SKILL BUILDING: Commercialization

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IN PARTNERSHIP WITH THE MCMASTER INDUSTRY LIAISON OFFICE (MILO)

INTELLECTUAL PROPERTY & REGULATORY CONSIDERATIONS HANDBOOK

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Industry Liaison Office

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Types of health innovations

Different types of health innovations may have vastly different considerations for commercialization. Therefore, throughout this handbook, intellectual property (IP) and regulatory considerations are outlined for each type. The following are descriptions of health innovation categories referred to throughout this handbook.

Note: This list of categories is not necessarily all-encompassing. Some innovations may relate to more than one.

	**THERAPEUTICS**	Agents used to prevent or alleviate a disease or condition. *e.g. small molecule drug, vaccine, treatment regimen*
	**MEDICAL DEVICES**	Instruments used in the treatment, mitigation, diagnosis, or prevention of a disease or condition. *e.g. implants, surgical tools, health monitors*
	**DIAGNOSTICS (includes biosensors)**	A device or technique used in medical assessment or diagnosis. Diagnostic devices often include a **biosensor:** A technology capable of detecting or measuring a biological molecule or substance of interest. *e.g. biopsy, home pregnancy test, blood glucose monitor*
	**DATA SCIENCES**	Solutions for collecting, storing, or interpreting information for a specific purpose. *e.g. genetic information database, clinical data registry, AI/ML applications*
	**DIGITAL APPLICATIONS**	Health products or services in the form of software. *e.g. electronic medical record software, phone app for psychotherapy*
	**RESEARCH TOOLS**	Encompasses reagents, animal models, methods, or other tools used to conduct research. *e.g. CRISPR, antibodies, PCR, drug screening platform*
	**HEALTH SYSTEM INNOVATIONS**	A wide range of offerings that augment the delivery of healthcare (e.g. faster, better quality, lower cost, ease of use). *e.g. policies, programs, services, institutional structures, Local Health Integration Network (LHIN) Act, Fast Healthcare Interoperability Resources (FHIR) standard for electronic medical information*

Introduction to Intellectual Property

Enablers of commercialization

1. A Problem that Customers (patients, caregivers, hospitals, government) Will Pay to Solve
2. Discovery/Idea: Research finding or concept that is new and unique
3. **Intellectual Property (IP): Legal protection of the discovery/idea to prevent use by competitors**
4. Team/Talent
5. Resources (e.g. investment, space, equipment)

Definition of intellectual property (IP)

Legally: "… legal rights to ideas, inventions and creations in the industrial, scientific, literary and artistic fields. It also covers symbols, names, images, designs and models …" (Government of Canada)

More simply:

- 'Creations of the mind', such as inventions, artistic works, designs, or names
- Assigned protection of innovative creations to prevent use by competitors
- One innovation may be protected by multiple pieces of intellectual property

Types of IP

PATENT	Exclusive legal rights granted in exchange for public disclosure of an invention. Relevant health innovations: therapeutics, medical devices, diagnostics (Invention: Product or process that solves a technological problem.)
TRADE SECRET	Formula, process, or design kept "under wraps." Relevant health innovations: experimental or production methods
COPYRIGHT	Exclusive legal right to produce, reproduce, publish or perform an original work of art. Relevant health innovations: data sciences and digital apps, clinical questionnaires
TRADEMARK	Name, phrase, design or symbol recognized for association with a brand.

Where do I go if I'm thinking of seeking IP protection?

Make a confidential disclosure to the McMaster Industry Liaison Office (MILO) using the online disclosure form available at http://milo.mcmaster.ca.

What if my IP isn't formally protectable?

You may find that your intellectual property doesn't meet the criteria for protection by patent, copyright, or trademark. Despite this, opportunities to protect it from use by competitors, or to generate revenue from it, may still be available.
Moving forward, ask yourself the following questions:

- Could the technology be kept as a trade secret?
- Is there opportunity to license/share it for collaborative purposes?
- Are there other viable strategies for remaining competitive?

IP OWNERSHIP AT MCMASTER, HHS AND SJHH

Whose names are associated with the IP?

Author(s)/IP Creator(s): Made a contribution to the invention involving skill and judgement. Not necessarily everyone who contributed otherwise (e.g. editing, providing ideas or the problem, changes, following protocol or instructions to carry out experiements, providing funding only).

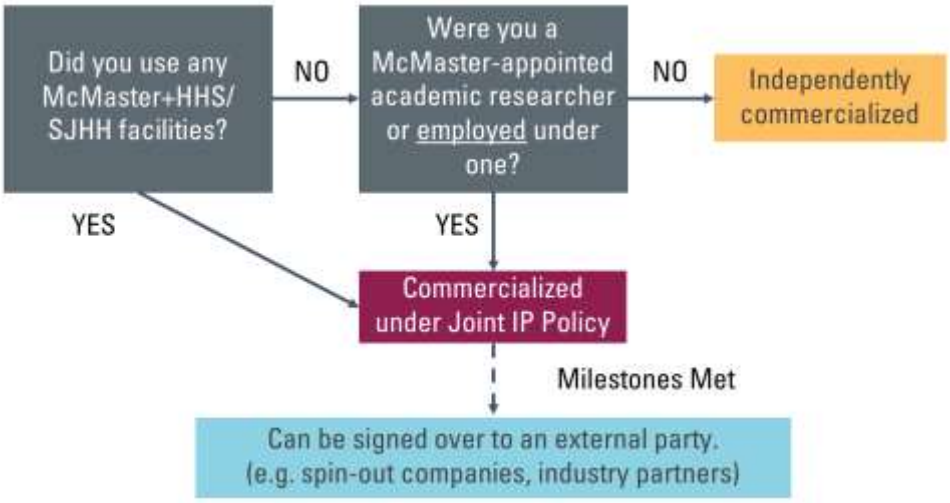
Owner/Assignee: Has the legal right to exclude others from making, using, selling, or importing the invention.

Who owns IP generated at McMaster, HHS, or SJHH?

Usually, it's the "Institutions"– the University and, if involved, SJHH and/or HHS – if McMaster carries out the commercialization.

Typically, net revenues generated from licensing agreements are shared 50/50 between the Institutions and the IP Creator(s). McMaster shares the institutional share when SJHH and/or HHS researchers are involved.

The diagram below may help delineate situations when IP is to be commercialized under the McMaster / HHS / SJHH Joint IP Policy versus independently. ***Note:*** *There are exceptions to these guidelines, such as If the Invention is created using personal time and resources, while being employed by the Institution. The Invention being signed over to an external company Indicates a licensing agreement or sale of the Invention.*



INTELLECTUAL PROPERTY: PATENTS

Patents protect ideas and inventions by providing limited-time exclusivity, which confers a competitive advantage.

- **How long?** 20 years of protection from the filing date.
- **Where do they apply?** Only in countries for which the patents are approved and granted.
- **What's the process?** Involves making claims about the invention, which undergo examination to assess validity.

Types of patents

UTILITY PATENT (Most Common)	Protects compositions and/or methods of use for an invention or its application for 20 years.
DESIGN PATENT	Protects the physical design of an object for 14 years.

