APACMed
The voice of MedTech

DIAGNOSTICS DEVELOPMENT HUB

Digital Health Regulation In Asia-Pacific

Overview And Best Practices

APACMed Digital Health Committee
Regulatory Working Group

Contents

Introduction

The Asia-Pacific Medical Technology Association (APACMed) is the trade association for the MedTech industry in Asia-Pacific (APAC). Following the launch of a Digital Health (DH) Committee in 2020, APACMed is seeking greater harmonization on topics such as regulation, interoperability, and cybersecurity.

This position paper is intended to be shared with regulators with the aim of aiding the creation of a fit-for-purpose regulatory framework for DH across the APAC region. While current regulations ensure the safety and effectiveness of traditional In-Vitro Diagnostics (IVD) and medical devices, they do not fit the fast-paced innovation that characterizes software and DH.

To bring safe and effective digital technologies into healthcare at a pace that matches the speed of what's possible – and that patients deserve – we must redesign our regulatory approach to accommodate the shorter timelines and iterative nature of software development.

Development of tailored and risk-based software regulatory frameworks will enable greater access to software innovation, better use of limited regulatory resources, and ultimately drive us to the next generation of personalized healthcare with more informed health decisions and improved patient outcomes. Convergence of DH regulation across APAC countries will ensure greater consistency and predictability in regulatory review processes, which, in turn, will enable safe, effective, and innovative DH solutions to reach patients and healthcare professionals in an expeditious manner. Harmonization of regulatory approaches for DH will benefit regulators, software developers, and, most importantly, patients.

With this paper, we provide a review of current regulatory measures for DH solutions in Singapore, Australia, Japan and the US with the aim of providing recommendations to regulators. We also include two use cases of companies that have gone through the regulatory process for their DH solutions: Pear Therapeutics and Digital Diagnostics. Finally, we conclude with a best practices framework that we strongly recommend regulators to leverage as they implement fit-for-purpose regulation for DH solutions.

Overview of Digital Health Regulation in Asia-Pacific

Within a region as diverse as APAC, with different levels of both healthcare provision and regulatory expertise, there is inevitably a wide variation in how DH solutions are brought to market. Unlike traditional therapeutic, medical device or IVD products, many DH solutions use platforms such as mobile devices that are universal and inexpensive and are therefore available to benefit a wider population, creating unique regulatory challenges and opportunities.

In this section, we discuss the current approaches applied in three APAC countries (Australia, Japan, and Singapore) that have been active in the regulation of DH.

Each of these countries has a unique regulatory approach, although there are similarities. In order to summarize the DH regulation in each of these three countries, this section focuses on five key areas:

1. Software Qualification
2. SaMD Classification
3. Alternative Regulatory Pathways
4. Pre-Submission Consultation
5. Framework for regulation of Artificial Intelligence (AI) / Machine Learning (ML)

1. Software Qualification

Software qualification is the process by which regulators determine whether or not a software product meets the "medical device" definition and is thus regulated by health authorities. Given the prevalence of software within the healthcare community (from electronic health records to clinical decision support systems), guidance and/or regulation on software qualification must provide regulators and the industry with a clear understanding of those digital products that must fulfil medical device regulatory requirements.

Australia

In its "Consultation: Scope of regulated software-based products" published in March 2020, Australia's Therapeutic Goods Administration (TGA) provided a comprehensive overview of software products that do not qualify as medical devices, such as software for administrative support of healthcare facilities and software that is used for transferring, storing, converting formats or displaying laboratory test or other device data and results. Additionally, the TGA has proposed two modes by which software may be carved out from the medical device scope or from selected requirements: exclusion and exemption. Excluded software products would not be subject to regulation by TGA, while exempted products would not require premarket review but still be monitored for safety and performance. This published consultation reflects TGA's efforts in developing a risk-based approach in this area.

Japan

In Japan, Ministry of Health and Labour Welfare (MHLW) addresses the concept of qualification via MHLW notification - PFSB/CND Notification No. 1114-5, by the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 14, 2014. The scope of qualification outlined in the notification aligns with international regulatory best practices and excludes, for example, software for transferring data and software for health management, from the Pharmaceutical and Medical Devices (PMD) Act. However, the notification does not take into account the qualification of low risk clinical decision support systems as addressed by US FDA, Health Canada and TGA.

Singapore

In Singapore, the Health Sciences Authority (HSA) has published "Regulatory Guidelines for Telehealth Products" and "Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach." Both of these guidance documents briefly discuss software qualification and clarify that software is regulated as a medical device if its intended use falls under the definition of a "medical device" as stipulated in the Health Products Act. The "Telehealth" guidance indicates that, if a software product is intended by the developer to be used as a wellness product (e.g., intended for fitness tracking) but is able to perform a medical function (such as monitoring heart rate), the developer is required to add "clarification statements" to the "labelling" to inform users of the software's appropriate use. The guidance also includes a basic flowchart with a few examples to be used in determining if software qualifies as a medical device.

The above referenced guidance documents do not describe HSA's approach to the qualification of low risk clinical decision support software, as addressed by US FDA, Health Canada, and TGA, nor do they describe HSA's approach to the qualification of other low-risk software products commonly used in healthcare environments, such as Laboratory Information Systems (LIS) or software that is used to digitize publicly available guidelines.

2. SaMD Classification

When it has been determined that a software solution meets the "medical device" definition and is thus software as a medical device (SaMD)[1], it is then necessary to classify the SaMD. Regulatory authorities apply a classification system to medical device products, including SaMD solutions. This classification is very important, as it dictates pre- and post-market regulatory requirements. The approaches to SaMD classification employed in Australia, Japan, and Singapore are described below.

[1] IMDRF defines software as a medical device in the following manner: Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.

Australia

On 12 December 2019, TGA made regulatory changes related to SaMD classification that are effective from 25 February 2021 (with a transition period ending 01 November 2024). These new SaMD classification rules are represented in the table below.

The classification rules consider the harm that could be caused by the provision of incorrect information in carrying out the medical device's functions of the software and also take into account the recipient of the software's output (experienced users such as healthcare professionals vs. inexperienced users such as patients). These SaMD classification rules are broadly aligned with the software classification rules described within the European Union's Medical Device Regulation (Regulation EU 2017/745). They also do not apply to software solutions that qualify as IVD SaMD.

DIAGNOSING / SCREENING AND / OR SPECIFYING OR RECOMMENDING TREATMENT / INTERVENTION FOR A DISEASE OR CONDITION		
	INFORMATION TO AN INDIVIDUAL	INFORMATION TO A HEALTH PROFESSIONAL
RISK TO INDIVIDUAL OR PUBLIC HEALTH: DEATH / SEVERE DETERIORATION / HIGH PUBLIC HEALTH RISK	III	IIb
SERIOUS DISEASE OR CONDITION / OTHERWISE HARMFUL / MODERATE PUBLIC HEALTH RISK	IIb	IIa
ANY OTHER CASE	IIa	I
MONITORING THE STATE / PROGRESSION OF A DISEASE OR CONDITION		
IMMEDIATE DANGER TO A PERSON / HIGH PUBLIC HEALTH RISK	IIb	
OTHER DANGER TO A PERSON OR ANOTHER / MODERATE PUBLIC HEALTH RISK	IIa	
ANY OTHER CASE	I	
FOR PROVIDING THERAPY THROUGH PROVISION OF INFORMATION		
MAY RESULT IN DAETH / SEVERE DETERIORATION	III	
MAY CAUSE SERIOUS HARM	IIb	
MAY CAUSE HARM	IIa	
ANY OTHER CASE	I	

Figure 1: TGA new SaMD classification rules.

While TGA has created classification rules specifically for SaMD, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and Singapore's HSA continue to rely on existing, traditional medical device classification schemes to classify SaMD.

Japan

PMDA employs the Global Harmonization Task Force (GHTF) classification system when classifying SaMD. This system is described in Table 1 below:

CLASSIFICATION	DEVICE	RISK
I	General Medical Device	Low
II	Controlled Medical Device	Relatively Low
III	Specially Controlled Medical Device	High
IV	Specially Controlled Medical Device	Invasive, Potentially Life Threatening

Software that is determined to be class I is not considered to be a medical device and therefore is not regulated by MHLW. As such, no SaMD is classified as class I in Japan.

Table 1: PMDA classification scheme for Medical Devices

Singapore

HSA's approach to medical device classification is described within its GN-13 guidance, "Guidance on the Risk Classification of General Medical Devices." SaMD is classified according to the same classification rules as traditional medical devices. This approach is described further in HSA's "Regulatory Guideline for Telehealth Products," which provides examples and a flowchart for making a SaMD classification decision. Figure 2 below graphically depicts HSA's approach to SaMD classification and provides related examples.

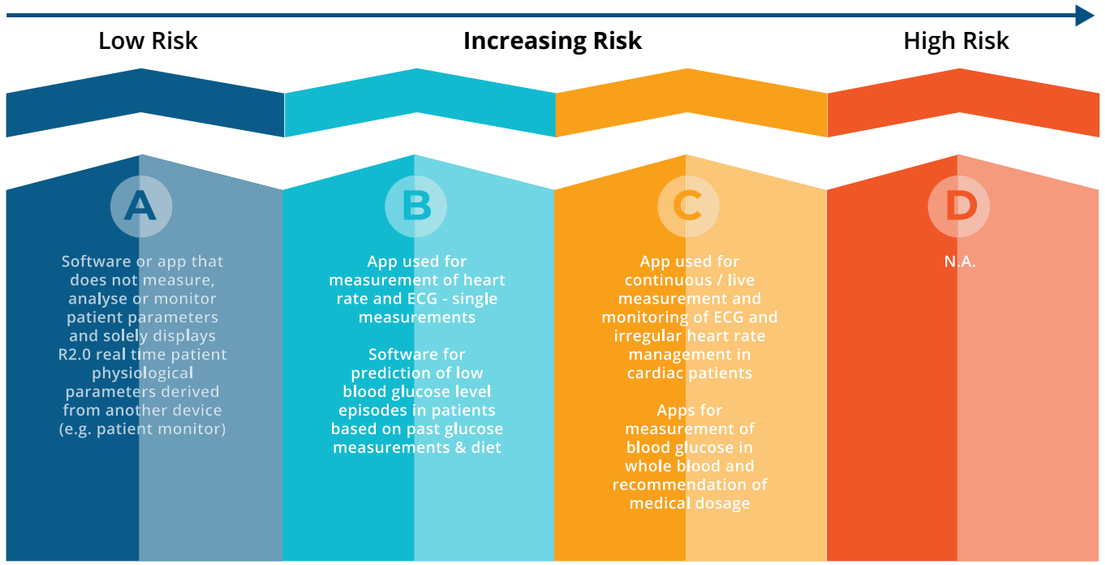


Figure 2: HSA's SaMD classification approach..

