ICMRA Innovation Project 3D Bio-Printing Case Study: Summary of Discussions and Considerations for the New Informal Innovation Network[1]

EXECUTIVE SUMMARY

The International Coalition of Medicines Regulatory Authorities (ICMRA) Innovation Project identified 3D printing, artificial intelligence and gene editing as emerging disruptive technologies that challenge traditional health product regulatory systems. In an attempt to identify novel regulatory approaches to license health products manufactured or developed through these technologies, the Innovation Project team launched a case study on 3D bio-printing. Health Canada led these discussions with the following ICMRA members participating: the Therapeutic Goods Administration (TGA) of Australia; the Agência Nacional de Vigilância Sanitária (ANVISA) of Brazil; the European Medicines Agency (EMA) of the European Union; the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency (MHLW/PMDA) of Japan; and the Health Sciences Authority (HSA) of Singapore.

From a public health, biotechnology and tissue engineering perspective, engineered therapies for musculoskeletal and vascular applications are advancing to address patient treatment demands. A **hypothetical** 3D bio-printed human knee meniscus was chosen for this case study, based on the current developments seen in the field and in the literature. The goals of the case study were to better understand key challenges for regulating this product, identify emerging regulatory solutions, and suggest areas for further scientific and policy discussions.

There are many components of 3D bio-printing that could require regulatory oversight. These may include the printer itself, software, production processes, living and non-living printing material, and the deployment of the technology. 3D bio-printing technology challenges regulators with respect to classification of the output, and regulating different models of manufacturing (centralized model versus point-of-care production).

For this 3D bio-printing case study, agencies suggested that standards could be used to support regulatory processes. Standards would be especially important for the point-of-care production model of 3D bio-printing, although it was acknowledged that they have thus far been established only for centralized production settings. There would be a need to review standards to address specific aspects pertaining to the point-of-care production model.

[1] **Disclaimer:** ***This report reflects the outcome of an exercise based on a hypothetical product, and none of the content of the report should be taken as the regulatory thinking or position of any of the ICMRA members.***

Agencies called for risk-based oversight that combines regulatory requirements that are “fit for purpose”, so that quality evidence can be generated to support short-term and long-term product safety and efficacy. Other suggestions by agencies included fostering regulator capacity building to fill the knowledge gaps, engaging with other regulatory authorities and stakeholders to mitigate uncertainties, and clarifying the roles and responsibilities of regulators vis-à-vis stakeholders.

Throughout the discussions, agencies suggested regulatory approaches that were highly convergent. Agencies agreed to the importance of product risk management plans and maintaining product registries for traceability. Three out of the six agencies reported that they were developing new regulatory frameworks (i.e., ANVISA and HSA) or implementing new legislation (i.e., Health Canada) aimed at facilitating innovative product development. 3D bio-printed products would be addressed in these new frameworks/legislation.

The agencies concluded that certain new approaches and challenges that would require further discussion among regulators could continue as part of the newly established ICMRA informal Innovation Network.

1. BACKGROUND

In 2017, the International Coalition of Medicines Regulatory Authorities (ICMRA) launched the Innovation Project as a strategic priority. This project is devoted to exploring how regulators across the globe can better identify and prepare for emerging and disruptive technologies, and facilitate access to innovative health products. Through this project, ICMRA members identified three focus areas of advanced technologies: additive manufacturing (3D printing), gene editing and artificial intelligence. ICMRA recently published a report and a public statement from this work. As a final step of the ICMRA Innovation Project Work Stream 3 on Novel Approaches to Licensing, Health Canada led a case study on 3D bio-printing for an in-depth discussion concerning novel licensing approaches to address regulatory challenges associated with this emerging advanced technology.

2. WHAT IS 3D BIO-PRINTING

3D printing is the creation of an object by successively layering raw materials, such as biopolymer and biodegradable nonliving materials. 3D bio-printing uses 3D printing-like technology to combine biological materials, growth factors, and often living cells, to fabricate tissue-like structures (See **Box 1** for an example). 3D bio-printing is also used to combine nonliving and biological materials. The process is highly dependent on software, printing techniques, and an apparatus that requires continuous updating. Current health applications vary and can include implants, prosthetics, surgical tools and guides, anatomical models, and bio-printed tissues and organs for transplantation, pre-clinical testing, and personalized medicine development. This technology opens new doors in the design of tissue by allowing multiple different cell types to be precisely located and combined seamlessly during printing. 3D bio-printing allows for tremendous product customization and enables distributed models of manufacturing and production, including manufacturing at the point-of-care (e.g., hospitals, private clinics).

3. WHY ARE WE STUDYING 3D BIO-PRINTING

From discussions through the ICMRA Innovation Project, 3D bio-printing has emerged as a particularly disruptive technology for clinical care and the health product regulatory systems. There are many aspects of 3D bio-printing (technology development, production process, living and non-living printing material, deployment, etc.) that are potential areas for regulatory oversight. This technology challenges standard product

Box 1

Future is Here - 3D Bio-Printed Human Heart

On April 15, 2019, findings of a successfully printed human heart were published in Advanced Science, a peer reviewed and open access journal. The researchers reported that the printed thick, vascularized, and perfusable cardiac patches, and the heart, "completely match the immunological, cellular, biochemical, and anatomical properties of the patient".