Patentable subject matter

Generally Patentable	Difficult or Impossible to Patent
Composition of matter e.g. compounds, biopolymers, antibodies/hybridomas, cell lines, lower lifeforms **Methods or processes** e.g. treatments, assays, experimental steps	• Laws of nature or scientific principles • Higher life forms • Unmodified genes • Drug targets • Unmodified natural products

Criteria for patentability

The invention falls under appropriate subject matter (above) and is:

1. **NOVEL:** There is no public disclosure or prior art.
2. **NON-OBVIOUS (ORIGINAL):** What it means to be "inventive." Not a logical "next step" for an expert in the field.
3. **USEFUL:** There is a demonstrated use or need.

Public disclosure

A **public disclosure** is any publicly available written, electronic, or oral description of the invention.

Examples:

1. Published paper
2. Conference presentation
3. Verbal or written conversation

Discussion internal to the organization (i.e. within McMaster/HHS/SJHH) does not count as public disclosure! For external discussion, can freely discuss research objectives and broadly the results as long as IP details (unique aspects or "secret sauce" of the invention) are left out.

Prior art

Any form of evidence to suggest that something you're calling IP does not satisfy the originality/non-obvious requirement. Can include any form of information dissemination.

Examples of prior art:

- Publications
- Patents
- Conference presentations
- Video or sound recordings

… or any other form of public disclosure.

Phases of obtaining a patent

1 PATENT APPLICATION	US Provisional Application (lasts 1 year) • Based on early-stage claims; not examined. • Can secure an earlier priority date; doesn't contribute to protection duration (i.e. can add 1 year to typical 20-year protection). Would need to provide evidence of the invention to support a priority date. • Acts as a low-cost "placeholder". • Not published (i.e. not publicly disclosed). Does not lead to a patent unless converted into a national/PCT application before expiration. National Application Application that leads to a patent for a particular jurisdiction (e.g. Canada). Usually published after 6 months. Patent Cooperation Treaty (PCT) Application Application that can lead to multiple granted patents. Published after 6 months.
2 GRANTED PATENT	National Grant The patent itself. Valid for a particular country or jurisdiction. Expires 20 years after the national/PCT application date.

Questions to ask when determining whether to seek patent protection:

If the answer is "YES" to any of the following questions, it may be a good time to seek patent protection. (Note: This is NOT a checklist of criteria for patentability.)

- Is there enough evidence to demonstrate that the idea is valid, yet has not been "done" before?
- Is there a need or attractive opportunity to disclose it publicly?
- Is the idea almost developed enough to be able to sell or earn revenue off of it?
- Is it likely that competitors will arise?

TRADE SECRETS

When should I keep a trade secret?

If your patent application is rejected but your innovation still confers an advantage, then you may find benefit from keeping it as a trade secret. Note that applications are typically published unless you withdraw them before publication. Trade secrets are useful early in development or with protecting intangible assets like:

- Formulations
- Manufacturing processes
- Quality control/assurance
- Interactions with governing bodies
- Sales and commercial data

Deciding whether to patent or keep a trade secret

	PATENT	TRADE SECRET
Advantages	• **Stronger protection** (includes reverse-engineering)	• **Immediate** effect • No expiration • **No criteria**
Disadvantages	• Time and cost to **obtain** • **Strict criteria** • **Expires** after 20 years • Must publicly disclose invention	• Time and cost to **maintain** • Potential "reverse-engineering" • Can be leaked or coincidentally discovered • Does not legally exclude others

COPYRIGHTS

Copyright protection covers tangible art forms

"Literary, dramatic, artistic, and musical works, performances, sounds recordings and communication signals" e.g. articles, questionnaires, Standard Operating Procedures, posters, videos, music, databases, textbooks, images, software

How long?	Is registration required?	Why register?
Protection lasts for the life of the author plus additional time: 70 years in US and Canada.	Registration with an IP office is not required for protection. Copyright applies automatically once an original work comes into existence. Can register for copyright at any time.	Easy and inexpensive (only $50 in Canada), registration provides a legal form of proof of creation and is required for litigation or infringement lawsuits.

Example health innovations that may be protected by copyright:

- Clinical questionnaires
- Contents of data registries
- Digital applications/software (the underlying code)

Introduction to Regulatory Affairs

REGULATORY REQUIREMENTS: EXPLORATION TO EXECUTION

While regulatory affairs may not be encountered until later on in the commercialization journey, it is best to think and plan ahead for it during earlier phases.

The goal of regulatory agencies

To ensure safety and effectiveness of health-related products and services.

(Also includes marketing and communications of these.)

MAIN FUNCTIONS OF REGULATORY AGENCIES

- Review clinical trial applications
- Assess safety and efficacy of new products
- Grant marketing permission for new products
- Review information about the product available to health practitioners and consumers
- Ensure transparency to the public about the state of medical innovations with respect to review processes

In-Focus: Considerations for Therapeutics

COMMERCIALIZATION STRATEGIES: NEWLY DISCOVERED DRUGS

Small molecules

Chemicals of low molecular weight. Typically (but not always) organic compounds.

Natural	Extracted from a source occurring in nature.
Synthetic	Human-made 'from scratch' or derived from natural products.
Inorganic	Metals or other elements. (e.g. lithium)

Biologics & biosimilars

Biologic	Therapeutic made of or extracted from living cells (or modelled after such). Includes cell, gene, and immunotherapies.
Biosimilar	Therapeutic with bioequivalent effect of an existing biologic. Analogous to what "generics" are to "name-brand" small molecules.

'REPURPOSING' EXISTING DRUGS

There are plenty of opportunities for new pharmaceutical developments that improve functionality of existing pharmaceutically active ingredients, including:

Combination

Treatment that uses more than one therapeutic agent to treat a single condition.
Can be indicated for the same condition as the original components, or for a new condition.

Reformulation

New pharmaceutical development for an existing drug.

Group 0	Modification of active ingredient or "other" modification Change not modifying drug metabolism, or a change not fitting into another group.
Group 1	Modified release Same pharmaceutical form and route of administration, different metabolism.
Group 2	New pharmaceutical form Same or similar administration route, different drug metabolism.
Group 3	New route of administration Different pharmaceutical form, different route of administration.

Repositioning

New indication for an existing drug. Cases differ in:

Discovery Approach	Drug discovered serendipitously or chosen/designed rationally.
Therapeutic Target	Biological target the drug acts on to lead to therapeutic action.
Therapeutic Area	Degree of similarity among the indications to the original formulation.
Therapeutic Purpose	Use case for the drug (e.g. prevention versus treatment).

Therapeutics: Intellectual property

NEW & REPURPOSED SMALL MOLECULES

Beyond protecting novel small molecules and their applications, ip surrounding extensions and improvements, which fall under the realm of "repurposing," can encompass more nuances.

The following cases involving hiv drugs illustrate ip protection in different scenarios.