3. Alternative Regulatory Pathways

Given the significant differences between SaMD and traditional medical devices and IVDs, some health authorities have developed alternative SaMD regulatory approaches tailored to their unique and iterative aspects. Such approaches take a variety of forms, such as the use of:

- **Recognition and reliance models**
  1. **Recognition:** The acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority.
  2. **Reliance:** The act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative agency in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

- **Implementation of expedited review pathways**
  Regulatory pathways that are designed to provide a faster pre-market decision than traditional regulatory pathways.

- **Development of pre-certification type programs**
  Certain organizations may create regulator trust by demonstrating quality in their software development and maintenance practices, leading to a streamlined pre-market review process with increased post-market commitments.

- **Predetermined change control plans**
  Incorporation of predetermined change control plans during premarket review to support the rapid implementation of software modifications post-deployment.

Australia

TGA supports international collaborations, leveraging recognition and reliance models. Recognition and reliance represent smarter and more efficient ways of regulating digital products, as they bring benefits to patients and consumers, the industry, national governments and international development partners by facilitating and accelerating access to quality-assured and effective products. Australia has a number of bilateral Mutual Recognition Agreements (MRA) in place, one of which is an MRA with the European Union (EU) in relation to conformity assessment.

The underlying principle of this MRA is that both the European Union and Australia recognize and accept the technical competence of each other's conformity assessment bodies (CAB) to certify products for compliance with the regulatory requirements of the other party, largely eliminating the need for duplicative efforts when the goods are traded.

TGA places increased reliance on reports from international regulators to support Australian regulatory decisions and continues to contribute to the development of mutual reliance frameworks that reduce regulatory burden on manufacturers.

TGA is also actively engaged in work sharing, information sharing and regulatory convergence activities through international initiatives including:

- ACCESS Consortium of regulators from Australia, Canada, Singapore, United Kingdom and Switzerland.
- the International Medical Devices Regulators Forum (IMDRF)
- the International Organization for Standardization (ISO)

Japan

MHLW and PMDA launched a process called "SAKIGAKE", which allows for dramatically accelerated regulatory pathways for products designated as breakthrough devices addressing high, unmet medical needs. SAKIGAKE resulted in:

- Shorter lead time for PMDA's formal consultations (1 month instead of 2-3 months)
- Prioritized review
- Ability to submit materials, in English, for pre-review
- Shorter review period of 6-months from 12 months
- Assignment of a PMDA manager to oversee the entire approval process

SAKIGAKE Designation System

Criteria:
1. Innovativeness, 2. Severity of Targeted Disease, 3. High Effectiveness, 4. Development Plan in Japan.

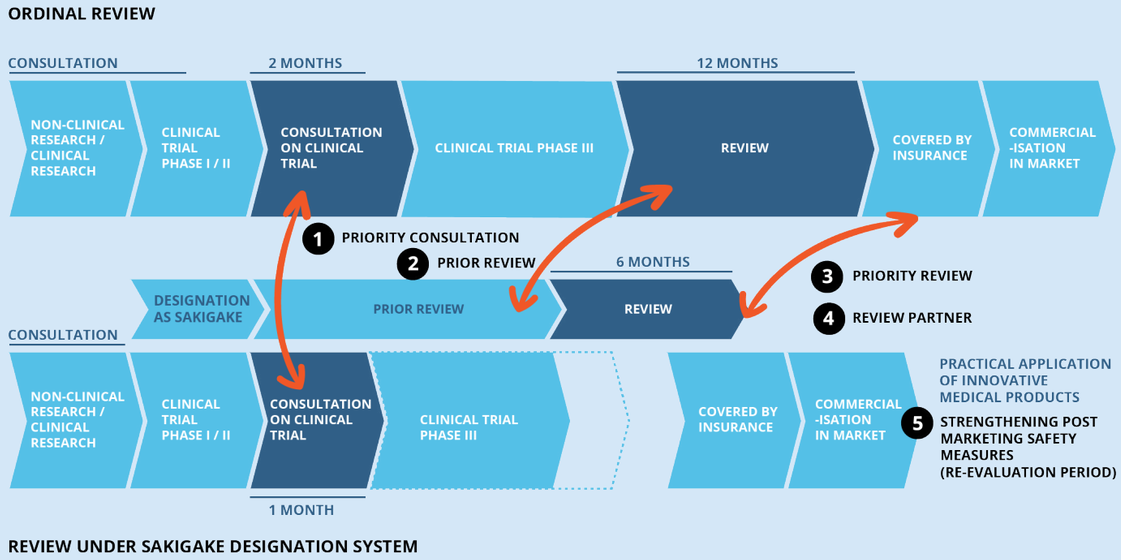


Figure 3: PMDA's 'SAKIGAKE' Designation System

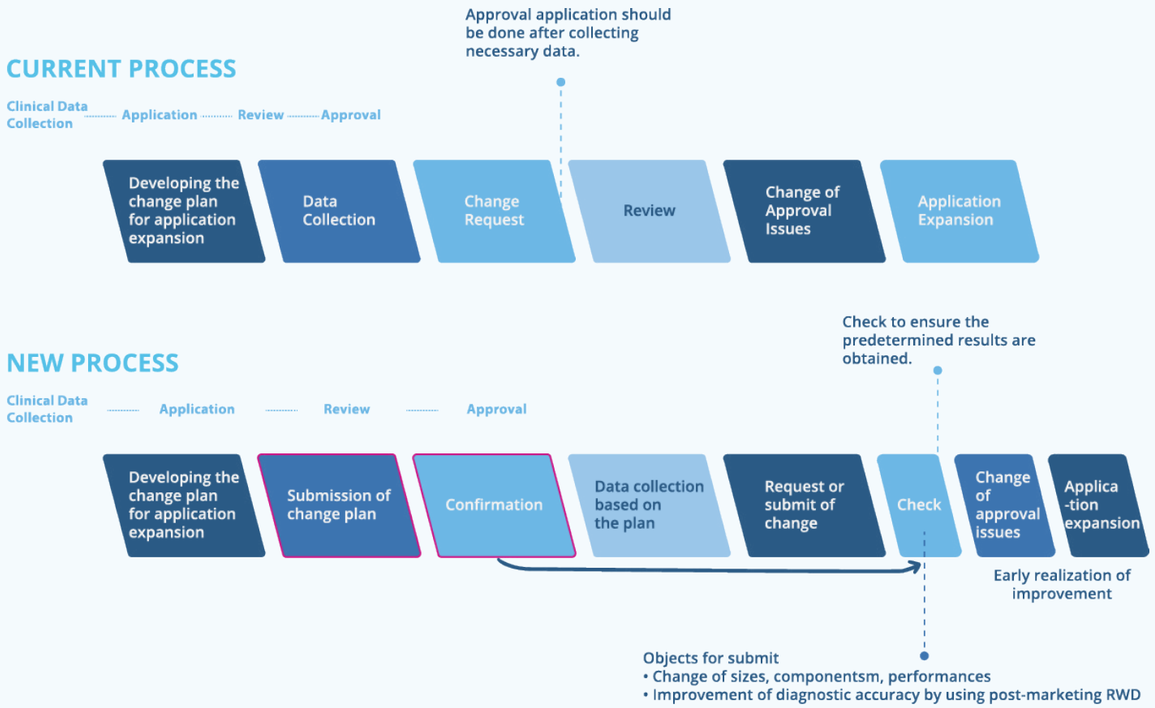
MHLW and PMDA have also introduced the IDATEN (Improvement Design within Approval for Timely Evaluation and Notice) process to help accomplish:

- **Early Realization of Change Plan**
  This provision allows both the market authorization holders (MAH) and the PMDA to more effectively monitor the effectiveness and safety of products. This framework involves review of the change plan, such as during the initial approval/review process, prior to the validation

and implementation stage. When a change is required later and implemented according to the agreed upon change plan, it can be conducted by notification instead of a partial change amendment, saving considerable time.

- **Post-Market Change Process for Continuously Improved Device**
  In addition to the requirements of the Early Realization of Change Plan are those related to the Post-Market Change Process for Continuously Improved Devices, applying to devices that undergo continuous lifecycle improvements, such as continuous learning AI/ML algorithms. The intention is to promote early introduction of improved features by reducing regulatory burdens.

Post-Approval Change Management Protocol introduced for medical devices to enable continuous improvements



Improvement Design within Approval for Timely Evaluation and Notice (IDATEN)

Figure 4: PMDA's Improvement Design within Approval for Timely Evaluation and Notice (IDATEN) process.

