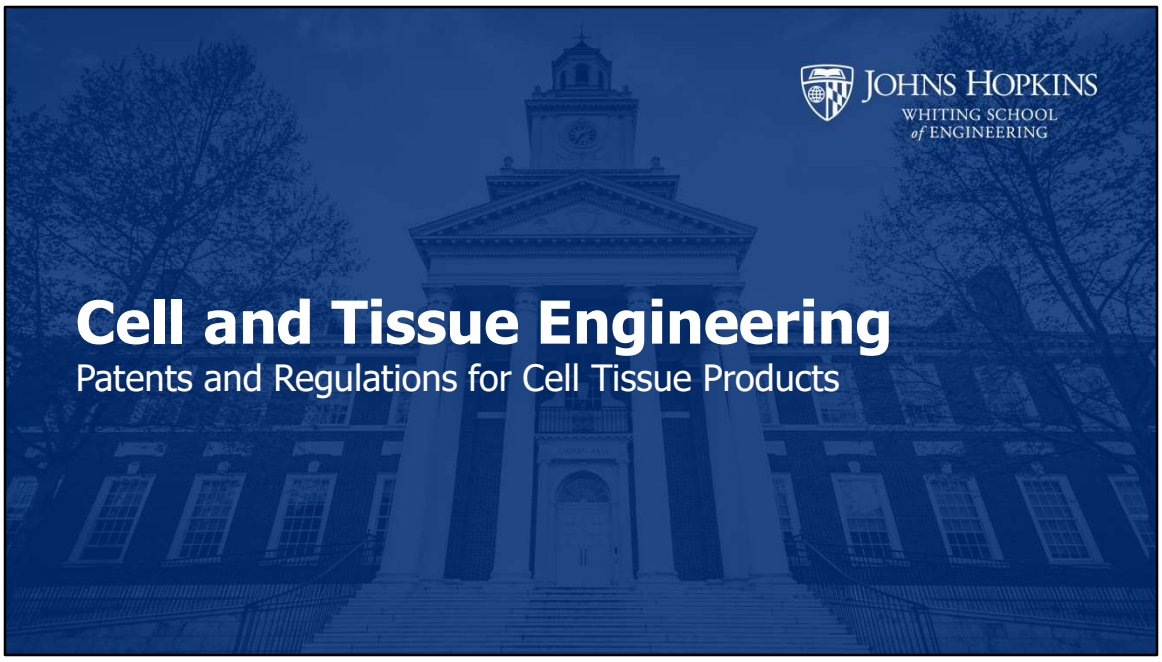
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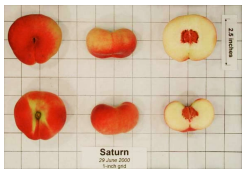
Cell and Tissue Engineering
Patents and Regulations for Cell Tissue Products

Patent Protection

Utility Patent – "new and useful process, machine, manufacture or composition of matter"	**20yrs**
Design Patent – "new, original and ornamental design embodied in or applied to an article of manufacture"	**14yrs**
Plant Patent – "new and distinct, invented or discovered asexually reproduced plant"	**20yrs**



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Uspto

Outside of the science and engineering you need to be thinking about the intellectual property -- patent protection and commercialization. We'll start by talking about patent protection. Patent protection is absolutely critical for a cell and tissue engineered solution. Without patent protection it is extremely unlikely that funds can be obtained to develop the product to the commercial level.

There are three types of patents – **utility**, **design**, and **plant**.

A **utility patent** will be issued for the invention of a new and useful process, machine manufacture or composition of matter. This category includes tools, methods for making products (including computer algorithms), or new drugs.

Design patents are what they sound like – they are issued for the design of something. This could be the design of your new cell phone, a car, jewelry, drink containers, and computer icons. On the right middle, you are looking at the original drawings for the patent of the first coke bottle from 1915.

The last type of patent is issued for **plants** – both newly **discovered** or **invented**. This includes cannabinoids for use as antioxidants and neuroprotectants, as well as

different varieties of fruit – like this donut peach on the bottom right.

You can see that the type of patent determines the **length of issue** – with design patents being 6 years shorter than the other patent types.