Case study: Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) drugs

Reverse transcriptase inhibitors for HIV/HBV:

Small molecule creation	**Retrovir®**	(azidothymidine or "AZT")
	FDA-approved for HIV (1987)	Patent US5905082, covering molecular structure and use for treating viral infections including HIV.
Reformulation (new pharmaceutical form)	**Videx EC®**	(didanosine)
	FDA-approved for HIV (1991)	Videx EC covered by patent US6224910, encompassing method of preparation for the enteric coating (EC) that gives the drug its "extended release" properties.
Reformulation (new route of administration) **Repositioning**	**Viread®**	(tenofovir disoproxil fumarate or "TDF")
	FDA-approved for HIV (2001), HBV (2008)	Tenofovir's molecular structure (US4605658) and use for treating viral infections; method of preparing tenofovir-df (US5814639) and use for treating HIV/AIDS.
Combination	**Truvada®**	(tenofovir disoproxil fumarate/emtricitabine)
	FDA-approved for HIV (2008), PrEP (2012)	Synergistic combination (non-obvious), therefore expected to reduce side effects, covered by patent US8592397.
Combination	**Atripla®**	(tenofovir disoproxil fumarate/emtricitabine/efavirenz)
	FDA-approved for HIV (2006)	Combination argued by the court to be obvious despite trying to protect via patent EP0582455.

FINDING IP INFO FOR DRUGS

US Food & Drug Administration "Orange Book" – Contains key patent information for approved drugs | https://www.accessdata.fda.gov/scripts/cder/ob/

DrugBank.ca – Like 'Wikipedia for drugs,' also containing relevant patent histories for drugs | https://www.drugbank.ca/

BIOLOGICS & BIOSIMILARS

Therapies for inflammatory disorders

Biosimilars are a relatively new area of development. They present opportunity for patent infringement against the original biologic. In response, the US Food & Drug Administration created the "patent dance" process (Biologics Price Competition and Innovation Act of 2009 (BPCIA)) which outlines how biosimilar manufacturers should communicate with biologic manufacturers to avoid patent infringement. However, engaging in the process is not actually required by law.

Case study: Biologics for inflammatory and autoimmune conditions

TNFα blockers for autoimmune and inflammatory bowel diseases:

Biologic	**Remicade®**	(infliximab) FDA-approved for inflammatory bowel & autoimmune disease. First patent (US6284471): DNA sequence and use for treating inflammatory diseases.
Biosimilar	**Inflectra®**	(infliximab-dyyb) FDA-approved for inflammatory bowel & autoimmune disease. Not patented.

Note: Today, antibodies themselves are generally not patentable due to "obviousness" of this method for blocking activity of a biological target. Patentable aspects must exhibit novelty (e.g. novel structural changes that provide a functional benefit, novel use cases/dosages/formulations, antibody combinations).

Influenza virus vaccines

The active ingredient in a vaccine typically includes a dead or weakened pathogen (e.g. virus, bacteria). Despite the use of such natural products, the chemical structures of which would not be patentable, technologies enabling vaccines can still serve as valuable IP. Looking at influenza virus vaccines presents a few examples.

Case study: IP covering different influenza virus vaccine designs and formulations

Method of production: How the biological component is isolated, made or engineered
Example: Inactivated influenza virus vaccine
Key patent: US5166097, covering the expression system used to generate vaccines against the different strains that circulate within the population during each season.

Method of reformulating the biologic: Altering its structure or properties for therapeutic benefit
Example: Live (attenuated) influenza virus vaccine for use in delivery via nasal spray
Key patent: US6022726, covering the concept of inactivating genes of influenza virus to weaken it for use in a vaccine.

Chemical structure of the biologic: Engineering it to elicit an unexpected/unnatural activity
Example: Structure of influenza viruses used in "universal" vaccines capable of protecting against all strains.
Key patent: US9371366, covering the structure of engineered influenza virus surface proteins and their application in a "universal" flu vaccine.

Therapeutics: Regulatory considerations

US Food & Drug Administration's definition of a 'drug'

A formulary/pharmacopeia-recognized substance, or any substance used for the diagnosis, prevention or treatment of a disease, or that is used to affect the structure or function of the human body.

This excludes things like food, supplements and other "natural health products".

US FDA DRUG APPROVAL PROCESS

On average, the FDA approval process takes **12 years** and costs **$1 billion**:

Types of FDA applications

IND (Investigational New Drug)	Approval to ship drugs across state borders (for use in clinical trials).
NDA (New Drug Application)	Approval to manufacture and market a **new drug** in the US.
ANDA (Abbreviated NDA)	Approval to manufacture and market a **generic drug** in the US.

Main areas of assessment within clinical trials

Area	Definition	Example (Vaccines)
SAFETY	Determines highest tolerable or optimal dose for desired clinical benefit + associated adverse effects.	Do any adverse reactions occur as a result of receiving the vaccine?
EFFICACY	Ideal case: Whether the drug has positive clinical benefit over placebo or other intervention.	Characterizing peoples' immune responses to the vaccine.
EFFECTIVENESS	"Real" case: Determines clinical benefits in the "real world" e.g. including comorbidities, other meds, lack of strict guidelines.	Observing, in the population, to what extent the vaccine has reduced infection rates.

Clinical trials can have up to five phases

Tracks to FDA approval may depend on disease area

Fast Track	For serious conditions creating an unmet medical need. May qualify for Accelerated Approval or Priority Review.
Breakthrough Therapy	For drugs providing substantial improvement over existing therapy.
Accelerated Approval	Similar to Fast Track; approval based on a surrogate marker (indirect measure of efficacy).
Priority Review	FDA's goal is to act on the application within 6 months. Many reasons may apply.

Fda market exclusivity differs from patent exclusivity

Patent Exclusivity	Exclude others from making, using, or selling. Granted by a patent office (i.e. USPTO), 20 years of protection from the application date, covers claims in the patent.
FDA-Granted Exclusivity	Exclude others from selling or applying for regulatory approval. Granted by the FDA, < 7 years of market exclusivity from the approval date, prevents others from submitting an ANDA.

Each runs independently of each other. May cover some of the same things.

KEY DIFFERENCES IN DRUG APPROVALS BY JURISDICTION

EUROPE - Similar to the FDA until the formal approval stage, in which there are 4 methods of getting approval.

I. Centralized - Approval by the European Medicines Agency joint-committee; valid across all EU states and mandatory for some categories of drugs
II. National - Authorization by a single nation's regulatory body
III. Mutual Recognition - Authorization in one member state can be used to gain approval in another
IV. Decentralized - Simultaneous application to multiple EU states; used if drug is new and not covered by I.

JAPAN - Process mirrors FDA, but infamous for approval "drug lag" due to stringent clinical requirements, causing approvals to take longer than other countries.
CANADA – Similar to the FDA.

IN-FOCUS: INVESTIGATIONAL NEW DRUG (IND) APPLICATIONS

INDs are situational applications made to the US Food and Drug Administration (FDA). They are filed when it is necessary to seek permission to transport drugs across state borders for the intent of performing clinical trials. For INDs, there are 3 pathways for submission:

Investigator IND	Standard IND application; physician submits application and oversees the following investigation. FDA may respond within 30 days with mandatory/suggested changes.
Emergency IND (EIND)	Specifically for emergency situations involving serious conditions; requested by physicians for single-patient usage.
Treatment IND	Used for promising drugs who have yet to complete trials; typically used for serious conditions where patients have had little success with other therapies.

Steps to obtain an investigator IND

Three main requirements for an IND application

Designing IND-enabling studies

IND-enabling studies often have specific targets; it may be beneficial to have a **Target Product Profile** (**TPP**).

Think of it as "beginning with the end in mind."