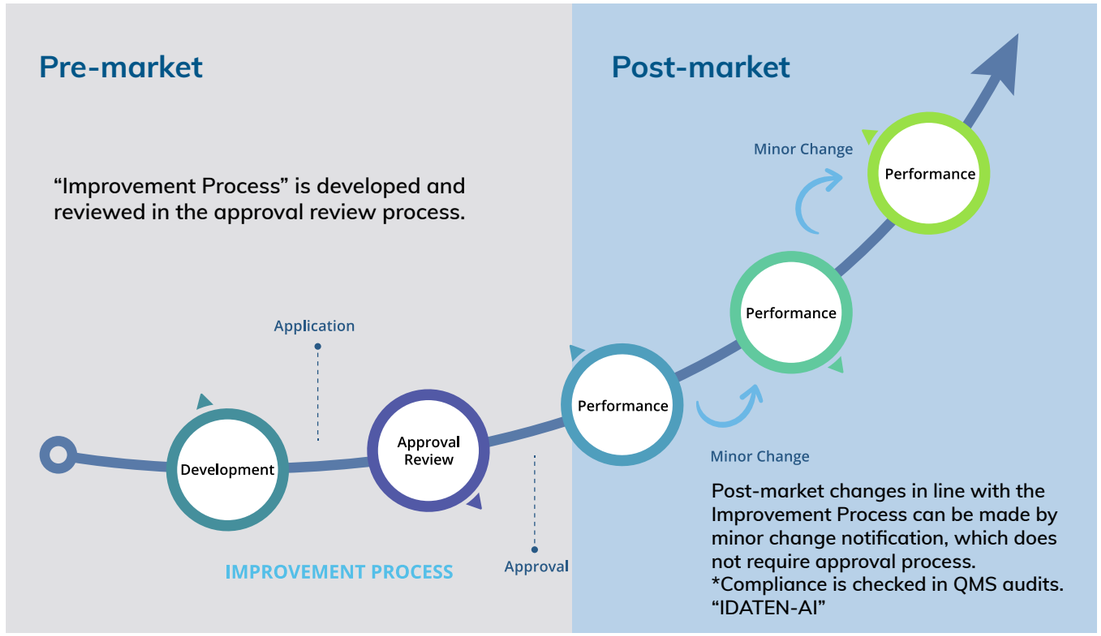


Figure 5: Post-market change process for devices with AI.

The IDATEN approach enables SaMD developers to more rapidly implement software modifications post-deployment. As long as the SaMD developer gains agreement on its approach to change management with MHLW during the initial review process, it can make changes according to that approach under its quality management system without the need for regulatory authority premarket review.

Singapore

HSA also supports confidence-based regulation through recognition and reliance models – The evaluation routes for products are set out, according to a confidence-based approach, by leveraging the approvals of HSA's reference regulatory agencies (TGA Australia, Health Canada, the US FDA, European Union Notified Bodies, and Japan's MHLW) and/or prior safe marketing history of the products. The submission requirements outlined in HSA's "GN-15: Guidance on Medical Device Product Registration" are titrated according to the evaluation routes for which the product qualifies. To facilitate expedited review there is provision for:

- **Abridged Evaluation Route**
  - Any new product that has been approved by at least one reference regulatory agency is eligible for an abridged evaluation route.

- Immediate Class B Registration (IBR) Evaluation Route (Condition 1 or 2)

  Condition 1
  - Products can be eligible if approved by at least 1 of HSA's independent reference regulatory agencies.
  - A product must be marketed for at least three years in one of the independent reference regulatory agency's jurisdictions.
  - There can be no rejection/withdrawal of the medical device from any of the independent reference regulatory agencies due to quality, performance or safety issues.
  - There can be no safety issues globally associated with the use of the product in the last 3 years or since market introduction of the product globally.

  Condition 2
  - Products can be eligible if approved by at least 2 of HSA's independent reference regulatory agencies.
  - There can be no safety issues globally associated with the use of the product in the last 3 years or since market introduction of the product globally.
  - There can be no rejection/withdrawal of the medical device from any of the independent reference regulatory agencies due to quality, performance or safety issues.

- Immediate Class B Registration (IBR) Evaluation Route (Solely for Standalone Medical Mobile Applications)
  - Products can be eligible if approved by at least 1 of HSA's independent reference regulatory agencies.
  - There can be no safety issues globally associated with the use of the product in the last 3 years or since market introduction of the product globally.
  - There can be no rejection/withdrawal of the medical device from any of the independent reference regulatory agencies due to quality, performance or safety issues.

- Immediate Class C Registration (ICR) Evaluation Route (Solely for Standalone Medical Mobile Applications)
  - Products can be eligible if approved by at least 1 of HSA's independent reference regulatory agencies.
  - There can be no safety issues globally associated with the use of the product in the last 3 years or since market introduction of the product globally.
  - There can be no rejection/withdrawal of the medical device from any of the independent reference regulatory agencies due to quality, performance or safety issues.

HSA is actively engaged in work sharing, information sharing and regulatory convergence activities through international initiatives including:

- ACCESS Consortium of regulators from Australia, Canada, Singapore, United Kingdom and Switzerland.
- The International Medical Devices Regulators Forum (IMDRF).
- HSA-Thailand Food and Drugs Administration Reliance Pilot.

4. Pre-Submission Consultation

Pre-submission consultation (PSC) is an opportunity to discuss specific aspects of a future regulatory submission with regulatory bodies to ensure that statutory requirements will be fulfilled (for example, consultation for a clinical trial design supporting a novel claim). Under the PSC scheme – regulatory agencies allow manufacturers / sponsors of DH technologies to seek innovation support during a DH product's pre-submission phase to expedite patient access to the product in a safe and effective manner. Manufacturers / sponsors can consult the regulatory authority on regulatory requirements during the DH product development phase, or seek feedback on dossier completeness before submission. For novel DH products, which do not fit naturally into current regulatory systems, PSC is crucial to expedite registration and facilitate early patient access to DH products.
TGA, PMDA and HSA have all implemented the PSC scheme.

5. Framework for regulation of Artificial Intelligence / Machine Learning (AI/ML)

The use of Artificial Intelligence (AI) / Machine Learning (ML) is increasingly prevalent in DH products and creates new regulatory challenges and opportunities. Many regulatory authorities are actively creating regulatory frameworks that address products leveraging AI/ML, such as Japan's MHLW/ PMDA and Singapore's HSA.

Japan

As noted previously, on 04 December 2019, the amended PMD Act was published in Japan and introduced a provision for predetermined change control plans called "IDATEN" which allow both manufacturers and the PMDA to more effectively monitor the effectiveness and safety of medical products. The framework involves review of the change plan, such as during the initial approval/ review process, prior to the validation and implementation stage. When a change is required later, it can be conducted by notification instead of partial change amendment, saving considerable review time.

IDATEN also helps to appropriately regulate changes that are related to the Post-Market Change Process for Continuously Improved Devices (continuously learning AI based algorithms / SaMD), applying to devices that undergo continuous lifecycle improvements. The intention is to promote early introduction of improved features by reducing regulatory burdens.

Singapore

Singapore's MOH (Ministry of Health) and HSA have jointly issued a draft guidance titled "Guidelines for Safe Development and Implementation of AI in Healthcare." This guidance describes important aspects, such as explainability and data quality, to keep in mind during AI/ML-based SaMD development, promotes the shared responsibility of developers and implementers in ensuring safe and effective AI/ML-based SaMD use, and proposes innovative considerations, such as the use of synthetic data for algorithm training and development. HSA's final guidance "Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach" also devotes a section to AI/ML-based devices, outlining regulatory requirements and providing change modification flowcharts.

Best Practices and Gaps in Regulation

While it is encouraging to see countries in the APAC region establishing regulatory frameworks specific for DH, it is important that such frameworks converge with global approaches and implement innovative pathways to enable timely delivery of safe and effective DH solutions to the market. Convergence of DH regulation across APAC countries will ensure greater consistency and predictability in regulatory review processes, which, in turn, will enable safe, effective, and innovative DH solutions to reach patients and healthcare professionals in an expeditious manner. Further, implementation of regulatory pathways tailored to the unique needs of DH products will foster innovation that will benefit developers and patients alike. With these concepts in mind, the following sections provide an overview of best practices for the regulation of DH.

In Table 2 below:

current regulatory framework encompasses the recommended best practices.
some guideline is currently available, however, further improvements are recommended.
the best practices are not currently adopted.

	Qualification	Risk Classification	Software with Multiple Functions	Alternative Pathways for DH	Pre-submission Consultation	Framework for AI/ML
Best Practices	**Software must have an intended purpose that fulfils the definition of a medical device in order to qualify as a medical device.**	**IMDRF's N12 guidance describes that the two key factors that should be taken into account when assessing the risk categorization of a SaMD product are: 1. State of the healthcare situation or condition that the SaMD is intended for. 2. The significance of the information that is provided by the SaMD to the healthcare decision.**	**For software products with multiple functions, regulatory authorities exercise oversight only over those functions with an intended purpose that fulfils the medical device definition.**	**Approaches to regulatory review that are tailored to the unique needs of DH products.**	**Opportunity to engage with regulatory authorities prior to premarket submission review.**	**Guidance and/or framework describing the regulation of AI/ML technologies.**
Australia (TGA)						
Japan (PMDA)						
Singapore (HSA)						

Table 2: Global DH Best practices and gaps across selected APAC countries.

SaMD Qualification

In the International Medical Device Regulators Forum (IMDRF) N12 guidance, "Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations", it is recognized that only a subset of software used in healthcare meets the definition of a medical device (i.e., qualifies as a medical device). Software must have an intended purpose that fulfils the definition of a medical device in order to qualify as a medical device. If software is used in a healthcare setting but does not have a medical purpose, such as software used to transfer information, it should not be considered as a medical device.

Examples of software functions that should not qualify as a medical device include:

- Software for the administrative support of a health care facility;
- Software for the management of prescription information;
- Software for medication adherence (treatment regimens);
- Electronic patient records;
- Software for clinical workflow and support;
- Software for education, training, or guidance;
- Software for transferring, storing, converting formats or displaying clinical laboratory test or other device data and results (medical device data systems, MDDS);
- Health information management/database systems;
- Software for maintaining and encouraging a healthy lifestyle;
- Software that extracts data from clinical trials/patient records;
- Laboratory information systems;
- Software that helps patients self-manage a specific disease/condition;
- Software that provides "class-based or population-based analyses" rather than patient-specific diagnosis or treatment;
- Low-risk clinical decision support software.