Guide to patent searches: https://guides.library.jhu.edu/business/patents
Hopkins FAQ for Students and IP: https://ventures.jhu.edu/wp-content/uploads/2019/12/Students-and-IP-FAQs.pdf

Patent Protection - Criteria

- Novelty
- Usefulness
- Non-obvious

- ***Timing!***

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Pbs.org

Regardless of the patent type, in order to obtain a patent you must meet three criteria:

- it must be new or **novel**,
- it must be **useful** to society in some way and
- it must be **non-obvious**.

This non-obvious criteria is the one that gives people the most trouble. For something to be non-obvious is must be **different** than existing art in the field.

So for CTE that means it can't be a *logical improvement* on an existing solution. For example, a chemist working to make an improved road salt for the winter roads this holiday week may decide to substitute potassium chloride for sodium chloride. However this is an obvious improvement and since sodium chloride is already patented as part of a road salt formulation, this idea would not be patentable.

As a student it is important to also consider the **timing** of your patent application. A patent only provides so many years of protection, which you may want to maximize. In order to protect your work, you must file the patent prior to public disclosure. That means before you submit a paper for review, before you present your work at a conference, and often before you defend or submit your thesis.

US Commercial Development - FDA

- Public Heath Service – PHS
- Food and Drug Administration – FDA
- 6 Centers

CDRH Center for Devices and Radiological Health
CDER Center for Drug Evaluation and Research
CBER Center for Biologics Evaluation and Research
Food Safety and Cosmetics Veterinary Medicine Toxicological Research

Tissue Engineered Medical Products

(TEMPS)

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Adapted from Tissue Engineering, Palsson & Bhatia

Regulatory approval is a must for CTE products – sometimes called TEMPs for tissue engineered medical products.

In this US, this is managed by the Food and Drug Administration – which is an agency that provides public health service. This agency covers oversight of many things – medical devices, drugs, food, and biologics through six different centers.

CDER and CBER regulate monoclonal antibodies, cytokines, growth factors, immunomodulators, and proteins used for therapeutic use – including recombinant versions.

TEMPs typically fall under Devices or Biologics as we'll see in a minute

We should note here that the National Organ Transplant Program and the National Marrow Donor Program are overseen by the Health Resource Services administration which is separate from the FDA.

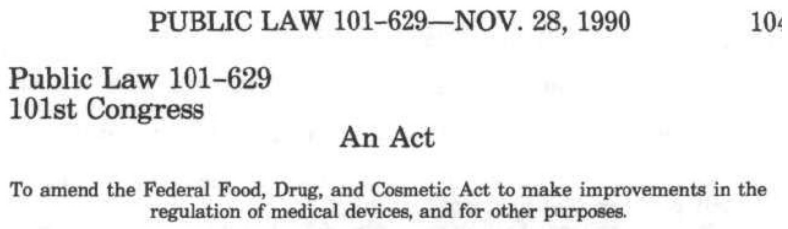
Combination Products

Public Heath Service – PHS

Food and Drug Administration – FDA

Office of Combination Products
Office of Orphan Products
Office of Regulatory Affairs

Safe Medical Device Act of 1990
Medical Device User Fee and Modernization Act of 2002



PUBLIC LAW 101-629—NOV. 28, 1990 10

Public Law 101-629
101st Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to make improvements in the regulation of medical devices, and for other purposes.