TPP - Strategic document created to establish a drug's labeling claims. The areas to consider are as follows:

Indications & Populations	Dosage & Administration	Safety & Efficacy
- Specific diseases - Specific populations - Market considerations	- Amount per dose - Dosing number & schedule - Dosage form & strength - Route of administration - Storage, shelf life	- Adverse reactions - Drug interactions - Contraindications

ENGAGING REGULATORY AGENCIES EARLY

Regulatory agencies have consultation meeting programs in place to help drug developers ensure they fulfill the necessary requirements for INDs (US FDA) or Clinical Trial Applications (CTAs; Health Canada).

Contact the appropriate division of each regulatory agencies using the links below:

FDA Pre-IND Consultation Program:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm

Health Canada Pre-Clinical Trial Application (CTA) Consultation Meetings:
https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/pre-clinical-trial-application.html

Health Canada's public consultations on improving the regulatory process for drugs and devices:
https://www.canada.ca/en/health-canada/programs/consultation-regulatory-review-drugs-devices.html

In-Focus: Considerations for Medical Devices

Medical Device: Instruments used in the detection or prevention of a disease or condition. Medical devices include diagnostic devices. There are three classes of devices defined by the FDA that are separated by risk.

- Class I: Tongue depressor, bandages, scalpel
- Class II: Contact lens, powered wheelchair, pregnancy test,
- Class III: Pacemaker, vagus nerve stimulator, joint replacement

Diagnostic Device: A tool that is used to detect diseases/conditions or to monitor an individual's health to help cure, treat, or prevent diseases. e.g. biopsy, home pregnancy test, blood glucose monitor

- Often includes **biosensors**: technology capable of detecting or measuring a biological molecule or substance of interest (**biomarkers**)

PATENTING A MEDICAL DEVICE

Utility Patent	Design Patent
• Protects compositions and/or methods of use for a device; can include single aspect of device, or processes associated with device software • Maintenance fees required • 20 years of protection • Contains multiple claims • Claims may exhaust the need for a design patent Examples: • Special features of a smartphone (bounce back features, multi-touch touch screen) • Cervical collar that has multi angle positioning • Automatic injector with an attenuation feature	• Protects the physical design or ornamental features of a medical device • No maintenance fees • 14 years of protection • Contains one claim for design of the device • Cheaper than a utility patent Examples: • Shape and colours used in a smartphone digital application icon • Pad design of a cervical collar • Design of body of an automatic injector

Note: As new features and designs are changed/added to a medical device, more patents can be filed to create a patent portfolio for the device. The type of patent filed is dependent upon the protection your device needs.

'Best practices' for patent filing

Product Development		Intellectual Property
Idea generation	→	Conduct a prior art search
Working on idea (potentially in early-stage prototyping)	→	File for a US Provisional Application
Finalize Device	→	File a Patent Application (National or PTC)

Other approaches to patent filing

Approach will depend on circumstance of your innovation and extent to which important details have been developed.

Patent then prototype (most protective)	Not required to create a prototype before filing for a patent application. Patent must contain enough detail to describe the function and interactions of the device.
Multiple patent approach	Can file more than one patent application. If there are changes or additional details during later prototyping, can file a second application.
Prototype then patent	Any third parties must sign NDAs so that the device to prevent public disclosure before a patent application can be filed.

Breakdown of patenting expenses

Patent Search (Optional)	Utility patent: $660, Design patent: $180 (from USPTO)
U.S. Provisional Application	$250 to file, up to $10K for using an agent
PCT Application	$10K, $4K PCT filing fee for Canada + US
Filing outside of Canada & US	Additional fees for other jurisdictions (e.g. $15K for EU, $10K for JA)
Patent Maintenance Fees	Varies per jurisdiction. e.g. US: 3.5 years - $1,600 7.5 years - $3,600 11.5 years - $7,400
Total lifetime cost	$20-30K per jurisdiction (will vary)

Note: McMaster can help pay for the expenses of developing and filing U.S. Provisional Applications, PCT Applications, and filing outside of Canada & US. Their approach will vary based on commercial viability and agreed upon milestones of your innovation.

PATENT STRATEGIES

1) **Be proactive**. Think about the specific markets your device will be entering. It is important to patent where your device will be commercialized. Published pat applications or manuscripts accepted for publication may count as prior art and can affect filing for a patent in certain jurisdictions.
2) **Make claims broad and put up a patent fence**. Think about ways competitors may design around your patent when making claims and filing patents.
3) **File as early and as often as your budget allows and your device needs**. A strong patent portfolio is important for securing investments, licensing agreements, and capturing market share.

OTHER IP STRATEGIES FOR MEDICAL DEVICES

Copyright	Trademark	Trade secret
Protection of any software, algorithms, or processes associated with a medical device.	Important for consumer facing products to protect against competitors or generic brands.	Another option for protection of algorithms or processes associated with a medical device.

Medical devices: Regulatory Considerations

CONSIDERING REGULATORY DURING PRODUCT DEVELOPMENT

Product Development		Regulatory
Idea generation	→	Search for applicable predicates
Building idea	→	Start developing QMS for compliance
Finalize idea	→	Determine market and correct classification
Final product		Pursue approval Plan for studies if necessary

OBTAINING US FDA APPROVAL

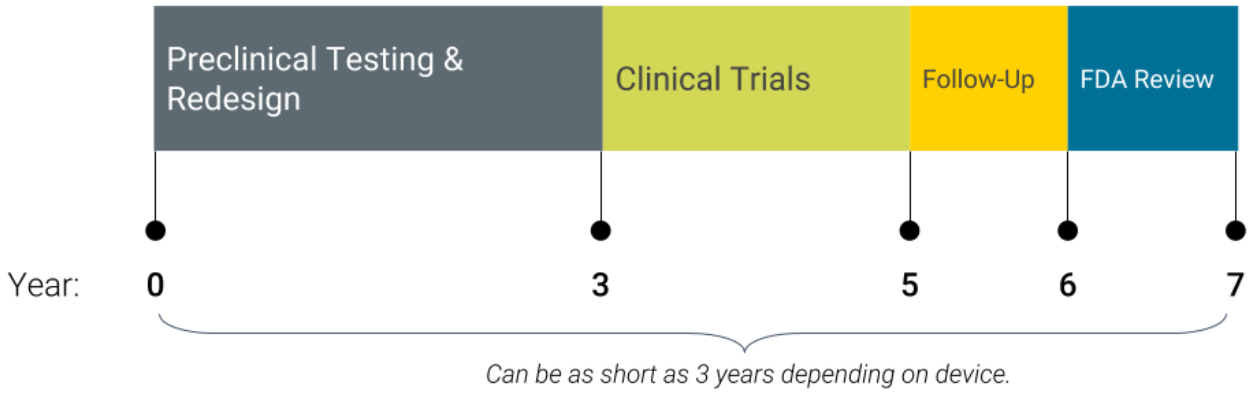
Definition of a medical deviceInstrument, apparatus, implement, machine, contrivance, implant or an in vitro reagent that is either:

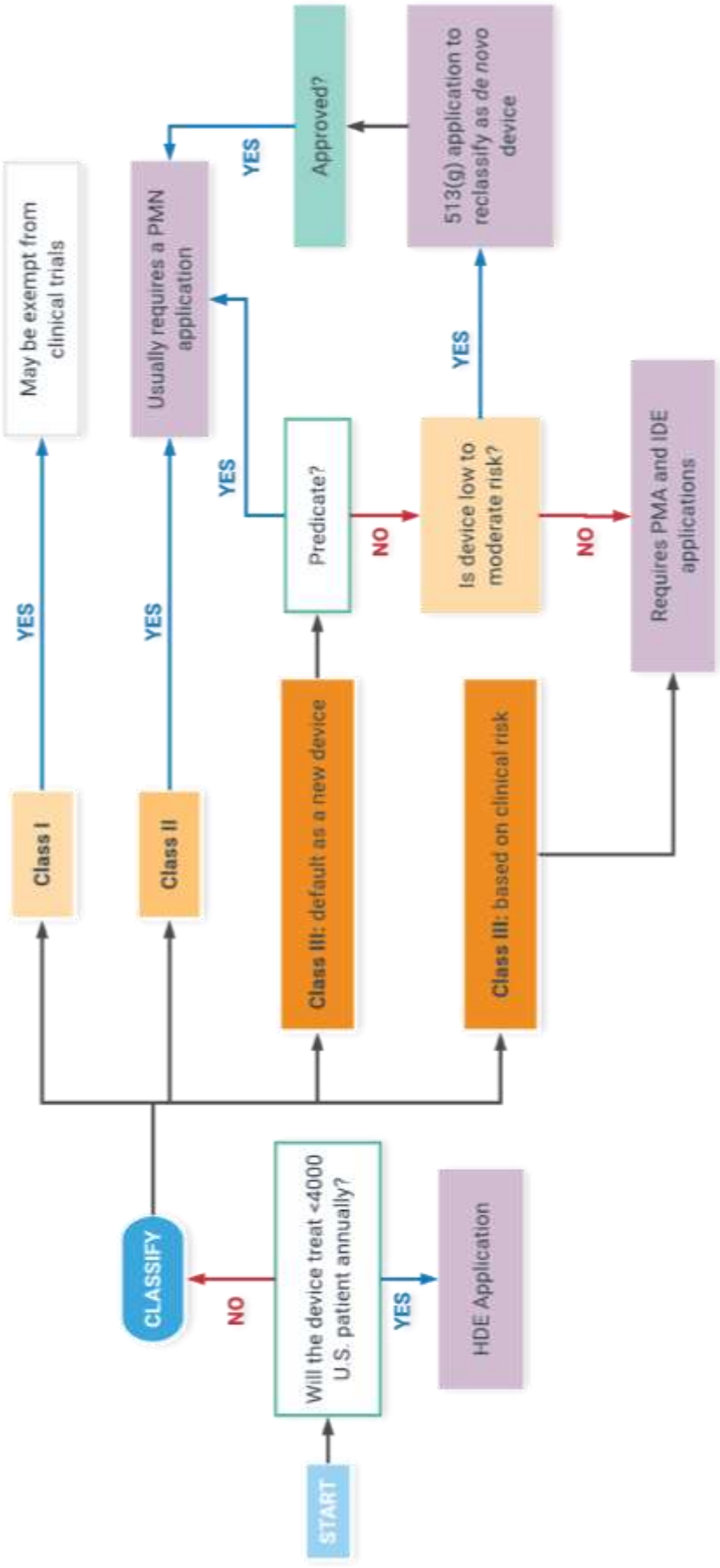
1. Is recognized in the official National Formulary or the U.S. Pharmacopeia,
2. Is intended for use in the diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease, or
3. Is intended to affect the structure or function of the body of humans

Devices must be classified based on the difficulty to prove its safety and effectiveness:

Class I	Low Risk Minimal potential harm to the user. e.g. tongue depressors
Class II	Med Risk Includes most regulated medical devices. Require meeting mandatory performance standards, post-market surveillance. e.g. sutures
Class III	High Risk Usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury. e.g. pacemakers

Overview of the approval pathway




START
Will the device treat <4000 U.S. patient annually?
NO
YES
CLASSIFY
HDE Application
Class I
Class II
Class III: default as a new device
Class III: based on clinical risk
YES
YES
Predicate?
YES
NO
Is device low to moderate risk?
NO
Requires PMA and IDE applications
May be exempt from clinical trials
Usually requires a PMN application
Approved?
513(g) application to reclassify as de novo device
YES

Summary of approval pathways

Class I → General Controls only			
General Controls: basic requirements for all devices Elements include: • Purity/unadulterated • Correct labeling & free of misbranding • Registered manufacturers/importers/distributors • Compliant manufacturing practices			
HDE	PMN / 510(k)	de novo / 513(g)	PMA
Humanitarian Device Exemption	Pre-Market Notification		Pre-Market Approval
Devices treating conditions affecting <4000 US individuals per year • Efficacy evidence not required (difficult to gather enough participants) • Safety evidence required • Can only be used by institutions with review boards to oversee use	Must show that new device is substantially equivalent to an existing, approved, and marketed device (see Predicates).	New devices are sorted to Class III by default. If device is not supported by a predicate but is actually a low-med risk (i.e. class I or II), then can submit a 513(g) application to gain de novo status. With de novo status, can apply through PMN application.	Most rigorous approval pathway. Class III devices must show sufficient evidence of safety & efficacy Will require an Investigational Device Exemption (IDE) to conduct studies with device

Predicates

Can use multiple predicates to support variety of features in new device. Can also use a reference device to support technological characteristics (not a predicate).

Same intended use as predicate	AND	Same technological characteristics OR Different technological characteristics with safety & efficacy evidence

Technological characteristics: e.g. change in materials, design, energy source, etc.

Intended use: Claims that approval is based on. Very important for regulatory compliance (i.e. cannot claim anything beyond this). Includes indications for use (IFUs). e.g. "to measure blood warfarin levels"

IFUs: Disease/condition device will affect, and a description of the patient population. New IFUs in new device may not change intended use. e.g. "to measure warfarin levels in capillary blood by an adult patient in the home"

EXAMPLES OF PREDICATE SYSTEM IN PRACTICE				
Predicate	New Device	Intended Use	Substantially equivalent	Notes
IUD for prescribed use in the home	IUD for OTC use	Same	Likely	Clinical data may be needed to show expanded patient population does not affect safety & effectiveness
Surgical device for ablating cardiac tissue	Same surgical device + treatment of atrial fibrillation through ablation of cardiac tissue	Different	NO	Predicate established safe & effective ablation of cardiac tissue. BUT, atrial fibrillation is a more complex disease, thus need extra evidence for new IFU
Mechanical device used for embryo dissection	Electrical device used for embryo dissection	Same	NO	Different technological characteristics raises new safety concerns. These were not answered by predicate, thus need new evidence

Pre-submission meetings

Can request informal feedback from the FDA prior to application submission. These are free, and completely voluntary.