Several international regulatory authorities have introduced legislation and/or guidance to address software qualification. For example, Section 3060 of the 21st Century Cures Act in the USA clarifies those software functions that are not subject to US FDA oversight, and Health Canada has published "Software as a Medical Device (SaMD): Definition and Classification" and "Software as a Medical Device (SaMD): Classification Examples" guidance documents to clarify the types of software products that are not subject to medical device regulation. Canada and the US are well aligned in their approaches to software qualification, with software products ranging from health and wellness apps to low-risk clinical decision support software excluded from the medical device definition.

Appropriate software qualification is critical, as it enables regulators to focus their limited resources on those products that represent the highest risk to individuals and public health and reduces the regulatory burden for those developing low-risk software products. Further, it ensures that low-risk or non-medical device software will reach patients and healthcare professionals in a timely manner. As such, it is important that APAC regulators clearly articulate their expectations with respect to

software qualification, either through guidance or legislation. Global convergence with respect to software qualification is also important to ensure that software is regulated consistently across international markets.

In Australia, TGA's recent "Consultation: Scope of regulated software-based products" provides a comprehensive overview of its approach to software qualification. It outlines a risk-based approach to software qualification that excludes or exempts many types of low-risk software products, such as software that serves as electronic patient records and software used for clinical workflow and support. The Consultation also supports global convergence, taking into consideration aspects from international markets such as the US and Canada.

In Japan, PFSB/CND Notification No. 1114-5 provides a detailed overview of those software products that are and are not subject to the PMD Act. The scope of qualification outlined in the notification supports global convergence and, for the most part, aligns with international regulatory best practices. An area lacking in clarity that the notification does not take into account is low-risk clinical decision support software. While such software is addressed in software qualification guidance by the US FDA, Health Canada, and TGA, it is not addressed in this notification nor in separate guidance by MHLW/PMDA.

In Singapore, HSA's "Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach" and "Regulatory Guidelines for Telehealth Products" do not provide sufficient detail to guide stakeholders in determining when software is / is not subject to medical device regulation. In particular, stakeholders could benefit from more robust software qualification guidance that addresses topics such as low risk clinical decision support software, Laboratory Information Systems (LIS), software that digitizes publicly available guidelines, and other examples where software qualification decisions are not always clear and where flowcharts are not always useful for reaching a qualification decision. It would also be ideal if such guidance is aligned with international best practices, such as those described by the US FDA, Health Canada, and TGA, in support of global convergence.

Risk Classification

The IMDRF N12 guidance proposes a risk classification for Software as a Medical Device (SaMD) based on two factors:

1. State of the healthcare situation or condition that the SaMD is intended for.
2. The significance of the information provided by the SaMD to the healthcare decision.

State Of Healthcare Situation Or Condition	Significance Of The Information Provided By SaMD To The Healthcare Decision		
	Treat Or Diagnose	Drive Clinical Management	Inform Clinical Management
Critical	IV	III	II
Serious	III	II	I
Non-Serious	II	I	I

Table 3: IMDRF SaMD risk classification matrix.

This matrix results in four categories of risk (I, II, III, IV) that are based on the levels of impact on the patient or public health, where Category I is the lowest level of risk and Category IV is the highest level of risk. This IMDRF SaMD Risk Categorization Framework provides a risk-based approach to SaMD classification. Key to this framework is that regulators, when making classification decisions, take into account not only the state of the healthcare situation or condition that the SaMD is intended for but also the significance of the information provided by the SaMD. For example, a SaMD product that diagnoses and automatically initiates treatment for a cancer patient has a much different risk level than a SaMD product that provides publicly available information to a healthcare professional concerning possible cancer treatments for a patient.

Use of the IMDRF SaMD Risk Categorization Framework globally will create consistency in SaMD classification and support regulatory convergence. However, many regulatory authorities have found it challenging to implement this framework into their existing medical device classification systems. Rather than attempting to retroactively fit this risk categorization framework to existing medical device classification systems, it is recommended that regulators create a classification scheme specific to SaMD using IMDRF's framework as a foundation.

In Australia, TGA has created a new classification system specifically for SaMD and has indicated that the rules are broadly aligned with the EU MDR classification system, which was not developed using the IMDRF SaMD Risk Categorization Framework as a basis. In reviewing TGA's SaMD classification rules, the IMDRF factor of "state of healthcare situation or condition that the SaMD is intended for" is clearly taken into account when making a classification determination. On the other hand, the IMDRF factor of "the significance of the information provided by the SaMD to the healthcare decision" is not explicitly taken into account in the TGA SaMD classification rules. The rules do incorporate the recipient (experienced vs. inexperienced users) of a SaMD product's output in the classification decision, but this does not clearly distinguish software that is treating/diagnosing vs. driving vs. informing, as recommended by the IMDRF SaMD Risk Categorization Framework. As such, the TGA SaMD classification rules are missing a key factor that is very important in the IMDRF framework.

In Japan and Singapore, PMDA and HSA respectively, have not created classification rules unique to SaMD products or based on IMDRF's SaMD Risk Categorization Framework. Rather, both of these health authorities rely on existing medical device regulatory frameworks to classify SaMD. While these classification systems do take into account the "state of the healthcare situation or condition that the SaMD is intended for," they do not take into account "the significance of the information provided by the SaMD to the healthcare decision." Thus, an important factor is missing when making SaMD classification decisions in these countries.

In Singapore, HSA does take into account IMDRF's SaMD Risk Categorization Framework when determining the level of clinical evidence required for a SaMD product, as described in its "Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach." Specifically, the

guidance indicates that, for a SaMD product, the "level of clinical evidence required depends on the significance of the information generated by the software medical device (to treat or diagnose, drive clinical management or inform clinical management) and the state of healthcare situation or condition." Thus, although HSA does not take into account the IMDRF SaMD Risk Categorization Framework when determining SaMD classification, HSA does take the Framework into account when determining the level of clinical evidence required. This is positive and supports a globally convergent approach to SaMD clinical evidence requirements. We therefore encourage HSA to adopt a similar approach for SaMD classification that takes the IMDRF SaMD Risk Categorization Framework into account.

Software with Multiple Functions

Software products with multiple functions may break down into a significant number of applications that include medical device and non-medical device functions. In such instances, it is important that regulators appropriately qualify and evaluate the intended use of each module or function independently, as the various modules may have medical or non-medical device functionality, even while residing on the same platform.

Internationally, it has been recognized that, for software products with multiple functions, regulatory authorities should only have oversight over those functions with a medical device intended use. For example, in the EU, MDCG 2019-11 guidance ("Guidance on the Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR) states that, in a software product with multiple modules, medical device modules are subject to medical device regulatory requirements while non-medical device modules are not. In the U.S., a similar concept is included in the 21st Century Cures Act legislation, stating that the Agency shall not regulate those functions that do not meet the definition of a medical device when software has multiple functions. The US FDA provided further thinking in its guidance on "Multiple Function Device Products," which is broader than just software. In both the EU and US approaches, it is important that software developers clearly define the boundaries between medical device and non-medical device functions and assess the impact that non-medical device functions can have on medical device functions.

An example of a software product with multiple functions is a smart phone software application that detects skin cancer from photos of suspicious lesions of moles. The software application has a medical device intended purpose and is thus regulated as a medical device. The smart phone operating system and camera, however, are consumer product functions that do not have an intended use that fulfils the medical device definition. Therefore, regulatory authorities should only have oversight over the software application. Additionally, in its product development, risk assessment, and validation, it is important that the software developer assesses the impact that the smart phone operating system and camera can have on the software application performance and mitigates any risks imposed by these non-device functions.

To our knowledge, TGA, PMDA and HSA have not yet described regulatory approaches to software products with multiple functions.

Alternative Regulatory Pathways

Given the significant differences between SaMD, traditional medical devices and IVDs, it is important that health authorities consider alternative SaMD regulatory approaches tailored to their unique and iterative aspects. Such approaches will spur DH innovation, leading to advanced solutions for patients and healthcare professionals. Alternative pathways to DH regulation may take a variety of forms, such as the use of recognition and reliance models or the development of precertification type programs.

As noted in section 2, TGA supports international collaborations, leveraging recognition and reliance models. We recommend that TGA make use of assessments from comparable overseas regulators (CORs), where possible, in the regulation of DH products and that ACCESS consortium opens up a working group for collaborating to jointly regulate DH products amongst the 5-member consortium of regulators – Australia, Switzerland, Canada, Singapore and UK. Beyond recognition and reliance, it is recommended that TGA implement SaMD-specific regulatory pathways that enable more rapid deployment of significant modifications.

Japan has implemented the SAKIGAKE framework as an expedited review pathway, and this enables bringing innovative DH solutions to the market in a more expeditious manner. However, one major drawback of the SAKIGAKE designation criteria is that this regulatory track is only available to technologies developed in Japan, and it should ideally be open to technologies developed overseas. Similar to developers located in Japan, international organizations have the capability of bringing innovative products to market that could greatly benefit patients, and these organizations should be afforded a similar, accelerated review pathway so that such products can reach patients more quickly.

Japan's IDATEN process is an innovative approach to change management that enables PMDA and software developers to align on a product improvement process during premarket review so that changes post market can be rolled out in a streamlined manner. This has significant benefit for developers, as it facilitates the iterative nature of software and allows for continuous improvement during the software's product lifecycle. It also benefits regulators, as it alleviates the time and resources needed for constant review of the many potential changes associated with software products.

Like TGA, Singapore's HSA supports international collaborations, leveraging recognition and reliance models. We recommend that HSA make use of assessments from comparable overseas regulators (COR), where possible, in the regulation of DH products and that ACCESS consortium opens up a working group for collaborating to jointly regulate DH products amongst the 5-member consortium of regulators – Australia, Singapore, Canada, Singapore and UK. Beyond recognition and reliance, it is recommended that HSA implement SaMD-specific regulatory pathways that enable more rapid deployment of significant modifications.

Framework for Artificial Intelligence/Machine Learning

Japan's IDATEN framework is a model that enables the rapid deployment of significant modifications for medical device products, including SaMD products. This approach is particularly suitable to SaMD products that leverage AI/ML, including those that make use of continuous learning, or adaptive, algorithms. Given its importance in supporting devices that leverage AI/ML, it is recommended that the IDATEN approach be replicated in other APAC countries.