The study concluded that "the cellularized hearts with a natural architecture were engineered, demonstrating the potential of the approach for organ replacement after failure, or for drug screening in an appropriate anatomical structure".

classification, as well as usual models for regulation of manufacturing.

As innovations are fast-paced, it is important to engage scientific, regulatory, and policy experts to consider the regulators' approach to the regulation of this technology and contribute to international regulatory oversight discussions. By obtaining a better understanding of the key challenges and identifying areas for further scientific and policy investigation, the regulators will be better positioned to adapt and prepare the regulatory systems for this imminent disruption.

4. CASE-STUDY METHODS

A case study of 3D bio-printed products was developed for discussion among regulators. Each regulator was asked to choose one of two hypothetical (but realistic) 3D bio-printed products, i.e., the human knee meniscus or heart patches (See **Annex B**).

The case study was conducted by six regulators, including the Therapeutic Goods Administration (TGA) of Australia, the Agência Nacional de Vigilância Sanitária (ANVISA) of Brazil, Health Canada of Canada, the European Medicines Agency (EMA) of the European Union, the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency (MHLW/PMDA) of Japan, and the Health Sciences Authority (HSA) of Singapore. Each agency held internal discussions with experts from relevant areas and filled out a survey (see **Annex C**) to summarize the essential regulatory considerations revealed from these internal discussions. Subsequently, a follow-up teleconference among the regulators was held. EMA and HSA presented a summary of the discussions from their respective agencies. Health Canada presented on its latest legislation for implementing a "regulatory sandbox" as a novel approach to licensing, and MHRA (the United Kingdom) presented on regulatory models for point-of-care manufacturing. The following summary is based on the survey responses and presentations mentioned above.

5. SUMMARY OF DISCUSSIONS

With the ICMRA's strategic mandate in mind, the following sections focus on a high level summary of regulating the life cycle of a hypothetical 3D bio-printed product. The regulators' challenges and suggestions on their regulatory approach were synthesized and potential topics for ongoing discussions in the informal ICMRA Innovation Network were described.

All six participating agencies chose the hypothetical 3D bio-printed meniscus to stimulate their internal discussions. The discussions covered all the regulatory stages around the product life cycle, including classification, early advice, clinical trial, pre-market assessment, and post-approval monitoring.

Three out of the six agencies reported to be developing or advancing new regulatory frameworks or legislation aimed at facilitating agile product development. There was a relatively high degree of convergence of the suggested regulatory approaches for a centralized

production model. It was evident that agencies were exploring the necessary regulatory methods for a point-of-care production model, especially for the pre-market assessment stage.

One common theme of the discussions was the adoption and update of the established standards to ensure the printed product would be consistent, effective, safe, and of good quality. These standards would include Good Manufacturing Practice (GMP), International Council for Harmonisation (ICH) standards, and applicable International Organization for Standardization (ISO) standards such as a Quality Management System (QMS). The standards would be especially important for the point-of-care production context. However, it was acknowledged that these standards were mostly established for centralized production settings. Further discussions among regulators would be necessary to identify how to regulate point-of-care manufacturing effectively.

Other common themes included the need to fill the knowledge gap among the regulators, such as through training or hiring the necessary expertise, and the importance of educating and communicating with stakeholders, including patients and new stakeholders unfamiliar with the regulatory process. These would be critical for managing the uncertainties associated with the meniscus. On a related note, production of the meniscus would touch a zone where manufacturing and the practice of medicine overlap, it would thus be necessary to hold conversations among the involved parties to clarify the roles and responsibilities.

5.1 Product Classification

The agencies consider product classification as the first step to commence product navigation through regulatory systems. All agencies provided their proposed classification of the meniscus and their rationale. The production model, i.e., central or at point-of-care, impacted product classification. See **Table 1** in **Annex A**.

5.1.1 Centralized Production Classification

For a centralized production model, five agencies would categorize the product as an advanced therapy medicinal product (ATMP), a regenerative medical product, a biologic, or as a “cell, tissue and gene therapy”, as the primary mode of action of the product would be taken by the cells. These agencies also acknowledged that regulatory requirements for medical devices would need to be taken into consideration when regulating the meniscus. Health Canada would classify the product under its recently ratified “regulatory sandbox” to tailor the most appropriate requirements from different regulatory frameworks that would be fit for purpose.

5.1.2 Point-of-Care Production Classification

For a point-of-care production model, the end product would be theoretically no different from those produced in central sites, as such, four agencies would classify the meniscus the same as those manufactured centrally.

For EMA, should the product be for non-routine manufacture and treatment of individual patients within a hospital setting, the EU medicinal product legislation would consider it either as a "hospital exemption" (ATMP legislation) or a "magistral preparation for individual patients" in one hospital, in which case the EU medicinal products legislation would not apply.

For PMDA, the end product (the meniscus), which would not be marketed or distributed like through centralized production, would be subject to the *Act on Securing Safety of Regenerative Therapies* that regulates the procedures for physicians to use regenerative therapies. This Act is administered by MHLW instead of PMDA. The appropriateness of procedures would be secured by the review process by the designated bodies and by the Minister of MHLW depending on the risk of therapies. There would be no "market authorization" requirements for the meniscus produced at the point-of-care under the *Pharmaceutical and Medical Devices Act*.