Meetings help with:

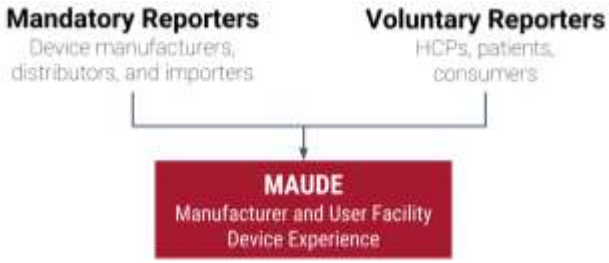
- Clarify specific questions and feedback
- determine study protocols and end-points
- familiarize FDA with new technology

Useful for:

- Do not have a clear regulatory pathway
- Utilize a novel technology
- Have IFUs which qualify them as a “first of a kind”

After FDA approval

Some devices are approved conditionally based on completion of clinical studies later. Some devices may require post-market surveillance reports.
Adverse events related to devices are publicly published on the FDA’s MAUDE database. Device manufacturers, distributors, and importers must report adverse events to MAUDE. Quality management systems (QMS) must have processes for collecting and reporting adverse events.



Evidence for safety & efficacy

Pilot Study	Small study (10-30 affected) to determine preliminary safety and performance
Pivotal Study	Small study (10-30 affected) to determine preliminary safety and performance
Post-Approval	To collect long-term data

COMPLIANCE WITH REGULATORY GUIDELINES

Not complying with regulatory guidelines can result in enforcement actions from the FDA. Examples include warning letters, fines, or criminal prosecutions.
Standards in product development, and a QMS will help comply with regulatory requirements

Standards

- Streamline product development
- Establishes universal protocols (e.g. GCPs, GMPs)
- Helps promote compatibility and speed up time to market
- Three most common for medical devices are ISO, IEEE, and ASTM standards

QMS Standards for FDA Compliance are outlined by **21 CFR 820**

QMS

- Set of processes and policies to ensure consistency in quality and safety of devices
- All device manufacturers must use a compliant QMS

GLOBAL REGULATORY CONSIDERATIONS

Comparison of US classification to Canada and the European Union

US	Canada	Relative to US	Examples
I	I	also exempt from clinical trials	toothbrush, hospital beds
II	II	Similar to a simpler PMN	contact lenses, catheters
III: predicate	III	Similar to PMN	glucose monitors, hip implants
III: clinical risk	IV	Similar to PMA	pacemakers, coronary stent

US	Canada	EU	Relative to US	Examples
I	I	I	also exempt from clinical trials	gauze, gloves
II	II	IIa, IIb, III	Predicate - no clinical evidence needed	IIa: surgical blades IIb: radiotherapy equipment
III: predicate	III			
III: clinical risk	IV	IIa, IIb, III	Like PMA - need clinical evidence	III: pacemakers, implantable defibrillators

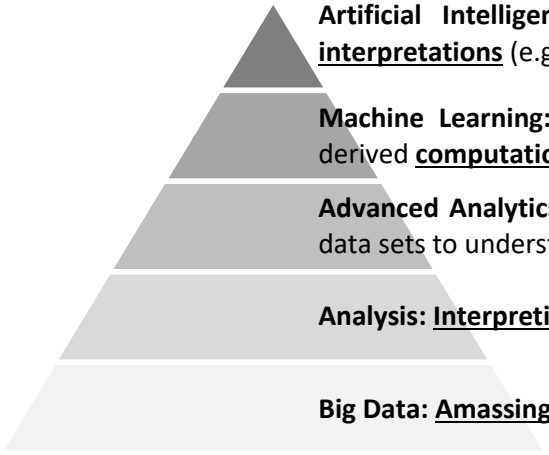
QMS Standards by Market

	US	21 CFR 820
	European Union	ISO 13485:2016 Almost analogous to US
	Canada	ISO 13485:2016 & CMDCAS Canadian Medical Devices Conformity Assessment System

In-Focus: Considerations for Data Sciences

Data Sciences in Health Innovation: Solutions that enable the acquisition, storage and interpretation of data for a health-oriented or scientific purpose. Within the MGDII Health Innovation Categories, **Data Sciences** is defined as those innovations that focus on leveraging advanced analytics and algorithms for data interpretation. Note: Based on complexity in processing (e.g. for insight derivation) and sensitivity of information acquired, different intellectual property and regulatory considerations will be required.

HIERARCHY OF DATA SCIENCE CAPABILITIES



Artificial Intelligence: Querying data sets with continuously developing machine-derived **interpretations** (e.g. IBM Watson)

Machine Learning: Answering relevant questions through continuously developing machine-derived **computations** (e.g. Multi-factorial algorithm as hospital re-admission model)

Advanced Analytics: Answering relevant questions through **higher-order analytics** (e.g. Linking data sets to understand social determinants contributing to patient health outcomes)

Analysis: Interpreting data (e.g. forecasting trends based on patient data set)

Big Data: Amassing large amounts of information (e.g. registry data set)

GENERAL INTELLECTUAL PROPERTY FOR DATA SCIENCE CAPABILITIES

Big Data	Analysis	Advanced Analytics	Machine Learning	Artifical Intelligence
Copyright Trade Secret	Trade Secret	Copyright Trade Secret Patent	Copyright Trade Secret Patent	Copyright Trade Secret Patent

IP & REGULATORY CONSIDERATIONS OF DATA REGISTRIES

Data Registry: A mechanism for data collection and assembly, to answer specific research question(s). They can be used for patient management, longitudinal studies, analyses of outcomes for specific patient groups, etc.

Public registry	Private registry
Designed for use by the general public or a certain sub-population. Accessible to anyone (through website, app, software).	Designed for restricted use and/or storage of confidential information. Typically involves barriers to accessing information (e.g. security requirements, pay wall or need to request access).
Internally generated information	**Externally generated information**
Information generated by an organization to collate for the registry. May be compiled using existing research or clinical practice.	Information generated outside of registry to be used as part of information source. This external information may be subject to copyright.

Types of Data Registries

Patient – Clinical	**Input:** Clinical patient information and measures, patient outcomes and distribution of outcomes among a specific population.
	Output: Information that is used to directly influence a clinical setting.
Patient – Biologics	**Input**: Partially characterized (e.g. demographic info) patient samples.
	Output: Information that is used to directly influence a clinical setting or for research purposes.
Population Health	**Input:** Aggregate health information of a specific disease population.
	Output: Information used for research purposes.
Non-human	**Input:** Collection of information that does not pertain to patients but maps, characterizes, or standardizes relationships and interactions that serve a healhcare purpose.
	Output: Information that is used for direct research purposes.

Intellectual Property	Compilation of data is under copright. IP requirements may be different for any algorithms involved. No IP can be filed for patient information or any information that you did not produce.
Regulatory Considerations	Patient privacy standards: • Ontario Personal Health Information Protection Act (PHIPA) • Personal Information Protection and Electronic Documents Act (PIPEDA): Use of personal information for commercial business. User/buyer considerations: • Additional privacy, information security, information storage, compatabilitiy (interoperability) • OBO Foundry principles for ontology development

IP & REGULATORY CONSIDERATIONS FOR SOFTWARE AS A MEDICAL DEVICE

Software as a Medical Device (SaMD): Software intended to be used for a medical purpose, that performs said purpose without being part of a hardware medical device (e.g. SaMD that analyzes heart rate data intended for a clinician to aid in diagnosis of arrhythmia). Can be used in combination with other medical devices, and can include mobile apps.

