APACMed
The voice of MedTech

Digital Health Regulation in Asia-Pacific

China and Korea

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Introduction

The Asia-Pacific Medical Technology Association (APACMed), trade association for the MedTech industry in Asia-Pacific (APAC), formally launched its Digital Health Committee in 2020. Given the rise in the adoption of Digital Health (DH) solutions in the region, especially as a result of the COVID-19 pandemic, the focus of the committee is to seek greater harmonization around topics such as interoperability, cybersecurity, and regulation.

On the latter, in January 2021, APACMed published its inaugural *Digital Health Regulation in Asia-Pacific: Overview and Best Practices* report[1] (https://apacmed.org/digital-health-regulation-in-asia-pacific-overview-and-best-practices/) calling for the development and convergence of tailored, risk-based software regulatory frameworks across APAC markets. The report highlights that implementation of such frameworks will enable greater access to software innovation, better use of limited regulatory resources, and ultimately empower countries in the APAC region into the next generation of personalized healthcare with more informed decision-making and improved outcomes. Such an achievement will benefit regulators, software developers, and, most importantly, patients.

The original report highlights the DH regulatory activities in leading markets in APAC like Australia, Japan, and Singapore, identifying best practices and gaps, and drawing comparisons to forward-thinking DH regulation from abroad such as in the United States. As a follow-up to the original effort, APACMed has expanded its review of DH regulation best practices and gaps to include those of the China and Korea markets. China and Korea are mature socioeconomic nations seen as leading-edge in their adoption of new technologies and techniques. Further, their MedTech regulatory authorities, the National Medical Products Administration (NMPA) and the Ministry of Food and Drug Safety (MFDS), respectively, are active in exploring regulatory approaches for DH solutions.

Within this report, APACMed reviews the China and Korea DH regulatory approaches alongside international best practices, reiterating the framework for fit-for-purpose regulation of DH solutions. In addition to reviewing published guidance, regulations, and other literature, the authoring team spoke directly to in country regulators and software developers to inform the paper's content.

The ultimate purpose of the paper is the same as that of the original:

To provide regulators with recommendations that enable the implementation of a harmonized framework, supporting the introduction of safe and effective DH solutions at a pace that matches the speed of innovation, for the benefit of regulators, software developers, and patients.

Thematic Best Practices: Assessment Areas of Focus

As in the original APACMed report, the following six key areas are used to assess the DH regulatory frameworks of China and Korea:

01
Software Qualification

Regulatory authorities should clearly articulate, through guidance or regulation, those software functions that do not qualify as a medical device. Approaches to software qualification should align with international best practices and ensure that software functions, such as those used for administrative support of a healthcare facility, general wellness purposes, transferring and displaying information, clinical workflow, and non-device clinical decision support, are not considered as medical devices.

02
Software Classification

Regulators should implement an approach to Software as a Medical Device (SaMD) classification that is SaMD-specific and takes into account the unique aspects of software products. Such an approach should be based on the International Medical Device Regulators Forum (IMDRF) SaMD framework described in its N12 guidance, "'Software as a Medical Device': Possible Framework for Risk Categorization and Corresponding Considerations." SaMD classification should be based on two factors:

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

Taking these two factors into account results in four categories of risk, as shown in Table 1[2].

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 1. IMDRF SaMD Risk Categorization Matrix[2]

03
Software with Multiple Functions

Software products with multiple functions may break down into a number of applications that include medical device and non-medical device functions. For such products, it is important that regulators have clearly articulated approaches by which they evaluate the intended use of each function independently, as the various functions may have medical or non-medical device functionality even when residing on the same platform. Regulators should exercise oversight only over those functions with an intended purpose that fulfills the medical device definition.

04
Alternative Pathways for DH Regulation

Given the significant differences between SaMD and traditional medical devices (including In-Vitro Diagnostics, or IVDs), regulators should consider alternative approaches to SaMD regulation that are tailored to their unique and iterative aspects. Such approaches may take a variety of forms and can include the use of recognition and reliance models, expedited review pathways, pre-certification type programs, and predetermined change control plans.