5.1.3 Ongoing Discussions

The classification for the meniscus produced centrally and at the point-of-care seemed to have a high degree of convergence among the agencies. While unique regulatory circumstances exist in each jurisdiction for the point-of-care production, the agencies would agree that the primary mode of action of the product would be taken mainly by the cells and that requirements for medical devices would need to be considered.

ANVISA and HSA are currently developing new regulatory frameworks and Health Canada is advancing a legislation that would enable their proposed classification of, and oversight for, the meniscus. Further discussions among the agencies on best practices and learned experiences could be carried forward as the new regulatory frameworks and policies evolve.

5.2 Early Advice

Generating safety, efficacy and quality evidence is critical during the drug and medical devices development process. The agencies would be willing to hold early discussions with sponsors during pre-clinical or non-clinical stages to facilitate agile product development.

The agencies suggested that early advice should allow for adaptation of the evidence to be generated, longer-term considerations be included, and processes be adjusted appropriately. Equally important, the agencies also acknowledged the potential knowledge gaps (e.g., the 3D printing technologies and their application, business model of the point-of-care production to inform quality control requirements, quality control technologies at each step of the production process, etc.) within their organizations. Early advice would allow regulatory experts to be prepared for the upcoming novel products and technology.

Some agencies have formal procedures, committees or functions to facilitate early scientific and regulatory advice. Others have the flexibility to schedule pre-submission-like meetings with the sponsors, and work with health technology assessment (HTAs) agencies to provide joint

early advice. The agencies would provide early advice to sponsors regardless of whether the product is aimed at the centralized or point-of-care production model.

5.2.1 Ongoing Discussions

It was acknowledged by the agencies that novel products would likely be complex and would require the involvement of multidisciplinary experts, internally and externally. EMA has the Innovation Taskforce and Scientific Advice Working Party, PMDA has the Science Board, HSA has the Innovation Office, and other agencies would be leveraging review committees and regulatory initiatives to support early advice. These mechanisms would connect a broad range of areas of expertise, including but not limited to biologics, biotechnology, biomedicine, software, 3D printer, medical devices, Real World Evidence (RWE), GMP and other relevant subject matter. Future discussions may look into collaborations, strategies and procedures that would allow agencies to develop, identify, and involve multidisciplinary scientific expertise in an effective and efficient manner.

5.3 Clinical Trials

In general, agencies would apply the clinical trial provisions as per the identified classification of the meniscus (see **Table 1** of **Annex A**), for both centralized and point-of-care productions. These requirements would address the study design, risk mitigation, quality control, and incidence reporting. Ideally, the evidence collected through randomized controlled trials in a sizable population should be used to determine if the benefit of a product outweighs the risks. Since the meniscus would be produced with individual patient cells and measurements, traditional trial designs in a large population may not be possible. Novel trial designs using smaller populations and the use of RWE may be considered.

In the EU, EMA is not responsible for the authorization of clinical trials, as it falls under the member states' jurisdiction. There is a need for knowledge transfer between member states and EMA to ensure convergence in early advice and clinical trials, and throughout the product life cycle.

For the point-of-care production, Japan's MHLW would require efficacy and safety data of the therapy for review by a committee as per the *Act on Securing Safety of Regenerative Therapies* and then a review by the Minister of MHLW would be assigned depending on the risk of the therapy. The ethical guidance on clinical research would be applied.

5.3.3 Ongoing Discussions

Clinical trials are a critical component of quality by design for evidence generation, where efficacy and safety data is expected to inform regulatory decisions. For complex products such as the meniscus and many others enabled by advanced technologies, novel trials and methods that aim at establishing long-term product safety have been and will continue to be increasingly important in the regulatory process, especially for managing the uncertainties associated with these products. Building on the cumulative learnings to date, the regulatory community would

benefit from continued collaboration and exchanges pertaining to clinical trial design, endpoints, and methodologies. These discussions could be carried forward by international bodies that develop and maintain technical standards for regulating medicines and devices.

5.4 Pre-Market Assessments

The meniscus would involve many components that would be subject to regulatory oversight during its complex production process, including patient stem cell, hydrogel/polymer for printing, 3D printer, software, and the printed meniscus. The agencies showed a high degree of agreement on how the different components of a centrally produced meniscus could be regulated. Some unsolved challenges for regulating the meniscus produced at the point-of-care were also raised.

5.4.1 Pre-Market Assessment for Centralized Production Model

All agencies were in agreement that patient cell handling should be subject to the established cell processing standards. HSA suggested that for centralized production, the transportation of patient cell transfer from the collection site to the centralized manufacturing site, and from the central site to different health establishments should comply with Good Distribution Practice standards. Some agencies would require that the material for the scaffold, e.g., polymer or hydrogel, be of medical grade.

Five agencies would consider the 3D printer manufacturing equipment. EMA would require a mandatory European certification for any device (CE mark), including for ATMP manufacturing by the 3D printer, but the main criterion would be the quality of the product. All agencies would consider software a part of computer-assisted steps in manufacturing. Qualified operator of 3D printer and site requirements should be subject to certain GMP standards.

The end product meniscus could be subject to novel regulatory review pathways that vary from agency to agency, e.g., Advanced Therapeutic Products Pathway of Health Canada or Conditional and Time-Limited Approval of PMDA, based on the specific qualifying criteria. See **Table 2** of **Annex A** for more details.