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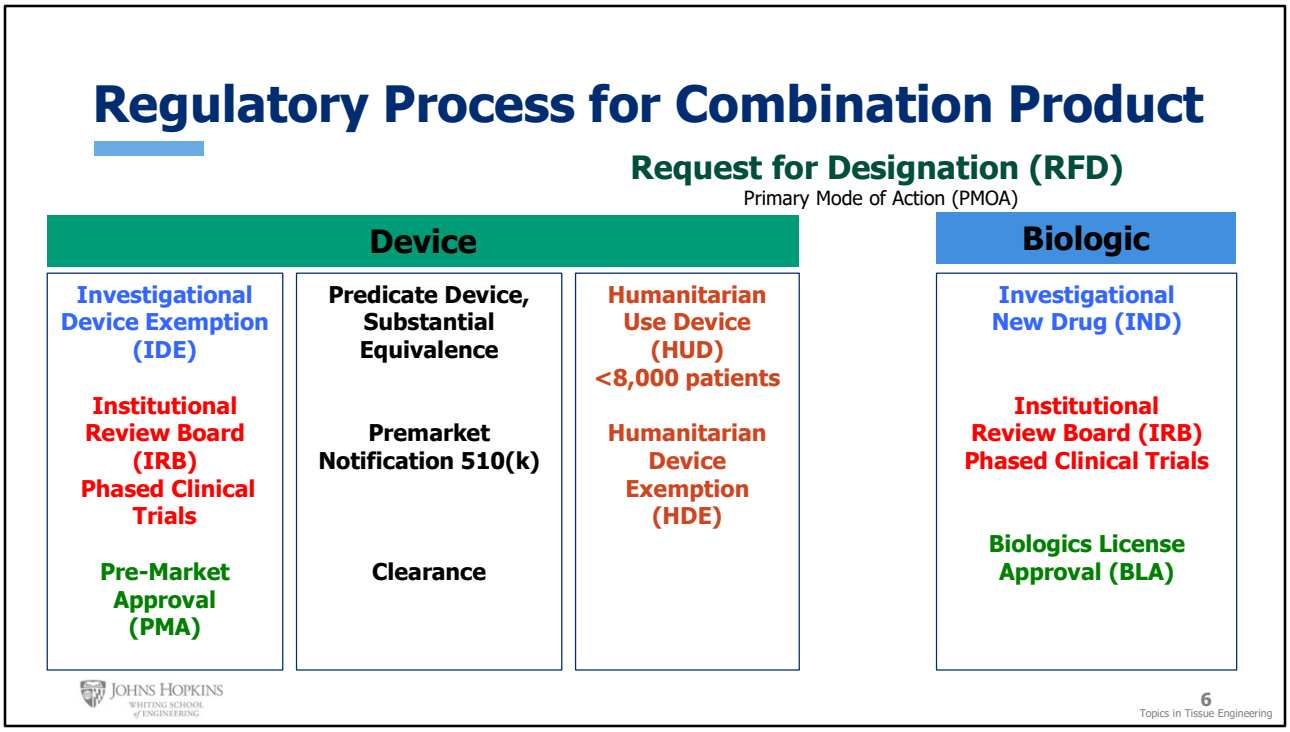
Adapted from Tissue Engineering, Palsson & Bhatia

With continued growth of products combining **devices** with **drugs**, or **cells** with **biomaterials,** the FDA has been adapting so that it can safely regulate these new solutions.

In 1990 Congress recognized the existence of combination products and enacted the **Safe Medical Device Act.** This act said that combination products would be classified by their primary mode of action – and that this mode would be used to determine the appropriate regulating center at the FDA. In 2002 a second act built the Office of Combination Products which makes these determinations (called Requests for Designation).

Based on the course so far, it should not surprise you that many CTE solutions are combination products.

Additionally the FDA's Office of Orphan products and the Office of Regulatory Affairs may be involved in more unique cases.



This figure gives you the run down of how the regulatory process works for combination products. There is a lot of information here but we'll try to get through it quickly.

The first thing that happens in that a **request is made for designation** – this leads to the product placed into one of two categories (typically either Device or Biologic, not normally a Drug for CTE products) based on the **Primary Mode of Action**. This request is made to the Office of Combination Products. .

That path we are probably all the most familiar with are the clinical **investigational studies** on the far left and far right.

IDE being **investigational device exceptions** and IND being **investigational new drugs**.

- These products must demonstrate **safety and efficacy** before getting to market.
- Their applications must not only give a **description** of the product but also the **manufacturing** process which we spoke about earlier, **how safety** will be evaluated and how the **design of preclinical studies** has already assessed both the **risks and benefits** of the product.
- The clinical protocols for the trials are included in this initial application and these

protocols must also be approved by (typically local) an institutional review board.

