls required during the transition from the 361 to the 351 pathways.

Roadmap and regulations checklist

The best way to take these controls into account, and our primary recommendation, is to create a checklist for the three spheres of regulations pertaining to HCT/P, 21 CFR 1271, 21CFR 600-680, and 21CFR 210/211. This means literally going through and evaluating the current process with the requirements listed in the abovecited regulations.

Identify the widest gaps between the regulations and the current process and determine the priority for changes to eliminate any gaps. Some of the major disparities may occur in the areas of Control of Materials, Laboratory Control Systems, Master Production and Control Records, and Package Labeling. Cross-functional teams must work together for the first deep dive into the existing process: this will ensure all the important or critical regulations are covered.

As daunting as the process sounds the results are valuable and can be the basis of training for the existing manufacturing facility. Manufacturing, Quality, and Development will be the important departments involved and leaders for specific tasks will have to be assigned and supported by upper management.

From a Regulatory perspective it is very important to make sure the correspondence between the sponsor company and the FDA covers and addresses all recommendations from the agency. If the FDA has requested certain analytical procedures to be added or refined, the sponsor has to demonstrate that measures are proceeding accordingly in the IND lifecycle.

The FDA is willing to meet, discuss, and propose the best pathway for a company to maneuver through the IND→BLA as a partner rather than an adversary. In terms of documents, the FDA will expect reports to contain generated data as well as documented references to support any rationale from the HCT/P sponsor.

Example of pharma divisions: Scale-up for upscale products. A real-life example is helpful as it describes a similar case to the topic at hand: the HCT/P world jumping from GTP to GMP. During the first wave of pharma diversification, a number of larger companies moved into new business opportunities by spinning off businesses from within the corporate structure.

In those years, I was responsible for the stability program being carved out of the existing research function of a pharmaceutical manufacturer. New divisions were created and added to an existing division that supported line extensions of the company’s currently marketed products. These were incorporated as Dermatology, Ophthalmic, Dental,

Nutritional, Animal and Beauty Care—led by a charismatic R&D executive and his team.

The new businesses were positioned to move from the research lab into a more restrictive regulatory environment, while keeping the existing business and sales on track. However, beauty care is a fast-paced business that has to be ready to change products and accommodate for seasonal changes.

Creativity on the bench is the norm and formulations were modified according to customers' immediate responses and needs. Parallel to this development function is the planning and manufacturing of modifications to ingredients, packaging, testing, and labeling.

In this case, placing a creative free-flowing existing process into a system that moves selectively on a project-by-project basis, and adding developmental testing within prescribed procedures created friction, and ultimately, led to stagnation.

The pharmaceutical business had a safety committee responsible for evaluating and reviewing the safety of every product either in development or being sold. As the beauty care division began to follow procedures and submit changes or modifications, the volume of products being evaluated and in review increased significantly.

Before long the safety committee was overwhelmed and needed to modify the procedure just to keep pace. Although the beauty care manufacturing facility was able to absorb the updated requirements, the development process suffered, thus halting the business opportunity. This was a case of creativity vs. science—and science won: after several years, the beauty care division was sold, as were the other divisions.

High expectations for tissue manufacturing

The tissue manufacturing business is going through similar expectations as it jumps from Section 361 of the Public Health Services Act (PHSA) and 21 CFR 1271 to the world of Section 351 and 21 CFR 210/211.

The potential operational impact to a manufacturing facility on a successful business can appear intimidating at the outset, but the transition can be implemented effectively with proper training, effective tools for implementation, and documentation supporting all updates.

The training of personnel is key and should be initiated as soon as possible so that everyday tasks can absorb the various refinements identified through gap analysis. Priority for each stage of implementation needs to be presented, understood, and agreed upon by upper management to ensure the conversion process encompasses the business needs.

About the Author: Lynn C. Hansen, RAC, is Director of Regulatory Affairs with Pharmatech Associates. Lynn has worked in the development and regulatory management of product programs within the pharmaceutical and bioscience industries for 30 years. Her experience spans the drug development lifecycle from product development and research, through to commercial launch and post-market monitoring for solid dose, parenteral, and combination products. She has held leadership positions in both large Pharma and virtual start-up organizations overseeing the regulatory submission and maintenance programs for multiple products. Lynn's expertise includes CMC, clinical and non-clinical modules and extends to both U.S. and global regulatory filings that utilize the eCTD format. She is an active member of the Regulatory Affairs Professional Society (RAPS) certification program and currently sits on the RACB (Regulatory Affairs Certification Board).

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