It was acknowledged that the product has a high level of uncertainty and that the long-term efficacy and safety data may not be readily available at the pre-market stage. As such, some agencies suggested that considerations should be given to measures that would allow for relevant data to be submitted to the regulators on a “rolling” or stepwise basis. Some agencies cautioned that the novel product may not reach the traditional market authorization stage due to the lack of long-term data in sizable populations.

EMA raised challenges specific to EU where legal frameworks for medicines and devices are administered by different entities. Regulating the meniscus under these unique circumstances would require fully developed coordination procedures between the regulatory entities, and clarified classification of the product to determine roles and responsibilities.

5.4.2 Pre-Market Assessment for Point-of-Care Production Model

Five agencies indicated that both the end product and key components of the production process would require risk-based regulatory oversight. It was suggested that the considerations for pre-market assessments for centralized production would be applicable for point-of-care, especially on the use of standards. Some agencies suggested that the pre-market assessments should consider "licensing" the production process for the end product, rather than granting "market authorization" to a product.

There are some emerging practices of risk-based regulatory oversight for the point-of-care production. For example, the risk classification under Japan's *Act on Securing Safety of Regenerative Therapies* specifies Class I, II and III (high, middle and low risk) regenerative medical technologies as per the different human cells and techniques used in the treatment. The higher the risk, the more specialized oversight would be in place. Under this Act, Class III (low risk) regenerative technology treatment plans would be reviewed by a certified committee, whereas Class I (high risk) regenerative technology treatment plans would be reviewed by a certified **special** committee **and** the Health Science Council.

Other risk-based practices, while not exclusively developed for the point-of-care production, also exist and may inform the risk-based oversight. For example, the *EUROGTP II Guide on Good Practices for Evaluating Quality, Safety and Efficacy of Novel Tissue and Cellular Therapies and Products* outlines the assessment of the novelty and level of risks of these therapies at the onset of the regulatory process, and the oversight would be informed by a "risk score" of the therapy. Health Canada is developing Canada's Advanced Therapeutic Products Pathway. As part of operationalizing the new pathway, various steps in the process are being designed where different types of risks may be taken into consideration.

The agencies suggested that a comparability study among the decentralized sites would be necessary should the product benefit from a single umbrella licence. These studies would help demonstrate that product quality and process are comparable among different sites as is the case for biologics produced by different centralised manufacturing sites. However, it was acknowledged that the various GMP standards were not designed for point-of-care production. Additional comparability studies would increase regulatory and financial burden for the sites.

It was raised by some agencies that product and manufacturing oversight vs. the health care practice would need to be considered carefully for the point-of-care production, as this oversight may affect different jurisdictions for some agencies or be subject to different legislative frameworks for others.

For the point-of-care production, Japan's MHLW would regulate the meniscus as per the *Act on Securing Safety of Regenerative Therapies*. The end product and the site would not be subject to market authorization requirements under the *Pharmaceuticals and Medical Devices Act* as the products would not be marketed or distributed. However, the patient cells processing, scaffold material, 3D printer and software would be subject to the *Pharmaceuticals and Medical Devices Act* and the operators to the *Medical Care Act*.

5.4.3 Ongoing Discussions

It is evident that the agencies attempted to enhance agility in pre-market assessment given the fast evolving innovation in the health care field. The agencies would be well experienced to provide pre-market assessments for centralized production. The suggestions from the agencies were prudent and diverse in managing the uncertainties associated with the meniscus produced at the point-of-care. Given that point-of-care production might be more broadly used as 3D bio-printing technology advances, this would clearly be an area that would require more capacity building, knowledge exchange, and strategic direction.

EMA and MHRA both discussed the thinking around a manufacturing master file for providing proper regulatory oversight to the point-of-care production. This is a concept where one licensed master site would be responsible for ensuring its satellite sites are qualified for, and comply with, the licensed procedures and requirements. Japan has a system that provides oversight for decentralized regenerative therapies. The agencies also mentioned that the Pharmaceutical Inspection Co-operation Scheme (PIC/S) is currently looking into point-of-care manufacturing models and considerations. These sources could be a good starting point to carry out discussions on regulatory oversight for point-of-care production.

5.5 Post-Approval Measures

The agencies suggested that post-approval measures would be critical steps for ongoing and long-term product safety, efficacy and quality oversight. Since the meniscus production would involve processes pertaining to both medicines and devices, a combination of post-approval measures of both types of products would be necessary. Should there be conditions attached at the time of product licensing, such conditions should be monitored and reassessment at a certain timeframe would be required. For both centralized and point-of-care production, the agencies recommended that a tailored risk management plan be established during the pre-market stage. Also, reporting and change notification from the sponsor would be required, and risk-based inspections would be conducted. These post-approval measures would be subject to standards, such as specific GMPs, that are under development or already established.

The agencies emphasized that traceability of the products and patients would be critical for collecting RWE to establish long-term product safety, especially in the case of small initial numbers of patients. Specific measures put forward by the agencies included: the establishment of product registries that contain traceable information about the source of production, medical procedure and patient information; mandatory requirements for physicians to document the procedure, products and patient information, leveraging electronic health records where possible, and report any incidents; and the establishment of a global product registry.