Intellectual Property	Associated with the data science capability used. Could be patented.
Regulatory Considerations	Similar to the innovation development process (need clinical evaluation): • **Problem Validation, Analytical Validation, Clinical Validation** May depend on class of SaMD: Class I, II, III, or IV. Independent reviews may be necessary for higher impact SaMDs (i.e. Class III and Class IV).

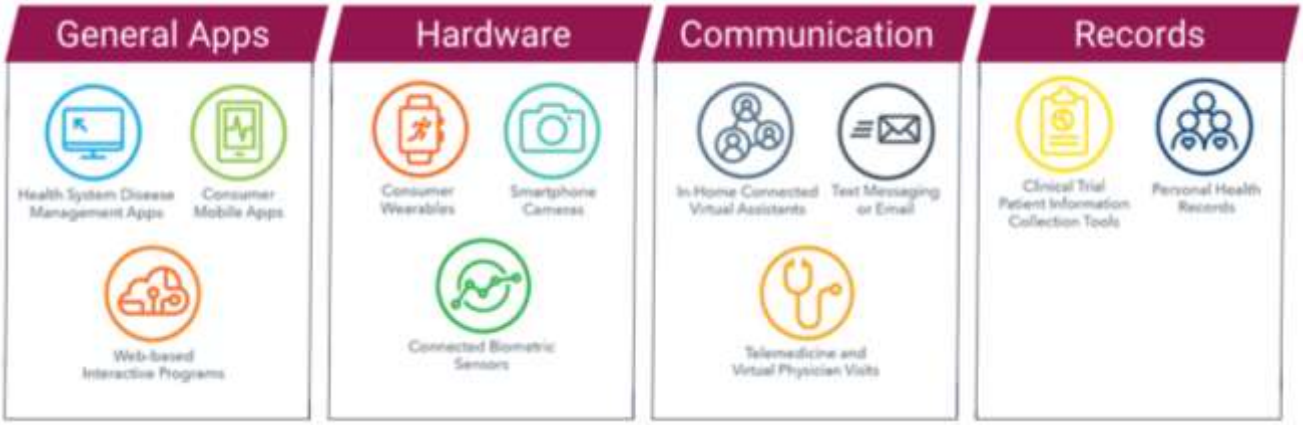
Problem Validation	Verify that the association between SaMD output and targeted clinical condition is supported using new or existing evidence.
Analytical Validation	Generate evidence that the output of your SaMD is as expected. Could be during verification and validation studies, curated databases, or collected patient data
Clinical Validation	Generate evidence that shown users can achieve clinically meaningful outcomes through predictable and reliable use. • Measurements of sensistivity, specificity, positive/negative predictive value, number needed to treat/harm, clinical usability/user interface, confidence intervals.

In-Focus: Considerations for Digital Apps

Digital Applications in Health Innovation

- A user-oriented health product or service, in the form of software and/or hardware

eHealth: The cost-effective use of information/communication technologies in support of healthcare, health surveillance, health education, knowledge and research.
mHealth: Health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices.



Innovations lay within gathering and simplifying data for an intended purpose. They are **all end-user focused**.

GENERAL INTELLECTUAL PROPERTY FOR DIGITAL APPLICATIONS

Digital Application	IP	Explanation
Mobile Apps/Website	Copyright	Protects the software coding/algorithms
	Trademark	Protects the company's logo and any affiliated design/artwork
Hardware (i.e. wearable technology)	Utility Patent	Protects the intended use or function ● Possibility for new devices if it has a unique feature
	Design Patent	Protects the physical design of the wearable
	Copyright	Protects the software coding/algorithm
	Trademark	Protects the company's logo and any affiliated design/artwork

Note: In the U.S., algorithms are not patentable. However, an individual can patent the use of an algorithm to achieve a specific outcome.

PRIVACY ACTS IMPLEMENTED TO PROTECT USER DATA

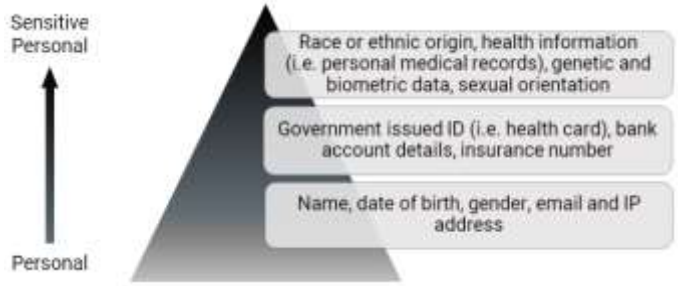
User Privacy Data: Privacy legislation seeks to protect users by requiring consent for the collection, use, disclosure or retention of personal information including sensitive health information.

In Ontario,

Personal Health Information Protection Act (PHIPA)
Describes rules for the collection, use, and disclosure of personal health information
Balances users' rights to privacy with the needs of healthcare organizations accessing and sharing this information

In United States,

Health Insurance Portability and Accountability Act (HIPAA)
Applies to any app or device that stores or transmits protected health information and generated by or on behalf of a covered entity like a physician, hospital, or health plan.
Mandates industry-wide standards for healthcare information



Adherence to the privacy acts is dependent on the data collected from users.

REGULATORY CONSIDERATIONS OF DIGITAL APPLICATIONS

Regulations are important for standardizing digital health approvals, promoting general public interest, and protecting developers from legal complications.

How is information regulated?

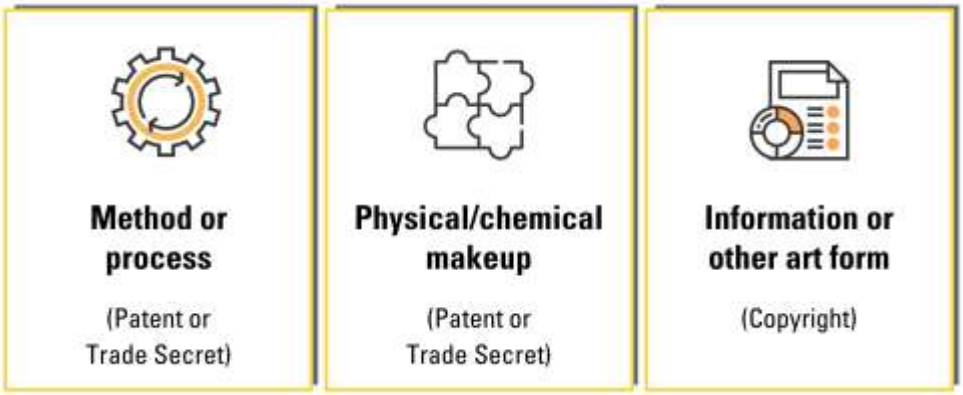
CANADA (Canada Health Infoway)	**CSA Model for Protection of Information**: Focused on protecting personal health information in the context of digital health solutions. **Digital Health Review:** Earlier this year Canada created a division which will support emerging technology. Goals: improving access to therapeutic products and alignment with stakeholders and regulatory bodies, responding to fast innovation cycles
U.S. (Federal Trade Commission)	**FTC Best Practices**: Set of recommendations for health application developers. **FDA: Digital Health Innovation Action Plan** 1. Revising the 21st Century Cure Act to meet the modern needs of consumers 2. Adopting a pre-certification program for products to reduce the time and cost of market entry for reliable software developers Hiring field experts in digital application software development

The **future of regulatory affairs** for digital application focuses on improving access for consumers, reducing costs, and improving privacy & security.