TGA currently does not have any regulatory frameworks that specifically address AI/ML.

In Singapore, MOH/HSA's draft "Guidelines for Safe Development and Implementation of AI in Healthcare" introduces some innovative approaches for the development and implementation of AI in healthcare, such as the use of synthetic data for algorithm training and development. Further, certain regulatory pathways, such as the aforementioned IBR and ICR Evaluation Routes Solely for Standalone Medical Mobile Applications, will help to facilitate the introduction of novel, AI/ML-based SaMD solutions to the market. On the other hand, approaches to change management for AI/ML-based medical devices described in "Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach" do not consider practices, such as Japan's IDATEN, that enable the rapid implementation of significant changes after initial product clearance. It is recommended that HSA consider regulatory pathways that enable more rapid deployment of significant modifications for AI/ML-based solutions and SaMD products in general.

Overview of US FDA Advances in Digital Health Regulation

Over the last several years, the US FDA has been very active in shaping the DH regulatory landscape. In this section, we highlight best practices and gaps associated with this regulatory authority, with a particular focus on two areas: the US FDA Software Precertification Pilot Program and AI/ML-based SaMD Regulatory Approaches.

	Qualification	Risk Classification	Software with Multiple Functions	Alternative Pathways for DH	Pre-submission Consultation	Framework for AI/ML
Best Practices	Section 3060 of the 21st Century Cures Act removes five software functions from the "device" definition, including low-risk clinical decision support software. The US FDA has issued extensive guidance describing when software is and is not a medical device.	The US FDA Software Precertification Pilot Program proposes an approach to risk classification that relies on IMDRF's N12 SaMD Risk Categorization Framework.	Per Section 3060 of the 21st Century Cures Act, for a SW device with multiple functions, the US FDA only has regulatory oversight over those functions with a medical device intended use. The US FDA has also issued guidance on this topic.	The US FDA is exploring alternative approaches to software regulation, such as the implementation of a Software Precertification Program and unique approaches to the regulation of AI/ML-based SaMD products.	The US FDA has a Pre-Submission Program whereby software developers and manufacturers can seek guidance prior to regulatory submissions.	In the Discussion Paper, the US FDA has outlined innovative regulatory approaches to the regulation of AI/ML-based products.
Gaps	The US FDA currently defines "low-risk clinical decision support software" very narrowly, and there is currently no clear guidance on this topic. There are a number of different software qualification guidance documents, which can lead to confusion when making qualification decisions.	Currently, the US FDA has not created a classification system unique to SaMD products and instead relies on its existing medical device classification system. This approach does not take into account the "significance of information provided by SaMD to the healthcare decision" and leads to the up classification of lower risk software products.	N/A	The Software Precertification Program is several years away from implementation. The Agency should work to implement unique approaches to DH regulation, such as streamlined premarket reviews and widespread implementation of predetermined change controls plans, in the short term to enable DH innovation.	N/A	As with Alternative Pathways, the US FDA should consider more widespread implementation in the short term of the concepts it has described within its Discussion Paper.

Table 4: Best practices and gaps in US FDA approaches to DH regulation.

US FDA Software Precertification Pilot Program

The Software Precertification Pilot Program (Pre-Cert Program) is a voluntary pilot program the US FDA is using to inform the development of a future regulatory model that will provide more streamlined and efficient regulatory oversight of SaMD products. Recognizing that traditional medical device and IVD regulatory models are ill-suited to the short development timelines and constant change associated with SaMD products, it desires to build a more efficient and streamlined approach to SaMD regulation that is based on existing standards of safety and effectiveness. To achieve this goal, it has partnered with industry pilot participants to create, evaluate, and iterate an agile regulatory framework known as the Pre-Cert Program.

The proposed Pre-Cert Program places a significant emphasis on the software developer, as opposed to individual products which are the primary focus of the traditional premarket regulatory review process. The US FDA envisions four key components, as described in v1.0 of the Working Model:

1. Pre-Certification Through an Excellence Appraisal;
2. Review Pathway Determination;
3. Streamlined Review; and
4. Real World Performance.

These are illustrated in the Figure on the next page and further described in more detail:

Figure 6: Overview of US FDA Pre-Cert Program.

Pre-Certification Through an Excellence Appraisal

Any organization intending to market SaMD in the US could become pre-certified. Organizations that are interested would submit an application and then undergo an Excellence Appraisal, where the Agency would assess the organization's culture of quality and organizational excellence. Specifically, the US FDA would review the developer's processes and Key Performance Indicators (KPIs) in relation to five Excellence Principles:

- Clinical Responsibility
- Patient Safety
- Proactive Culture
- Cybersecurity Responsibility
- Product Quality

The Agency has identified specific domains, such as Leadership and Organizational Support, Verification and Validation, Configuration Management, etc., that have been mapped to these Excellence Principles and would be the subject of their review. If a software developer is able to demonstrate excellence in the five Excellence Principles, then it would become pre-certified. The US FDA envisions two levels of precertification: Level 1 organizations would demonstrate excellence in all five Excellence Principles and have a limited track record in developing, delivering, and maintaining products, while Level 2 organizations would demonstrate excellence in all five Excellence Principles and have a proven track record in developing, delivering, and maintaining products.

Once an organization is pre-certified, it would commit to collecting real world performance data and sharing it with the US FDA. This data would be used to assess the organization's precertification status and improve its products and processes.

Review Pathway Determination

Once an organization has been pre-certified, it needs to determine the review pathway for bringing its products to market. In the Pre-Cert Program, the review pathway is based on three key factors: 1) The Pre-Cert level of the organization (Level 1 or Level 2); 2) The risk of the SaMD product, determined using IMDRF N12 SaMD Risk Categorization Framework; and 3) If the software developer is introducing a new product or a modification to an existing product.

The US FDA has published the table below in v1.0 of the Working Model for Review Pathway Determination:

Table 4. Level of Review for Level 1 and Level 2 Precertified Organizations' SaMD

IMDRF Risk Categorization			Level of Review for Level 1 and Level 2 Precertified Organizations' SaMD		
Type	**Sub type**	**Description**	**Initial Product**	**Major Changes**	**Minor Changes**
Type IV	9	Critical x diagnose / treat	SR	L1 - SR L2 - No Review	No Review
Type IV	8	Critical x drive			
Type IV	7	Serious x diagnose / treat			
Type IV	6	Serious x drive	L1 - SR L2 - No Review	No Review	
Type IV	5	Non-serious x diagnose / treat			
Type IV	4	Critical x inform			
Type IV	3	Non-serious x drive	No Review		
Type IV	2	Serious x inform			
Type IV	1	Non-serious x inform			

Figure 7: Level of review for a Precertified Organization's SaMD.

In this model, no US FDA review is required for SaMD products that are being initially introduced to the market by pre-certified organizations if the IMDRF SaMD risk categorization for the product is sub types 1-3. If the risk categorization is sub-types 4-6, then a US FDA streamlined review is required for Pre-Cert Level 1 organizations, but no review is still required for Pre-Cert Level 2 organizations. If the risk categorization is sub-types 7-9, then streamlined review is required regardless of the Pre-Cert level. A similar approach is applied for major product changes.

The benefit of the Pre-Cert Program for software developers is demonstrated very clearly in this table. Pre-Cert organizations can bypass US FDA premarket review entirely for certain products and product changes, depending on risk class and Pre-Cert level, enabling them to bring products to the market much more quickly than using the traditional premarket review processes (such as the de novo or 510(k) processes). The status of the developer as pre-certified provides additional assurance of safety and effectiveness of the products, as do the more rigorous post-market commitments.

This approach also leverages the IMDRF N12 Risk Categorization framework, adding an element of global harmonization/standardization to the approach.

Streamlined Review

For those SaMD products that must go through premarket review, the US FDA envisions a streamlined review pathway that maintains the current evidentiary standard but enables faster review times. To achieve this, the Agency foresees a more interactive review process that involves the use of product demonstrations and prototypes and also incorporates automation, where possible. Additionally, the Agency desires to remove duplication of information, and therefore intends to focus on product-specific elements and use information from the Excellence Appraisal and Real World Performance data to support some of the premarket review requirements.

Real World Performance

All Pre-Cert organizations will be required to demonstrate a robust program for monitoring real world performance data and sharing this data with the US FDA. This real world data will come in two forms: product performance and organizational performance. With respect to product performance, the US FDA will focus on three main categories: Real World Health Analytics (including human factors and usability engineering, clinical safety, and health benefits), User Experience Analytics (including user satisfaction, issue resolution, and user engagement), and Product Performance Analytics (such as cybersecurity and product performance). With respect to organizational performance, the Agency will review how an organization continuously operates in relation to the five Excellence Principles. Developers will be expected to share Real World Performance plans with the Agency and be very proactive in monitoring the safety and effectiveness of their SaMD products.

The US FDA initiated its Pre-Cert Pilot Program in July, 2017, published v1.0 of the Working Model in January, 2019, and has continued to iterate and evolve the various components of the Pre-Cert Program as it has gained experience through test cases and interactions with stakeholders. It should be noted that, at the time of this publication, the Pre-Cert Program is not final, and the Agency has indicated that it will continue to assess and evaluate the readiness of the Program before progressing to the next phases of development. Challenges that the US FDA must overcome include making the Excellence Appraisal process sustainable and scalable, implementing solutions to enable the sharing of Real World Data, and ensuring legislative authority for Program realization. As a result, implementation of the Program is still several years away.

This Program is one example of a regulator's effort to develop a novel regulatory framework tailored to the unique and iterative needs of SaMD products. While such a model may not be suitable for all countries and regions, health authorities should be encouraged to explore alternative, fit-for-purpose regulatory pathways for SaMD products.