05
Pre-Submission Consultation (PSC)

Regulators should have programs in place that encourage and support the use of PSCs to enable software developers (and device manufacturers in general) to discuss specific aspects of a future regulatory submission, so as to ensure that statutory requirements will be fulfilled.

06
Framework for Artificial Intelligence / Machine Learning (AI/ML)

The use of AI/ML in the development and commercialization of DH solutions is becoming more widespread. Regulators should ensure that AI/ML-based SaMD products are regulated based on their intended use and not unnecessarily burdened with regulatory requirements simply because they leverage AI/ML. Further, regulators should implement novel approaches to the regulation of AI/ML-based SaMD products, particularly with respect to change management, that foster innovation and enable safe, effective AI/ML solutions and their modifications to reach patients and healthcare professionals in an expeditious manner.

China and Korea – Digital Health Regulation Status, Best Practices, and Gaps

DH and its regulation are evolving quickly, with many markets in APAC establishing regulatory frameworks specific for DH solutions. However, these frameworks should converge with global approaches and include innovative pathways that enable timely delivery of safe and effective DH solutions to the market.

The table below provides a summary of the current regulatory status of China and Korea in relation to best practices for the regulation of DH solutions. The best practices have been introduced in the inaugural APACMed report and are based on the six assessment areas described in the previous section[1]. Following the table, we provide a detailed analysis of the DH regulatory approaches in China and Korea, and identify best practices and gaps.

	Qualification	Risk Classification	Software with Multiple Fuctions	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 solutions.	Opportunity to en-gage with regulato-ry authorities prior to premarket sub-mission review.	Risk-based guidance and/or framework suited to the unique regulatory challenges posed by AI/ML technologies.
China (NMPA)						
Korea (MFDS)						

Table 2 - Comparing the APACMed DH regulation best practices with the current state in China and Korea[1]

The best practices are not currently adopted

Some guideline is currently available, however, further improvements are recommended

Current regulatory framework encompasses the recommended best practices

Best Practice Theme 01 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 as such. Software must have an intended use that fulfills the definition of a medical device in order to be considered as a medical device.

China

Information describing NMPA's approach to software qualification can be found dispersed throughout various guidance documents. For example, in *Guidelines for Technical Review of Medical Device Software (Exposure Draft, Edition II)*, NMPA distinguishes between medical device and non-medical device software functions, and provides examples of non-medical device software functions such as software used for administrative purposes[3]. In *Guidelines for Classification and Definition of AI-Based SaMD*, NMPA notes that whether or not software is considered a medical device is based on its intended use, while taking into account its processing object, core functions, and other factors[4]. The guidance provides three specific examples of software products that are not regulated as a medical device:

- Software used to process non-medical device data (such as patient complaints and test report conclusions);
- Software having a core function that is not to process, measure, model, calculate, and analyze medical device data;
- Software that is not intended to be used for medical purposes.

Additionally, in *Guidelines for Technical Review of Mobile Medical Device Registration*, NMPA indicates that mobile software products intended for exercise, fitness, weight control, and healthy lifestyle management are not medical devices, while those intended for patient rehabilitation, medical treatment, disease management, and other similar purposes are medical devices. The guidance makes it clear that the intended purpose of the software is the driving factor in determining whether or not mobile software is a medical device.[5]

These concepts are well aligned with international best practices to software qualification, where software functions that do not have a medical device intended purpose (such as functions that aggregate and display medical information) are not considered medical devices. However, stakeholders could benefit from more cohesive, comprehensive guidance related to software qualification in China. For example, the software qualification approaches described in the various guidance documents could be consolidated into a single guidance for ease of understanding and reference. Further, NMPA's qualification approach to other common software applications, such as

non-medical device clinical decision support software or medical device data systems (MDDS), could be elaborated upon. Therefore, NMPA is encouraged to publish guidance that clearly articulates its approach to software qualification and to ensure alignment with international best practices, in which software must have an intended purpose that fulfills the definition of a medical device in order to qualify as a medical device.