In-Focus: Considerations for Research Tools

Research Tools: Encompasses reagents, animal models, methods, or other tools used to conduct research.

COMMON IP-PROTECTABLE ASPECTS OF RESEARCH TOOLS



EXAMPLES OF PATENTED RESEARCH TOOLS

The tools listed below may have more than one patent encompassing extensions or other aspects of the technology. Numbers provided with each technology are from what is deemed to be the "key patent."

US4965188: Polymerase chain reaction (PCR)

Molecular biology technique used to rapidly create many copies of a template DNA sequence. Has many extensions and applications in research and diagnostics. US4965188 covers the **general process** involved in PCR.

US4889818: *Taq* polymerase for use in PCR

A modified bacterial enzyme that serves as a critical component for many PCR applications. US4889818 covers the enzyme's **structure** and **unique characteristics**.

US4959317: Cre-Lox recombination

A method for editing genes in a particular organ or tissue type rather than throughout a whole organism. Usually employed in mouse models for research purposes. US4959317 covers the **underlying method**.

US8697359: CRISPR-Cas systems

A toolkit that can be used to edit (add, remove, modify) genetic information (i.e. DNA sequences). US8697359 covers **composition** of key components of the toolkit, along with **methods of use**.

US4736866: OncoMouse

A transgenic mouse carrying an activated cancer gene. Often used to study cancer in mice, as these animals readily contract the disease. US4736866 covers the **concept** of creating one such animal.

Experimental use exception to infringement

In the US and Canada, it is not considered patent infringement to make or use a patented invention for certain research purposes.

Example: Comparing a new technology to an existing patented standard to evaluate how well it works.

Research tools subject to copyright

Data Interpretation Tools
Clinical assessment **surveys** (e.g. Inflammatory Bowel Disease Questionnaire).

Software (e.g. **underlying code** of data analysis packages).

Information
Could be **contents** of a database (e.g. the Comprehensive Antibiotic Resistance Database, which contains genetic information pertaining to antibiotic resistance mechanisms).

Information Architecture
Underlying configuration governing how information is stored, organized, and accessed (e.g. database software).

Copyright would typically cover the **underlying code**.

In-Focus: Considerations for Health Systems

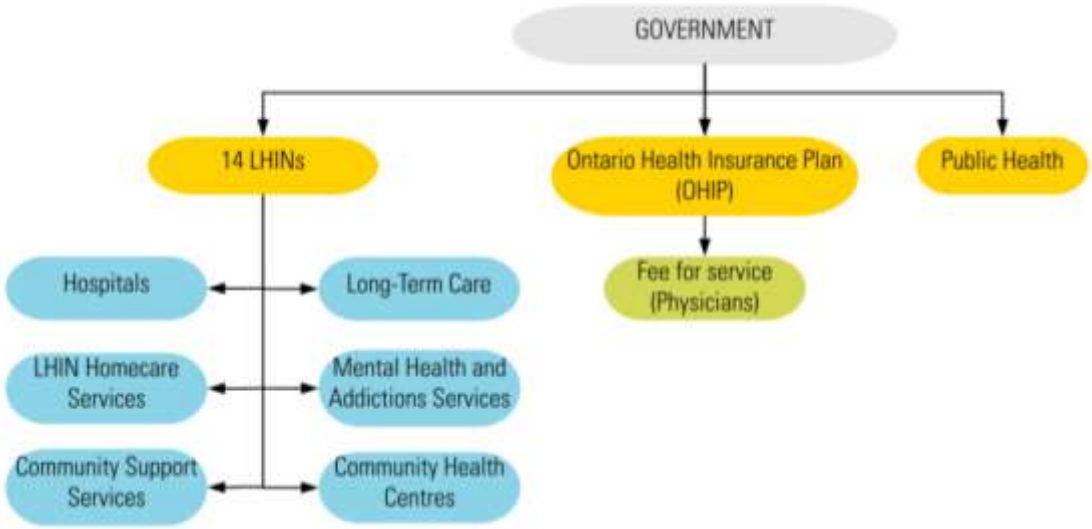
Health system innovation: A solution that augments the delivery of healthcare (i.e. faster, better quality, lower cost, ease of use).

Does not include tangible discoveries like a medical device or digital application. Can include things like policy, system programs, and services.

TYPES OF HEALTH SYSTEM INNOVATIONS

Public Policy	A guide for executing government or regulatory body's actions to achieve specific objectives; usually alters the way healthcare operations are funded, facilitated, or regulated within all applicable facilities across a geographical area. Example: Local Health Integration Network (LHIN) Act
Services (Products)	**For Provider/Facility:** Augments workflow or capacity. Example: Security risk assessment software (*Alexio*)
	For Consumer: Augments the experience of care. Example: Collecting patient health records (*MedChart*)
Program	Initiative targeting perceived gap in the care system through integration. Example: Integrated Comprehensive Care program at St. Joseph's Healthcare Hamilton

ONTARIO'S HEALTHCARE STRUCTURE (JULY 2018)



Policy: Top-down process – Works at government level to affect lower structures.

Service: Can integrate at any stage to augment healthcare.

Program: Bottom-up process – Implemented into lower structures to augment existing

Ontario hospital funding breakdown

Patient-Based Funding (PBF): Healthcare funding based on patient-needs and historial use of facilities. Comprises 70% of hospital funding. PBF is allocated based on type of case, estimated number of cases, and funding per case.
Challenge: Failure to meet number of estimated cases could result in loss of funding. Surplus of cases paid through global funding.
Global Funding: Base funding which generally supports hospital operations and staffing. Comprises 30% of hospital funding.
Challenge: May need to use funds to pay for gaps in PBF.

INTELLECTUAL PROPERTY FOR HEALTH SYSTEM INNOVATIONS

Public Policy	Services	Program
Public policies are typically not protected.	Copyright: Software Utility Patent: Format of delivery or process Trade Secret: Software or Algorithm	Utility Patent: Overall idea and methods of implementation of program Copyright: Literary or forms of art pertaining to program Trademark: Identifiable aspects of the program.

REGULATORY FRAMEWORK FOR HEALTH SYSTEM INNOVATIONS

1. Begin with the identification of how the innovation will be delivered within healthcare.
2. The innovation governs the legal considerations that must be followed.
3. The needs of the user/buyer of the innovation will dictate other regulatory considerations.

Start	Legal	User
Policy Service Program	Freedom of Information and Protection of Privacy Act (FIPPA) Personal Health Information Protection Act (PHIPA) Personal Information Protection and Electronic Documents Act (PIPEDA) Accessibility for Ontarians Disabilities Act (AODA)	Additional Privacy Concerns Information Security Information Storage Interoperability among Health Systems

Regulatory considerations for programs

Approval pathway and implementation techniques will differ based on where the program is introduced.

Implemented in:	Example:	Approval pathway:
Hospital	Integrated Comprehensive Care program at St. Joseph's Health System.	Buy-in across hospital and homecare stakeholders.
Multiple locations within a region	PHAST program in Burlington	Buy-in from hospital, and multiple organizations across city. Funding approval from LHIN.
Multiple locations across a region	INSPIRED program across provinces.	Proof of concept at original site. Buy-in from multiple sites. Funding support from national organization (CFHI).