5.5.1 Ongoing Discussions

The agencies acknowledged the importance of generating post-licensing evidence and establishing long-term product safety and efficacy through necessary post-approval activities. The agencies made it clear that the suggestions put forward were not new; however, it would be important to implement these measures in a coherent manner. In addition, sharing the best practices in this area with international partners could facilitate the identification of convergence and potential collaboration opportunities among the regulators, for example with respect to RWE and product registries. Should there be sufficient interest, these discussions could be carried out in the informal ICMRA Innovation Network.

5.6 Adopting or Updating Standards

The agencies suggested the adoption and update of standards, most notably GMPs, for regulating the end product and all components of the centralized and point-of-care production processes. The utilization of standards was deemed important for ensuring quality, i.e., consistency, comparability, predictability, and stability, of the end product.

It was recommended that each regulatory component of the production process be identified, including the raw material processing, sites, printer, software, qualified operator, data, and the end product. It was also recommended that all the identified components be subject to the applicable standards, while standards update might be needed. In addition, stakeholder education and compliance promotion activities would be necessary to support standard implementation.

5.6.1 Ongoing Discussions

The application of standards was raised repeatedly as being particularly challenging to manage. The current GMPs were established for a centralized model and they might not cover specifically some aspects of the point-of-care production. For example, according to a GMP provision, every fabricator and importer of an active ingredient shall establish the period during which each drug in the package in which it is sold will comply with the specifications for that drug. This provision would not be applicable to the point-of-care production, and new standards would be necessary.

Further discussions would be required on the adoption of updated or specific standards. Given that the topic is technical in nature, appropriate bodies such as ICH or PIC/S could carry out the technical discussions at the global level.

5.7 Managing Knowledge Gaps and Stakeholder Engagement

Other recurring themes of the discussion were the need for regulator capacity building, engagement of stakeholders and clarification of roles and responsibilities among the regulating authorities and the regulated.

The agencies indicated that there were apparent knowledge gaps that would need to be filled for licensing the product. For example, the reviewers would need to understand how 3D printing technology works and the inspectors would need to know how to ensure that the data provided by the software is reliable, robust, and accurate, e.g., results of tests on quality align with the data output. The agencies suggested that regulator capacity building would be a key enabler in the regulatory process.

On the other hand, some agencies expressed the need to have critical dialogue with stakeholders and other regulatory authorities, for determining the proper level of oversight to the meniscus production process and respecting jurisdictional responsibilities. The necessary stakeholder engagement would include patient education, sponsor understanding of regulatory processes, and dialogues among the authorities of different jurisdictions and the regulated parties on roles and responsibilities.

5.7.1 Ongoing Discussions

Regulator capacity building is a key element of the newly formed informal Innovation Network. It would be helpful to leverage the network activities to obtain a better understanding of advanced technologies. When opportunities arise, it would be beneficial to hold expert discussions or workshops on advanced technologies identified through horizon scanning. Similar methodology to what was applied to this 3D bio-printing case study could be used to assess other emerging disruptive technologies. It is also helpful for agencies to exchange best practices and lessons learned on stakeholder engagement.

6. CONCLUSIONS

The discussions among the agencies called for risk-based oversight that combines regulatory requirements that are “fit for purpose”, so that quality evidence can be generated to support short-term and long-term product safety and efficacy. The suggestions also included the adoption and update of regulatory standards such as ICH, GMP and QMS guidelines and standards, establishment of risk management plans, and the use of a product registry to maintain traceability. Other common themes that emerged included fostering regulator capacity building to fill the knowledge gaps and engaging other regulatory authorities and stakeholders to mitigate uncertainties.

Several of the new approaches and challenges identified would require future discussions among the regulators, which could be carried out in the informal Innovation Network. These topics included: new regulatory pathways; efficient procedures to engage internal and external experts; agile pre-market assessments that use standards and allow for the establishment of long-term safety and efficacy; post-approval evidence generation including RWE; product and patient registries; and regulator capacity building and stakeholder engagement.

This summary concludes the 3D bio-printing case study of Work Stream 3 (Novel Approaches to Licensing), the last component of the ICMRA Innovation Project. It serves as a bridge that connects the ICMRA Innovation Project and the newly established informal ICMRA Innovation

Network. Building on the summary of this case study, the international regulatory authorities will continue to proactively and cohesively tackle the regulatory challenges of advanced technologies. It also is a model to reflect on how legislation needs to evolve to facilitate access to innovative products while protecting patients, with obvious differences among countries or regions on the depth of the need for change.

Table 1 Proposed Product Classification

Table 1 - Proposed Classification

Centralized Production

- **TGA** would classify the product as a biologic class 4 product that would be subject to the biologics framework, since the product would contain human cells and tissues and the primary mode of action would be taken mainly by the cells.
- **ANVISA** would classify the product as an ATMP that would be subject to the resolution for market authorization of ATMPs (under development) in Brazil, as the primary mode of action would be taken by the cells.
- **Health Canada** would classify the product as a complex Product that would be subject to the "regulatory sandbox" under the *Food and Drugs Act* in Canada – a new pathway for products enabled by advanced technologies, as tailored requirements for biologics and medical devices components as well as the production process would be necessary to regulate the product.
- **EMA** would potentially classify the product as a tissue engineered ATMP combined with a device.
- **PMDA** would classify the product as a regenerative medicine that would be subject to the *Pharmaceuticals and Medical Devices (PMD) Act* in Japan, as the primary mode of action would be taken mainly by the cells.
- **HSA** will be promulgating the new Cell, Tissue and Gene Therapy Product (CTGTP) Regulations (in draft) under the *Health Products Act* in Singapore, and the product would be regulated under this new framework when the regulation is implemented.