Regulatory Approaches for AI/ML-based SaMD

The US FDA has also issued a Discussion Paper related to AI/ML-based SaMD. While this Discussion Paper describes independent considerations for such software, it does reference the US FDA Pre-Cert Program effort. Specifically, it describes a Total Product Lifecycle approach that is very similar to Pre-Cert Program and is critically important for AI/ML-based SaMD due to its ability to adapt and improve from real-world use.

The US FDA will assess the culture of quality and organizational excellence of a software developer and have a reasonable assurance of the high quality of their software development, testing, and performance monitoring. A figure in the Discussion Paper describing this approach (reproduced below) demonstrates how the Agency would apply the Pre-Cert model to AI/ML-based SaMD.

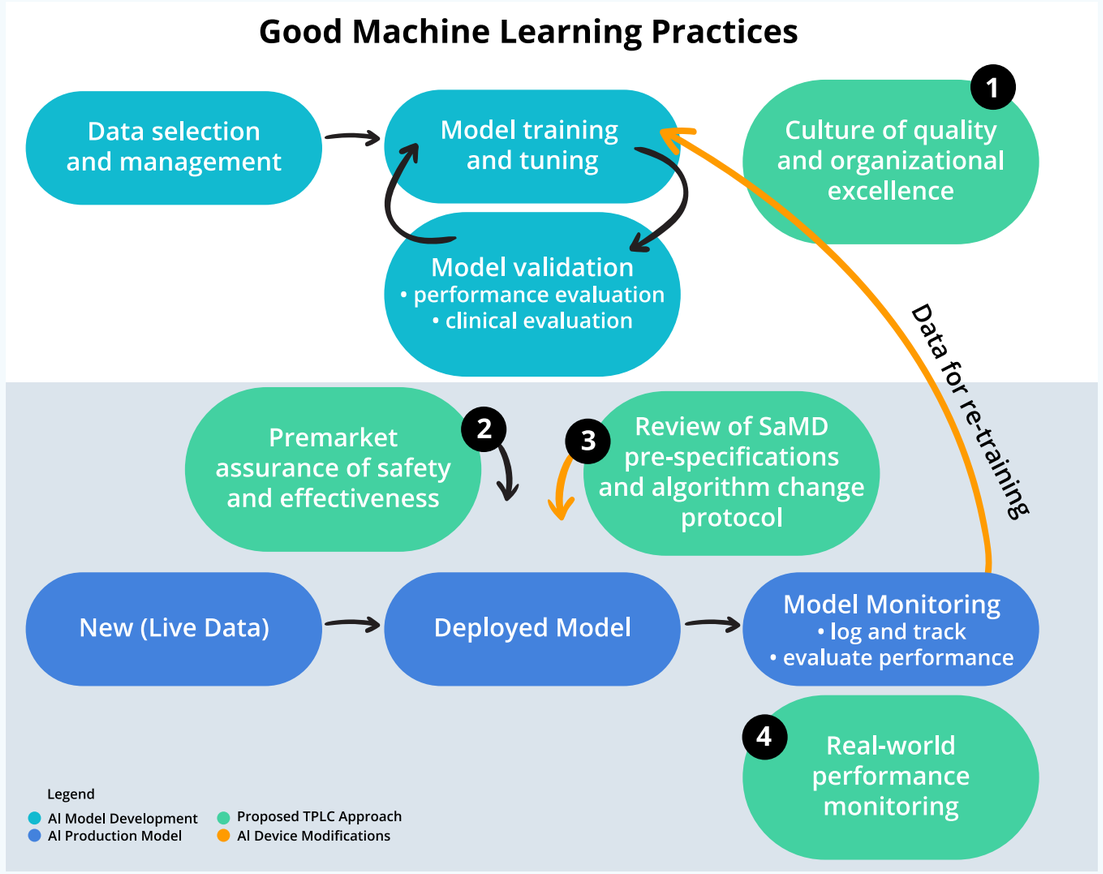


Figure 8: Approach to Good Machine Learning Practices Described in US FDA AI/ML Discussion Paper.

The Discussion Paper also describes an important approach for addressing future modifications to an AI/ML-based SaMD product in premarket submissions. Specifically, the Discussion Paper presents the concept of a "predetermined change control plan." In such a plan, a software developer would outline the modifications it plans to make in future versions of its software ("what" the software developer plans to change) in a SaMD Pre-Specifications document (SPS) and the methods the developer will use to achieve and appropriately control the risks of the anticipated types of modifications outlined in the SPS ("how" the software developer will verify/validate the change) in an Algorithm Change Protocol (ACP). The software developer then includes this predetermined change control plan as a part of its premarket submission and, when the US FDA clears the SaMD product for commercialization, it also clears the predetermined change control plan. This enables the software developer to launch significant changes to its software post-clearance without having to go back to the US FDA for premarket review, as long as the changes are within the scope of the predetermined change control plan that has been approved by the Agency. US FDA depicts this important concept in an illustration in their Discussion Paper:

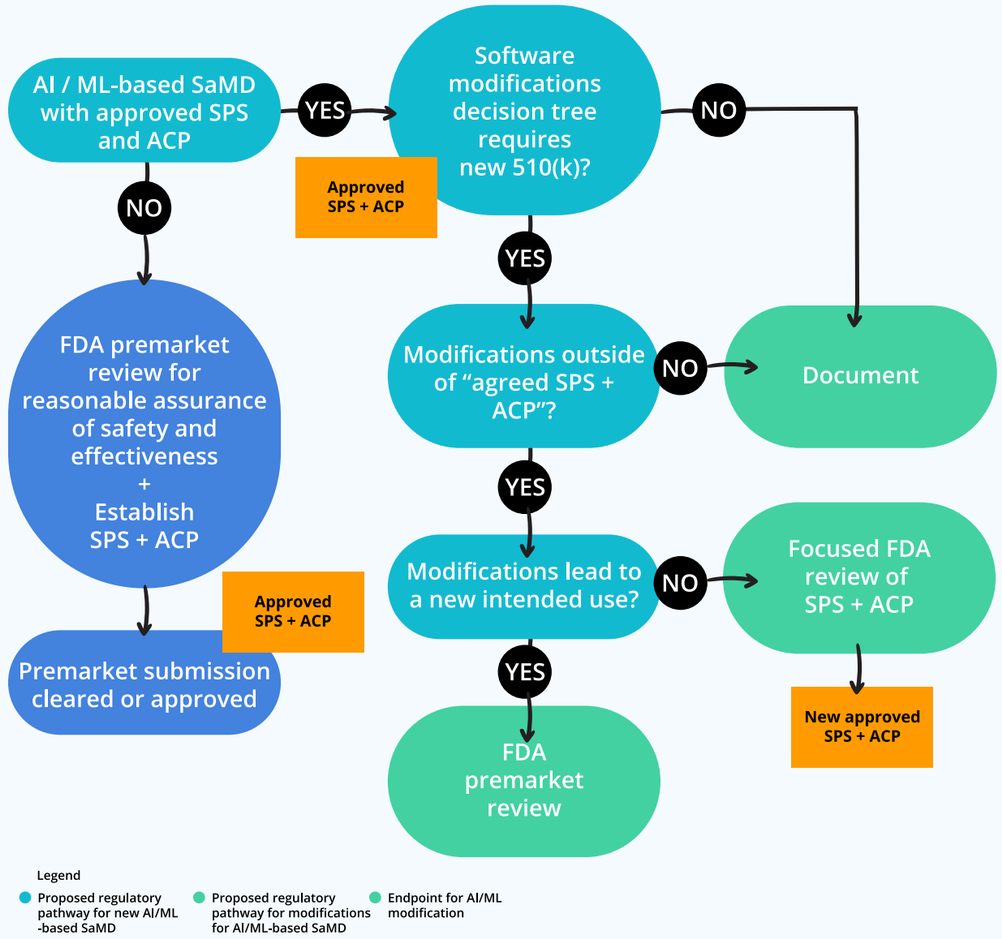


Figure 9: Modifications based on SaMD Pre-Specifications and Algorithm Change Protocol.

Essentially, once an SPS and ACP are approved as a part of a submission, the software developer can make changes to its software according to its SPS and ACP and document these changes according to its Quality Management System. If the software developer desires to make a change outside of the SPS and ACP, then it can amend the SPS and ACP for review by the Agency and subsequently make changes according to the revised SPS and ACP once the Agency has approved them.

Such a predetermined change control plan would be very valuable to developers of AI/ML-enabled SaMD products, and developers of SaMD products in general (the US FDA has also employed a similar approach for the regulation of Next Generation Sequencing[2]).

By defining in an initial premarket submission the scope of future changes and how the risks associated with such changes will be controlled, a software developer can gain agreement up front with the Agency regarding the implementation of future SaMD modifications. Once the initial product is cleared and the predetermined change control plan is approved, the software developer can roll out changes without having to wait for lengthy premarket reviews by the Agency. Such an approach greatly facilitates the iterative nature of software, particularly continuously learning AI/ML-enabled software, and is very similar to Japan's previously described IDATEN approach.

It is also important to highlight that the predetermined change control plan described within the US FDA's AI/ML Discussion Paper is more than just a concept: it has been implemented in at least two submissions involving SaMD products. DEN180001, a de novo submission for an ML-based SaMD that is intended for diagnostic screening of diabetic retinopathy, and DEN190040, a de novo submission for a Caption Guidance SaMD product that is intended to assist users in collecting high quality images, both reference predetermined change control plans within their respective decision summaries. We encourage other regulatory authorities to adopt a similar concept, as such an approach greatly enables the iterative nature of SaMD products.

US FDA Digital Health Best Practices

- The US FDA Pre-Cert Program represents one regulator's effort to create a novel regulatory framework tailored to the specific needs of software. We recommend that regulatory authorities explore similar, unique approaches to the regulation of SaMD, recognizing that the Pre-Cert Program may not be the most suitable option for all countries. In such instances, other options are available, such as the use of predetermined change control plans, that regulatory authorities can implement immediately under existing regulatory frameworks. Other options supporting the speed of innovation and iteration of SaMD products include recognition and reliance models and expedited review pathways.