Clinical Trials start small – You've likely already covered the different phases in other classes:
– **Phase 1** feasibility studies have a low number of participant, and **safety** endpoints. If these go well, everything moves to on the next phase, but often this early first in human experiment stops or redirects the product.
-- **Phase 2** which looks at **dosing** and **efficacy**.
-- Then **Phase 3** with is a full out study often with thousands of patients, that fully determines safety and effectiveness and will lead to the *application* for **premarket approval** , *approval,* and finally the *marketing* process to commercialize the product. For a biologic-based product instead of premarket approval it will receive a **biologics license**.

Running a set of clinical trials is complicated and expensive. There are a couple of other, less burdensome options to bring your product to market:

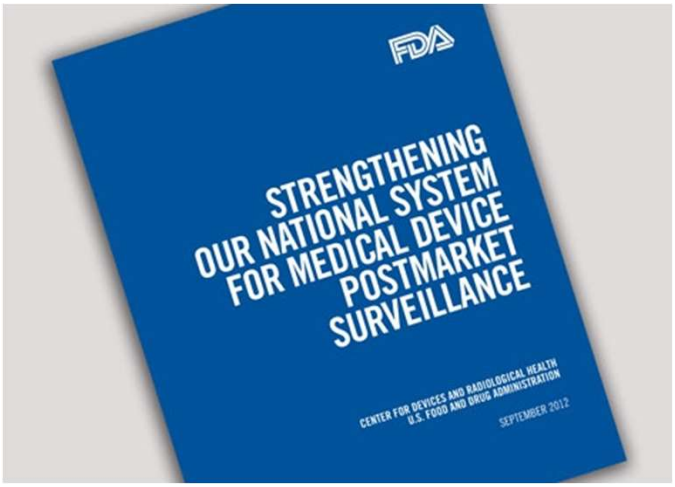
Substantial Equivalence with the 510(k) program:
- If you have a medical device <u>and</u> it is equivalent to a device already marketed in the US, then you can skip ahead and use premarket notification of 510k pathways to go directly to market. The key to this step is that the product must be similar to something that was on the market prior to May 28, 1976 AND not a high risk device.
- Please take note that it says **cleared** here not *approved* – these are different designations. Devices that go through the 510k pathway are not approved by the FDA but they are allowed (cleared) to go to market and be sold in the US.

The other pathway is the **humanitarian use devices** – or HUDs
- These are in place for medical products where the **<u>cost</u>** of obtaining premarket approval may be **prohibitive** to the development of that product and keep it from the small population it is intended for. By small population I mean **less than 8,000 patients in the US per year**.
- If you have a HUD, you can petition for a **Humanitarian device exemption** or HDE which gets you special considerations and exceptions to further reduce costs. The skin substitutes we talked about last week had the device exemption, which meant they didn't need to demonstrate a effectiveness to market their product. However, there are usage and profit restrictions with HDEs.

Substantial Equivalence: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k

Classifying your device according to risk: https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device
Humanitarian Use: https://www.fda.gov/medical-devices/premarket-submissions/humanitarian-device-exemption

What Comes After the Market?



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After your product goes to market, it is likely that it will be subject to monitoring processes and requirements. This is termed **post-market surveillance**.

Post-market regulations require that you **report adverse events** and that you get **approval** before **changing** the **labeling** on your product. Often, you may be required to maintain a patient registry or run additional clinical studies after reaching the market.

Many tissue engineered products are intended as **permanent implants** which means *failure* could cause serious consequences or even death (think of a replacement organ failure for example). Post-market surveillance will be used to report long term effects and ensure that your product is stable and capable of sustaining human life.

HCT/Ps Human Cellular-and Tissue-based Products

- Current Good Tissue Practice for Human Cell, Tissues, and Cellular-and Tissue-Based Products (cGTP Rule)
- **Task Force on Human Tissue Safety**

Kick-down Criteria for 361 Products

1. Minimal Manipulation of the source tissue (through processing)
2. Homologous use
3. Freedom from combination with another article
   (excluding sterilization, preservation or storage agents)
4. Absence of systemic effects or dependence on the metabolic activity of living cells
   (excluding autologous use, use in first degree relatives, or reproductive use)

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The incredible research efforts in cell and tissue engineering have drawn the attention of the FDA – and the establishment of additional rules for these products.