Point-of-Care Production

- **TGA, ANVISA, Health Canada, and HSA** would classify the meniscus produced at point-of-care, the same as that produced centrally.
- **EMA:** should the product be for non-routine manufacture and treatment of individual patients within a hospital setting, the EU medicinal product legislation may not apply as it would be considered a "hospital exemption." As such, the classification could be subject to relevant legislations of the member state where the product is manufactured.
- **PMDA** considers the meniscus produced at the point-of-care the first category of the regenerative therapy that would be subject to the *Act on Securing Safety of Regenerative Therapies* (Safe Regen. Act). Since the Safe Regen. Act regulates the procedure for physicians to use these therapies, there is no "approval" of the final product. However, other components involved in the production process (raw material, printer, software, sites) would be subject to different regulatory frameworks, including the *PMD Act* and *Medical Care Act*.

Table 2 Suggestions on Pre-Market Assessments

Table 2 – Pre-Market Assessments

Centralized Production

- **TGA** would use TGO88 standards for cellular starting material and critical materials. Hydrogel scaffold would likely be treated as critical material. GMP for oversight of equipment validation for 3D printer, software and operators. Australian cGMP or conformity assessment for devices. Product guideline may consider the European Pharmacopeia and the USFDA general monographs.
- **ANVISA** would apply the standards specified in Good Manufacturing Practice (GMP) in Cell Engineering, Genetic Therapy and Tissue Engineering Products, including requirements applicable to GMP for Medical Devices, for example, for raw material, 3D printer, software. Manufacturing locations must comply with ANVISA GMP Certificate and locations of use (health services) in accordance with Good Health Care Practice and Patient Safety requirements (monitored by local authorities).
- **Health Canada** would use the "regulatory sandbox" to identify the applicable standards and requirements for regulatory check-points in the product process. Raw materials would be subject to the established cell processing standard; 3D printer, software, the operator and the site would be subject to GMP standards that are adapted, as necessary; the end product would be subject to the requirements under the *Food and Drugs Act* and the applicable guidelines.
- **EMA** would apply ATMP legislation and EU GMP Guidelines for market authorization of tissue-engineered products, and additional PIC/S guidance on point-of-care manufacturing (when available). 3D printers would be subject to the European certification for devices. All results would be subject to test and batch release by a qualified person. Software would be subject to experiences gained through existing computerized manufacturing process, but overall it would be the quality of the finished product which would be assessed.
- **PMDA** would apply the Standard for Biological ingredients. The Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (GCTP) could be applied to the 3D printer, software, operator, and sites. For products, review would be case-by-case, the regulator could prepare points for consideration for product development to be included in the Assessment Standards for next Generation Medical Devices.
- **HSA** would apply Good Tissue Practice Standards for collection of starting biomaterials from patients. Other raw materials and the sites would be subject to HSA Guidelines on GMP for CTGTPs and CMC Requirements for CTGTP for Clinical Trials and Product Registration (in draft).

Point-of-Care Production

- **EMA** would not be involved in "hospital exemption" products in EU. If an ATMP is manufactured and used in one hospital in a small population, it is not required to seek EU level market authorization.
- **PMDA** considers the meniscus produced at the point-of-care the first category of the regenerative therapy that would be subject to the *Act on Securing Safety of Regenerative Therapies* (Safe Regen. Act). Since the Safe Regen. Act regulates the procedure for physicians to use these therapies, there is no "approval" of the final product. However, other components involved in the production process (raw material, printer, software, sites) would be subject to different regulatory frameworks, including the *PMD Act* and *Medical Care Act*.

Annex B - Product Description

Option A: [**Hypothetical**] 3D bio-printed knee meniscus tissue

Indication: Human meniscal autograft transplantation replacing severely damaged meniscus.

Medical need
Meniscal allograft transplantations frequently use the meniscus of a cadaver donor to treat severe meniscus damage. However, the availability of donor meniscus is inadequate, and between 21% and 55% of transplants fail within 10 years. In addition, non-ideal sizing of the transplant is a main cause of chronic pain which also affects the usable time of the transplant. This therapy is developed to mitigate the incorrect sizing and significantly improve the durability of meniscus transplants, which would improve the quality of patients' lives.

Description: The 3D bio-printed meniscus uses a fixed scaffold construct which is seeded with three types of cells derived from the patient induced pluripotent stem cells. The bio-printed meniscus replaces the damaged meniscus and promotes the regenerative process for the desired cartilage phenotype, matrix composition, mechanical features, and chondrogenesis.

Production (*This process could be "centrally" managed or performed at the point-of-care*)

Patient measurements
The patient's knee is measured by computed tomography to create a detailed three-dimensional tomogram. A computer software program uses this information to construct a digital model of the new meniscus to match the original.