[2] See "CDRH's Approach to Tumor Profiling Next Generation Sequencing Tests"; https://www.fda.gov/media/109050/download

- It is important to note that, when considering the importance of novel regulatory frameworks for SaMD products, a special focus should be placed on product modifications. Software iterates so frequently that, in order to promote innovation, health authorities need to have a streamlined regulatory approach for software modifications. Concepts such as a predetermined change control plan enable SaMD iteration while also ensuring device safety and effectiveness.

- Regulatory authorities are encouraged to consider novel approaches to the review of SaMD products, such as relying on product demonstrations and prototypes, carrying out interactive reviews, and relying on IMDRF principles, all in an effort to create a more predictable and efficient review process.

- A key aspect of the Pre-Cert Program is a reliance on the IMDRF SaMD Risk Categorization Framework in determining product risk and the need for independent, premarket review. We encourage regulatory authorities to rely on this IMDRF framework for creating a standardized approach to the evaluation of SaMD.

Use Cases

Both Pear Therapeutics and Digital Diagnostics are companies that went through the regulatory approval process for a DH solution. In this paper, we will identify the key success factors for approval. The example of Pear Therapeutics is particularly relevant in the context of this paper as it applies to both the US and the APAC region.

reSET®, Pear Therapeutics

Pear Therapeutics is a biotechnology and software company headquartered in Boston. It produces prescription digital therapeutics (PDT) for psychiatric and neurological diseases and was the first company to receive US FDA clearance (DEN160018) for a PDT – reSET®[3]. In June 2020, the Health Sciences Authority (HSA) in Singapore approved reSET® (DE0504590) as a prescription-only treatment to adults with substance use disorder (SUD)[4]. It was the first time Singapore had authorised a PDT, and it is the first country after the USA to approve Pear Therapeutics' solution.

reSET® comprises a patient application and a clinician dashboard intended to deliver cognitive behavior therapy (CBT) to patients with SUD. It consists of several therapy lessons (modules) and, after the lessons, patients undergo fluency learning. The clinician can use the dashboard to view the therapy lessons that the patient has completed, as well as patient-reported substance use, cravings, and triggers.

[3]https://peartherapeutics.com/
[4]https://peartherapeutics.com/pear-therapeutics-announces-market-authorization-of-reset-from-the-health-science-authority-in-singapore-for-the-treatment-of-adults-with-substance-use-disorder/

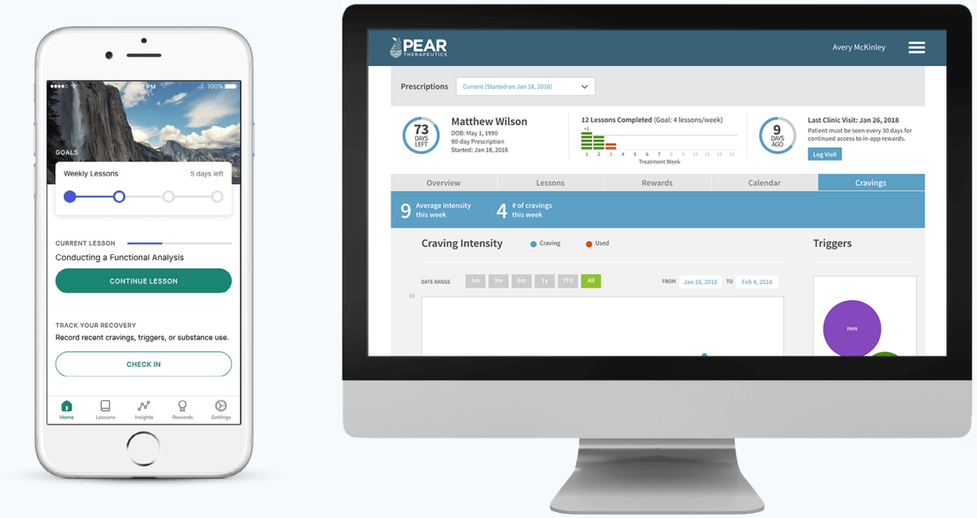


Figure 10: reSET® patient-facing smartphone application and clinician-facing dashboard.

reSET® is intended to provide cognitive behavioral therapy, as an adjunct to a contingency management system, for patients 18 years of age and older who are currently enrolled in outpatient treatment under the supervision of a clinician. reSET® is indicated for a 12 week (90 days) prescription-only treatment for patients with SUD, who are not currently on opioid replacement therapy, who do not abuse alcohol solely, or who do not abuse opioids as their primary substance of abuse. It is intended to:

- increase abstinence from a patient's substances of abuse during treatment, and
- increase retention in the outpatient treatment program.[5]

US FDA Classification Summary:

Regulation Number: 21 CFR 882.5801
Classification: Class II
Generic Device Type: Computerized Behavioral Therapy Device for Psychiatric Disorders
Definition: A computerized behavioral therapy device for psychiatric disorders is a prescription device intended to provide a computerized version of condition-specific behavioral therapy as an adjunct to clinician supervised outpatient treatment to patients with psychiatric conditions. The digital therapy is intended to provide patients access to therapy tools used during treatment sessions to improve recognized treatment outcomes.

reSET® is subject to special controls and general controls to ensure device safety and effectiveness. To achieve clearance, Pear Therapeutics provided evidence that it had fulfilled design control requirements during reSET® development through actions such as requirements management, hazard analysis, and verification and validation activities.

[5] https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160018.pdf
https://www.resetforrecovery.com/recovery-challenges

Additionally, Pear was required to ensure appropriate product labelling, implementing aspects such as a warning that the device should not be used as a standalone therapy, a statement that the software does not represent a substitution for a patient's medication, and a description of compatible mobile devices.

Pear Therapeutics also conducted an extensive clinical validation study to demonstrate the effectiveness of reSET® in providing cognitive behavior therapy when used as an adjunct to a contingency management system for patients with SUD.

Given that reSET® was the first digital therapeutic to be cleared by the US FDA, Pear Therapeutics had to navigate uncharted regulatory territory. The process was an arduous one as Pear had to create a new class of product that focused on delivering therapy as opposed to providing diagnostic or monitoring information like many medical device software products[6].

"The process was long because we were creating a new classification. It was a new area, with lot of education needed."

In the discussion with the US FDA, the key success factor was to be able to define the product's intended use. Having a therapeutic indication for reSET® was clearly a milestone for Pear Therapeutics.[7]

After obtaining US FDA clearance, having open discussions with HSA allowed Pear Therapeutics to understand the regulator's requirements concerning such a new product, enabling a smoother registration process in Singapore. Collaboration has been clearly pivotal to facilitate access to this digital therapeutic.

IDx-DR, Digital Diagnostics

Digital Diagnostics[8] is a leading AI diagnostic healthcare technology company located in Iowa in the USA. Digital Diagnostics's first US FDA-cleared product is a software-as-a-medical device product called IDx-DR. This software leverages deep learning algorithms to automatically detect more than mild diabetic retinopathy (mtmDR) in adult patients diagnosed with diabetes. After a De Novo submission that included results from a rigorous prospective, preregistered clinical study at primary care sites across the United States, IDx-DR became the first US FDA-cleared AI diagnostic system to make a diagnosis without physician input.

[6] APACMed interview with Pear Therapeutics
[7] APACMed interview with Pear Therapeutics
[8] https://dxs.ai/

The figure below provides an overview of the operation of the IDx–DR product:

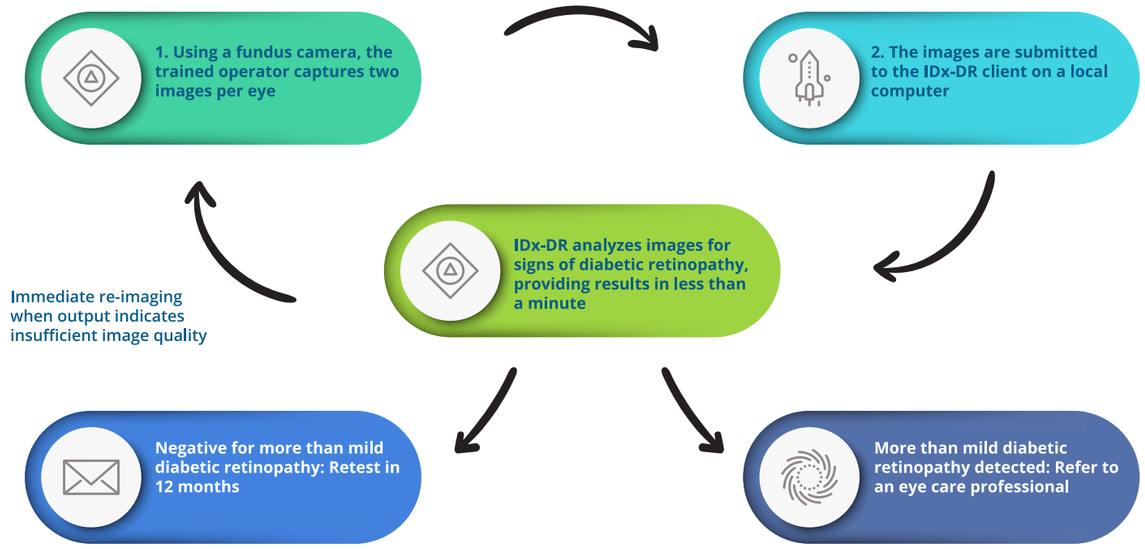


Figure 11: Mode of operation for the IDx–DR product.

A trained operator uses a fundus camera to capture images of the eye, and these images are sent to the IDx–DR software. The IDx–DR software analyzes the images for signs of mtmDR. If the results are negative, the software recommends the patient for retesting in 12 months. If the results are positive, the patient is recommended to a healthcare professional.

IDx-DR is intended for use by health care providers to automatically detect mtmDR in adults (22 years of age or older) diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy. IDx-DR is indicated for use with the Topcon NW400.[9]

US FDA Classification Summary:
Regulation Number: 21 CFR 886.1100
Classification: Class II
Generic Device Type: Retinal Diagnostic Software Device
Definition: A retinal diagnostic software device is a prescription software device that incorporates an adaptive algorithm to evaluate ophthalmic images for diagnostic screening to identify retinal diseases or conditions.