In 2005, the **CGTP** rule was put into effect. This acronym stands for the **current good tissue practice for human cell tissues and cellular and tissues-based products**.

This covers all products containing human cells or tissues for implantation, transplantation, infusion or transfer to a human recipient.

Under this rule products that meet certain kick-back criteria **do not need** to undergo pre market review. Products that are kicked-back would use the existing regulations we just looked at.

The kickdown criteria are given to you here- that….

IN addition to this rule the FDA established a task force on human tissues safety which specifically assess the effectives of CGTP products.

FDA Guidance on HCT/Ps and kick-down criteria: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal

What Does this All Mean?

FDA
evaluates
benefits/risks
for the population

Provider
evaluates
benefits/risks
for a patient

Patient
evaluates
benefits/risks
in terms of
personal values

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FDA

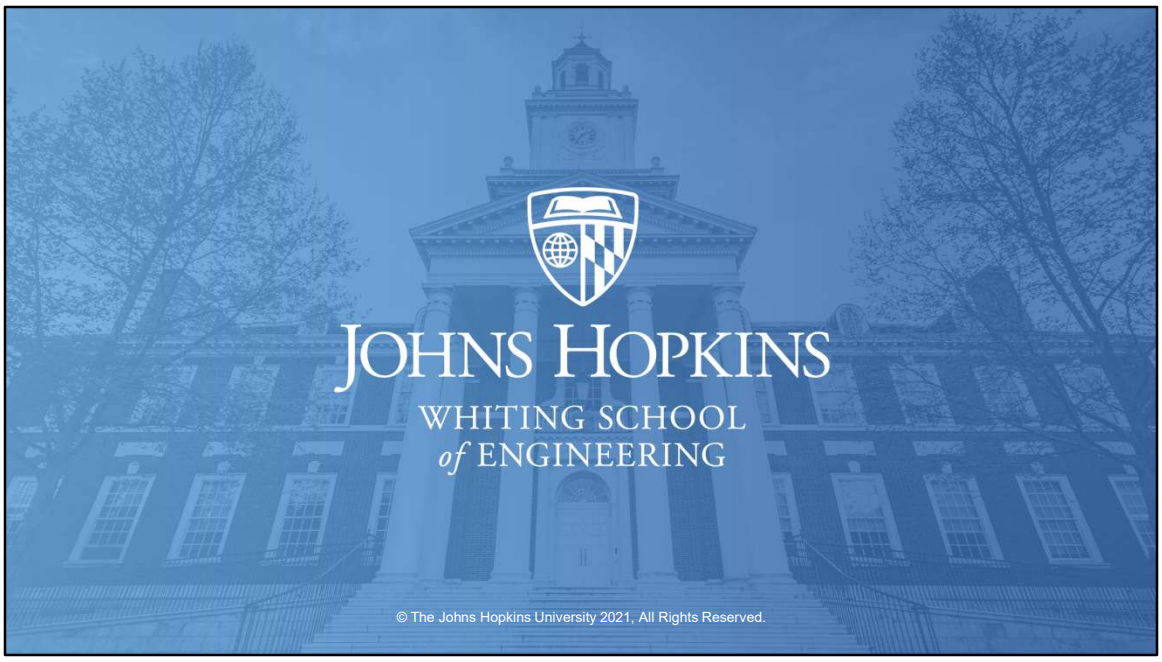
So we know the key considerations for commercialization and the process for FDA regulation of cell and tissue engineered products --- where does that leave us as we wrap up this course?

It leaves us here with **three levels of protection** for the patient.

- The **FDA** will scientifically weight the benefits and risks for the public,
- The **provider** -- perhaps the surgeon or primary care physician -- will look at those same risks but in the **specific context of their patients**. Their health and needs.
- And finally the **patient** themselves will (*often*) apply their personal values to the decision making processes.

You can see that just getting market isn't enough – these two other tiers are what cause your product to be adopted and used.

With all of this information, you can now appreciate the enormous challenges for cell and tissue engineers just beyond the bench.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