Cell isolation
Patient's cells are taken from their own system as per the established protocols. These cells are processed and/or reprogrammed in culture to become multipotent articular cartilage-resident chondroprogenitor cells (ACPCs), mesenchymal stem cells (MSCs), and chondrocyte cells, which are used in the printing process.

3D bio-printing
A 3D bio-printer uses a microfluidic platform to create and dispense cell-laden biocompatible matrix. The built-in software uses measurements from the patient's tomogram to print millimeter assembled construct while seeding the patient cells to mimic the natural tissue composition.

After printing, the meniscus is then matured in a bioreactor, conditioned and readied for patient implant.

Surgical Procedure
The meniscal allograft transplantation is done with arthroscopic assistance as well as open incision.

Available Evidence
Multiple studies have shown 3D bioprinted meniscus can be successfully transplanted to repair damaged meniscus in animals. The studies support the viability and proliferation of stems cells and the proper distribution of proteoglycans to the ACPC-laden (closer to surface) and MSCs-laden (deeper in the construct) zones. Also, significant improvement in the strong shock-absorbing qualities has been demonstrated. Assessment of the long-term therapeutic benefits, potential for immunological rejection and tumorigenesis will require continued studies.

Option B: [**Hypothetical**] 3D bio-printed myocardial tissue patches

Indication: Human myocardial tissue transplantation treating myocardial infarction subsequent to an ischemic event for patients with end-stage heart failure.

Medical need
For patients with end-stage heart failure, heart transplantation is considered the only definitive therapy for restoring cardiac function. However, the availability of donor hearts is inadequate, and even with a successful heart transplant, the patient's lifespan after transplantation is often limited. This therapy is developed to effectively limit adverse cardiac remodeling and regenerate or replace myocardial tissues that are lost to an ischemic event.

Description: The 3D bio-printed myocardial patches are scaffold-free tissues with microvascular network that resemble myocardial tissue as evidenced by the expression of myocardial markers and the exhibition of functional and structural properties that represent the characteristic of native myocardium.

Production (*This process could be "centrally" managed or performed at the point-of-care*)

Patient measurements
Magnetic resonance imaging (MRI) is used to create a detailed three-dimensional image of a patient's heart, particularly the areas affected by myocardial infarction. Using this image, a computer software program will construct a digital model of the new myocardial patches to match the original.

Cell isolation
Patient's cells are taken from their own samples as per the established protocols. These cells are reprogramed and converted to create iPS and then converted to the human inducted pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), fibroblasts and endothelial cells for the printing process.

3D bio-printing
Bio-printing is done with a 3D bio-printer using spheroid-based bio-assembly method, where the cells are organized into micro bulks and these bulks are placed near each other to allow them to fuse into a living material that demonstrates natural physiological properties of the native tissue. The process is controlled by the 3D bio-printing software using dimensions obtained from the patient's MRI.

After printing, the myocardial tissue patch is then matured in a bioreactor, conditioned to make it stronger and readied for patient implant.

Surgical Procedure
The myocardial tissue patch transplant is conducted with open heart or minimally invasive heart surgery.

Available Evidence
Multiple studies have demonstrated that 3D bio-printed myocardial tissue patches can be successfully transplanted to repair damaged myocardium in animals. The graft viability has been stable and the tissue vascularization demonstrated integration with host vasculature. Significant improvement in cardiac function has been demonstrated. While not observed at this time, the possibility for arrhythmias, immunological rejection and tumorigenesis will require continued studies.

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164915/pdf/materials-11-01749.pdf

Nguyen, A., Pavlovich, M. (2018). Engineering a Strong Bond between Stem Cells and Biotechnology. *Trends in Biotechnology, 4* (36), 2018, 337-339. https://www.sciencedirect.com/science/article/pii/S0167779918300349?via%3Dihub

Online Resources

Aspect systems
https://www.aspectbiosystems.com/technology

Biolife4D
https://biolife4d.com/

Creating Vascular Structures Using Low-Cost Desktop 3D Printers
https://3dprint.com/232504/creating-vascular-structures-using-low-cost-3d-printers/

Meniscus Tears
https://www.umms.org/ummc/health-services/orthopedics/services/knee/meniscus-tears

Meniscal Transplant Surgery
https://orthoinfo.aaos.org/en/treatment/meniscal-transplant-surgery

New Patch Can Heal Heart Muscle after Heart Attack
https://www.healthline.com/health-news/new-patch-can-heal-heart-muscle-after-heart-attack#1

Case Study – 3D Bio-Printing Input/Discussion Guide

From a public health, biotechnology and tissue engineering standpoint, engineered therapies for musculoskeletal and vascular applications are making significant and promising advances to address high therapeutic demands in these areas. There are currently clinical trials in progress involving bioengineered human inducted pluripotent stem cell (hiPSC)-derived approaches to treat musculoskeletal degeneration and myocardial infarction.

With this in mind, two hypothetical product descriptions have been developed for the purpose of examining regulatory issues: **Option A** - 3D bio-printed knee meniscus tissue and **Option B** - 3D bio-printed myocardial tissue patches (see page 8). These descriptions use the currently available information about products in development without excessive technical details for the purposes of this case study only.

Assume that your agency recently received a request concerning a product made of 3D bio-printed tissues for human therapies. Your agency has accepted the request and has committed to work with the applicant to facilitate product development and regulatory process, including the provision of regulatory and scientific advice related to the design of clinical trials and navigating the regulatory system throughout the product's life cycle.