Like Pear's reSET®, IDx–DR was cleared by the US FDA through the De Novo regulatory pathway. To achieve clearance, Digital Diagnostics provided evidence of software verification and validation, including information related to hazard analysis, analysis of residual bugs and anomalies, and performance testing. Additionally, Digital Diagnostics created a training program to ensure users

[9] https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN180001.pdf

could collect images of sufficient quality for use with IDx–DR and validated this training program through human factors and clinical validation testing. The IDx–DR team also conducted a rigorous clinical validation study, evaluating the performance of the product across 10 different primary care sites with a range of patients representing different ages, genders, ethnicities, and HbA1c levels. The product demonstrated levels of sensitivity, specificity, and imageability sufficient to secure a diagnostic screening claim.

One additional special control that was implemented for IDx–DR was a predetermined change control plan. Digital Diagnostics desired to make future algorithm improvements, and this predetermined change control plan was used to establish an understanding with the US FDA during premarket review regarding the types of changes that may be considered significant/major changes. The plan describes the level of change in device specifications that could significantly affect safety and effectiveness of the product and trigger a new premarket submission. Such an approach enables Digital Diagnostics to streamline its approach to change management and roll out changes to IDx–DR with greater predictability and in a more efficient manner.

For both Pear Therapeutics and Digital Diagnostics, balancing speed of approval with outcomes, quality, safety, and effectiveness is crucial to expedite the approval process for innovative solutions. This allows more patients to achieve improved health outcomes and better quality of life. However, as the space is new, regulators are still working to find the best way to increase the speed of premarket evaluation without lowering the safety and effectiveness bar. As such, it will be important to harmonize the regulatory requirements and/or leverage recognition and reliance models to enable international approvals in supporting product commercialization in different countries. In our analysis of the reSET® and IDx–DR use cases, we identified three major key learnings:

1. **Collaborate.** It is critical to engage and work together with the regulatory agencies. Manufacturers need to help regulators understand how the digital solution is developed and how it will be used. Regulators, in turn, should communicate the requirements for the solution to meet safety and efficacy standards and to prove the positive outcomes on a patient's health. Pre-submission meetings are vitally important in this respect.

2. **Harmonize.** It is desirable to have a common regulatory framework for DH solutions across different countries and ideally across regions. In this way, an innovative solution can be launched in multiple markets, optimizing manufacturer and regulator time and resources.

3. **Leverage.** In the absence of harmonized regulations, a country's regulatory agency could leverage the work undertaken to approve a certain product in another country. Mutual registration recognition or similar requirements for regulatory submission dossiers would allow products to be launched quickly throughout the APAC region.

Best Practices Framework

Based on a comprehensive assessment of the considerations described within this paper, we outline below best practices that health authorities should apply when implementing fit-for-purpose, risk-based digital health regulatory frameworks:

Fundamental Building Blocks for a Software-Focused Regulatory Framework

- Implement a clearly described approach to software qualification (determining when software is SaMD) whereby the health authority only has oversight over those software functions that have a medical device intended use. This approach should leverage international best practices such as those used in the US, Canada, and Australia.

- Create an approach to classification that is SaMD-specific, does not leverage existing classification schemes developed specifically for traditional medical devices, and is based on IMDRF's N12 SaMD Risk Categorization Framework. Specifically, the "state of healthcare situation or condition" and "the significance of information provided by the SaMD to the healthcare decision" must be taken into account when making SaMD classification decisions.

- For software products with multiple functions, implement policies by which the health authority only exercises regulatory oversight over those functions with a medical device intended use.

Pathways to Support Rapid Regulatory Review of SaMD Products and Their Modifications

- Implement recognition and reliance models, making use of regulatory assessments from comparable overseas regulators when conducting DH regulatory decision-making.

- Streamline regulatory pathways for the introduction of SaMD products and their modifications, such as developing expedited review pathways and endorsing the use of predetermined change control plans.

- Consider unique regulatory approaches tailored to the iterative nature of SaMD solutions that leverage artificial intelligence.

Collaboration and Convergence Opportunities in the APAC Region

- Support DH regulatory global convergence through the recognition and adoption of internationally recognized guidance documents and standards, such as those developed by IMDRF and ISO.
- Collaborate with software developers through Pre-Submission Consultations.
- Partner with industry through industry associations, private-public consortiums, and other fora to share best practices and evolve the DH regulatory landscape to enable the safe, effective, and timely delivery of innovative solutions benefiting healthcare professionals and patients.

Authors & Contributors

Jinyao Su
Diagnostics Development Hub – Regulatory Affairs Manager

John Thornback
Diagnostics Development Hub – Chief Operating Officer

Manan Hathi
Stryker – Sr. Manager, Regulatory Affairs – Software

Nathan Carrington
Roche Diagnostics – Head of Digital Health and Innovation, Global Regulatory Policy and Intelligence

Roberta Sarno
APACMed – Digital Health Manager

Varun Veigas
Roche Diagnostics – Regional Regulatory Affairs and Policy Lead, Asia Pacific

APACMed Digital Health Regulatory Working Group Members

Aileen Lai
Healthbeats – CEO

Alvin Hew
Smith & Nephew – Vice President, Marketing, Orthopaedics, APAC

Anantha Narayanan
Johnson & Johnson – Technology Regulatory Compliance

Aneesh Sathe
Qritive – CEO

Angeline Gog
Health BETA – Finance

Anju Vaishnava
Roche – Head Regulatory Affairs

Antoine Audry
Resmed – VP Global RA

Antoinette Patterson
Safespace – Cofounder and CEO

Asok Kumar Raghavan Nair
Abbott – Quality and Regulatory Director - Global Strategic Regulatory Affairs

Ching Hwee
Johnson & Johnson – Regulatory Affairs

Chloe Tan
Medtronic – QRA Lead | SEA Country Cluster 2

Dhruv Suyamprakasam
iCliniq – Founder

Encey Yao
Qritive – Regulatory Manager

Gloria Bustos
Baxter – Head of PV EMEA & APAC / Global Patient Safety

Grace Wong
Johnson & Johnson – Regulatory Affairs Lead

Hemant Sonawane
Ortho Clinical Diagnostiscs – Sr. Manager QA & RA ASPAC

Jacqui Cui
Abbott – RA Director

Jessica Liu
Steris – Regulatory Affairs and Compliance Manager, Asia Pacific

JinHo Jang
Abbott – RAQA Manager

Julien Willeme
Medtronic – Legal Director

Kae Yuan Tan
Health BETA – Senior Manager

Kayla Thum
Resmed – Regulatory Affairs

Linyan Tong
Draeger – Senior Regulatory Affairs & Clinical Affairs Manager

Mandy Kim
Johnson & Johnson – Lead, Regulatory Affairs

Marianne Yap
Align – RA Director

May Chen
Hologic –

Olaf Rusoke-Dierich
JD Sanmed – Founder

Pai Lin Lai
Siemens Healthineers – Head regulatory affairs ASEAN

Paul Chua
BD – CyberSecurity Officer, Greater Asia

Sandy Xiong
BBraun – Registration Affairs Manager

Sharad Shukla
Johnson & Johnson – Head Regulatory Affairs, SEA (Medical Devices)

Sheila Devi
Johnson & Johnson – Senior Manager Quality & Compliance

Shivkumar Hurdale
Stryker – Director Govt Affairs, Regulatory Affairs and QA

Steven Bell
Siemens Healthineers – Senior Vice-President Diagnostic Imaging and Digital Health, Asia-Pacific

Sufian Yusof
Safespace – Director of BD

Victoria Qu
Abbott – Director Regulatory Affairs Global Strategic Regulatory

Winson Teng
BD – Senior Executive Regulatory Affairs (Premarket, GA)

Xin Li
Johnson & Johnson – RA Associate Director

Xinyang Loo
Iota Medtech – Product Manager

Yinghui Gao
Siemens Healthineers – Regulation and Standards Manager

Yi-Shao Liu
Helios – VP/R&D

References

I. EU, MDCG 2019-11 – Guidance on the Qualification and Classification of Software in Regulation (EU) 2017/745 MDR and Regulation (EU) 2017/746 – IVDR

II. Health Canada – Guidance Document: Software as a Medical Device (SaMD): Classification Examples

III. Health Canada – Guidance Document: Software as a Medical Device (SaMD): Definition and Classification

IV. HSA – Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach

V. HSA – Regulatory Guidelines for Telehealth Products

VI. HSA – GN-13: Guidance on the Risk Classification of General Medical Devices

VII. HSA – GN-15: Guidance on Medical Device Product Registration

VIII. MoH & HSA - Guidelines for Safe Development and Implementation of AI in Healthcare - Draft

IX. IMDRF/SaMD WG/N12 FINAL:2014 – "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations

X. TGA – Consultation: Scope of Regulated Software based products

XI. TGA – Consultation: Regulation of Software, including SaMD

XII. US FDA – Developing a Software Precertification Program: A Working Model

XIII. US FDA – Multiple Function Device Products: Policy and Considerations

XIV. US FDA – Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)

XV. PMD Act Amendment (2019) - December 4, 2019, the amended Pharmaceuticals and Medical Devices (PMD) Act was published in Japan

XVI. MHLW – Strategy of SAKIGAKE

XVII. MHLW – IDATEN Framework

APACMed
The voice of MedTech

About APACMed

The Asia Pacific Medical Technology Association (APACMed) represents manufacturers and suppliers of medical equipment, devices and in vitro diagnostics, industry associations, and other key stakeholders associated with the medical technology industry in the Asia Pacific region. APACMed's mission is to improve the standards of care for patients through innovative collaborations among stakeholders to jointly shape the future of healthcare in Asia-Pacific. In 2020, APACMed established a Digital Health Committee to support its members in addressing regional challenges in digital health. For more information, visit www.apacmed.org.

2 Science Park Drive Ascent Tower, #02-03 Science Park 1 Singapore 118222 T(65) 6816 3180