Please select ONE product and navigate through your currently available regulatory system/pathways. Based on the given product information, identify the regulatory gaps and suggest possible regulatory methods to fill these gaps. Since this is an exercise concerning the regulatory process, please do **NOT** focus on technical details.

Step 1

Please select a product for this study [See Annex A on page 8 for product descriptions]

[ ] Option A: [Hypothetical] 3D bio-printed knee meniscus tissue

[ ] Option B: [Hypothetical] 3D bio-printed myocardial tissue patches

Step 2 - Scenario I: Centralized Production Process: Bio-printing takes place at a production centre before the product is transmitted to the health care setting for treatment.

Life Cycle	Activity of Regulators	Existing Tools and Challenges • What are the novel pathways, regulations, policy, guidance, standards you currently have to regulate this product? • Are there any gaps/lack of flexibilities associated with your **legal authorities** and **requirements** for **safety, efficacy and quality**?	Desired Tools/Promising Solutions • What are the known best practices, regulations, policy, standards, and regulatory methods that you would need to regulate this product? • What are the other promising tailored measures that would help you regulate this product, e.g. new legal authorities, regulatory sandbox, work sharing etc.?
1. Pre-clinical Development	Early Advice		
2. Clinical Trials (CT)	CT Assessment (including acceptable CT design)		
3. Market Authorization	3.1 Classification – (Drug, medical devices, Advanced Therapy Medical Products, other), How would product classification be determined? If you use defined factors, would certain product characteristics be more important than others?		
	Areas for regulatory oversight		
	3.2 Raw materials		
	3.3 3D printer		
	3.4 Software		
	3.5 Operator of 3D printer (clinicians, technicians)		

Life Cycle	Activity of Regulators	Existing Tools and Challenges • What are the novel pathways, regulations, policy, guidance, standards you currently have to regulate this product? • Are there any gaps/lack of flexibilities associated with your **legal authorities** and **requirements** for **safety, efficacy and quality**?	Desired Tools/Promising Solutions • What are the known best practices, regulations, policy, standards, and regulatory methods that you would need to regulate this product? • What are the other promising tailored measures that would help you regulate this product, e.g. new legal authorities, regulatory sandbox, work sharing etc.?
	3.6 Sites (manufacturer QMS, healthcare settings)		
	3.7 Product (e.g. tailored requirements, need for conditions on product authorization, uncertainty management)		
	3.8 Other		
4. Post-Market	Areas for surveillance/enforcement		
	4.1 Fulfillment of Market Authorization Conditions		
	4.2 Notification and reporting of adverse reaction		
	4.3 3D printer upkeep		
	4.4 Software upgrade		
	4.5 Operator qualification		
	4.6 Sites		
	4.7 Product safety		
	4.8 Other		
5. HTA	5.1 Parallel early advice		
	5.2 Aligned product review		
	5.3 Other		

Step 3 - Scenario II: De-centralized Production Process: Bio-printing takes place at the point-of-care in a health care setting/hospital where patient treatment is performed.

Life Cycle	Activity of Regulators	Existing Tools and Challenges • What are the novel pathways, regulations, policy, guidance, standards you currently have to regulate this product? • Are there any gaps/lack of flexibilities associated with your **legal authorities** and **requirements** for **safety, efficacy and quality**?	Desired Tools/Promising Solutions • What are the known best practices, regulations, policy, standards, and regulatory methods that you would need to regulate this product? • What are the other promising tailored measures that would help you regulate this product, e.g. new legal authorities, regulatory sandbox, work sharing etc.?
1. Pre-clinical Development	Early Advice		
2. Clinical Trials (CT)	CT Assessment (including acceptable CT design)		
3. Market Authorization	3.1 Classification – (Drug, medical devices, Advanced Therapy Medical Products, other), How would product classification be determined? ? If you use defined factors, would certain product characteristics be more important than others?		
	Areas for regulatory oversight		
	3.2 Raw materials		
	3.3 3D printer		
	3.4 Software		
	3.5 Operator of 3D printer (clinicians, technicians)		

Life Cycle	Activity of Regulators	Existing Tools and Challenges • What are the novel pathways, regulations, policy, guidance, standards you currently have to regulate this product? • Are there any gaps/lack of flexibilities associated with your **legal authorities** and **requirements** for **safety, efficacy and quality**?	Desired Tools/Promising Solutions • What are the known best practices, regulations, policy, standards, and regulatory methods that you would need to regulate this product? • What are the other promising tailored measures that would help you regulate this product, e.g. new legal authorities, regulatory sandbox, work sharing etc.?
	3.6 Sites (e.g., manufacturer QMS, health care settings)		
	3.7 Product (e.g. tailored requirements, need for conditions on product authorization, uncertainty management)		
	3.8 Other		
4. Post-Market	Areas for surveillance/enforcement		
	4.1 Fulfillment of Market Authorization Conditions		
	4.2 Notification and reporting of adverse reaction		
	4.3 3D printer upkeep		
	4.4 Software upgrade		
	4.5 Operator qualification		
	4.6 Sites		
	4.7 Product safety		
	4.8 Other		
5. HTA	5.1 Parallel early advice		
	5.2 Aligned product review		
	5.3 Other		