Korea

Similar to NMPA, Korea's MFDS does not have specific guidance nor regulation dedicated solely to the topic of software qualification. However, in its guidance document *Determination of Medical Device Eligibility for Products in the Border Area Between Medical Devices and Industrial Products*, MFDS indicates that software that only deals with general patient-related data and is not used for direct diagnosis and treatment is not considered as a medical device. As described in the guidance, examples of such software include prescription delivery systems, electronic medical records (EMR), and electronic health records (EHR).[6] MFDS further elaborates on its approach to determining when software is and is not considered a medical device in its *Guideline on Review and Approval of Artificial Intelligence (AI) and Big Data Based Medical Device*. Specifically, the basis for determination is the product's intended use (in relation to the definition of "medical device" in Article 2 of the Medical Devices Act) and the hazard it presents[7]. The guidance document also provides several examples of software functions that MFDS does not consider as medical devices, such as:

- Software that supports administrative work of a medical institution (e.g., management of wards and inventory, handling of electronic procedures, etc.);
- Software intended for exercise, leisure activities, and general health care;
- Software for education/research purposes;
- Software intended for managing medical records which are not related to treatment and diagnosis of diseases; and
- Software that provides a tool to organize and trace health/treatment information of a patient by a medical professional, or that helps a medical professional easily find medical information.

The non-medical device software functions that MFDS describes are consistent with international best practices with respect to software qualification. However, the examples should be expanded to include other software functions that do not qualify as a medical device, such as software used to transfer, store, and display clinical laboratory test results, unless the software is intended to interpret or analyze such results (often referred to as Medical Device Data Systems, or MDDS) and non-medical device clinical decision support software. It is therefore recommended that MFDS conduct a comprehensive review of its approach to software qualification to ensure robustness and that it aligns with international best practices.).

Best Practice Theme 02 Risk Classification

Risk classification is a very important concept for medical devices and IVDs, as a device's risk class determines its premarket and postmarket regulatory requirements. For SaMD products, regulators should leverage IMDRF's N12 guidance when making classification decisions and take two key factors into account:

1. The state of the healthcare situation or condition that the SaMD is intended for; and
2. The significance of the information provided by the SaMD to the healthcare decision.[2]

China

In China, SaMD products are classified in the same manner as traditional medical devices according to the *Rules for Classification of Medical Devices*. These Rules describe a risk-based approach in which medical devices are categorized, at increasing levels of risk, as Class I, Class II, or Class III (as outlined in Table 3 below). The Rules indicate that a medical device's classification is determined by its intended purpose, structural characteristics, pattern of use, status of use, and whether it contacts the body[8].

Classification	Description
Class I	Low-risk devices; safety and effectiveness ensured through fulfillment of routine quality system requirements.
Class II	Medium-risk devices; require controls to ensure safety and effectiveness.
Class III	High-risk devices; must be strictly controlled to ensure safety and effectiveness, such as those devices implanted into the human body and those used to support or sustain life.

Table 3 - NMPA Approach to Medical Device Classification[8]

The Rules also provide an Annex containing a "Table for Determination of Medical Device Classification." This table (reproduced in Table 4 below) is intended to assist stakeholders in classification decisions and has a section devoted to standalone software.

Non-Body-Contacting Device				
Non-Active Device	Status Of Use / Patterns Of Use		Little Impact	Minor Impact	Significant Impact
	1	Nursing device	I	II	-
	2	Device for medical device sterilization and cleaning	-	II	III
	3	Other non-active devices	I	II	III
Active Device	Status Of Use / Patterns Of Use		Little Impact	Minor Impact	Significant Impact
	1	Clinical laboratory instruments	I	II	III
	2	Stand alone software	-	II	III
	3	Instruments for medical devices disinfection and sterilization	-	II	III
	4	Other active devices	I	II	III

Table 4 - NMPA Table for the Determination of Medical Device Classification from the Annex of Rules for Classification of Medical Devices[8]

Further, in the *Catalog of Chinese Medical Device Classification*, NMPA has a sub-catalog devoted specifically to standalone software.This sub-catalog provides descriptions of various SaMD product categories and their corresponding classifications. It also provides some rationale regarding classification determinations for various SaMD products. For example, the sub-catalog states:

"The risk degree of diagnostic software is determined by the degree of risk, maturity, and openness of the algorithm used. It is not only based on the processing object (such as the images of cancer, malignant tumor, etc.). If the diagnostic software provides diagnostic suggestions through its algorithms and only has auxiliary diagnostic function without directly giving diagnostic conclusions, the related products in this sub-catalogue are managed as Class II medical devices. If the diagnostic software automatically identifies the lesions through its algorithms (e.g., CAD, except bone mineral density) and provides clear diagnostic hints, the risk level is relatively high and the related products in this sub-catalogue are managed as Class III medical devices."[9]

With respect to international best practices for SaMD classification, NMPA's approach does not appear to align with the risk categorization approach described within IMDRF's N12 SaMD Risk Categorization Framework[2]. Although the descriptive text in the standalone software sub-catalog does seem to indicate that the "significance of the information provided by the SaMD to the healthcare decision" is taken into account in the classification decision (as recommended by IMDRF), the classification rules in practice do not clearly distinguish software that is treating/diagnosing versus driving versus informing. For example, the recently published *Guidelines on Classification and Definition of Aided Medical Decision-Making Software (Exposure Draft)* indicates that all aided medical decision-making software that is regulated as a medical device is class III, regardless of the significance of the information it provides.[10] This does not align well with IMDRF principles. It

should also be noted that NMPA's current approach to SaMD classification, as illustrated in Table 4, precludes standalone software from being classified as Class I under NMPA's classification rules, despite the fact that some SaMD applications may be very low risk. Such an approach does not make full use of the NMPA medical device classification scheme, nor does it support a truly risk-based model for classification with respect to SaMD products.

As such, NMPA should reconsider its approach to SaMD classification. Rather than rely on a classification scheme that has been developed for traditional medical devices, it is recommended that NMPA consider a classification scheme based on IMDRF's SaMD Risk Categorization Framework that explicitly takes into account the "state of the healthcare situation or condition the SaMD is intended for" and the "significance of the information provided by the SaMD to the healthcare decision" in the classification determination. Such a revamped approach should enable full use of NMPA's entire classification system (allowing SaMD to be classified as class I, class II, and class III) and ensure a consistent classification interpretation for SaMD products that converges with internationally recognized best practices.

Korea

MFDS employs the Global Harmonization Task Force (GHTF) system in its approach to medical device classification[11]. The approach is a four-class system based on potential risk to human health, and is represented in the table below:

Class	Risk Level	Examples
I	Very Low	Ophthalmic microscope, radiation shielding glove, operation table, stethoscope
II	Low	MRI, pulse oximeter, sterilizer, electroencephalograph
III	Moderate	Cryosurgical (mechanical) system, anesthesia (gas) system, silk suture, condom
IV	High	Implantable defibrillator, coronary stent, biodegradable spine disc, intraocular lens

Table 5 - MFDS Approach to Medical Device Classification[12]

In October 2020, MFDS implemented a revision to the ***Regulation on Medical Device Codes and Classification*** (MFDS notification No. 2020-103) to introduce a new classification system to support SaMD products. The revision provides a "Software" category in the MFDS product classification system, divided into 11 sub-categories according to the therapeutic area. These sub-categories are further divided into 90 software product groupings and the class of each product group has been determined based on its potential risks to human health[13]. MFDS also implemented in May 2020 notification No. 2020-34, establishing five sub-categories for IVD SaMD, such as IVD software for diagnosis, IVD software for predisposition, and IVD software for prognosis. As with notification No. 2020-103, each of the sub-categories is further divided into software product groupings that are classified based on their potential risks to human health[14].

While it is encouraging that MFDS has focused efforts on the classification of SaMD products, the approaches employed do not appear to be based on IMDRF's SaMD Risk Categorization Framework. In particular, it appears that the classification decision for most SaMD product groupings is based on the "state of the healthcare situation or condition the SaMD is intended for" and that the "significance of the information provided by the SaMD to the healthcare decision" is not explicitly taken into account. For example, any SaMD product that has an intended use related to cancer is Class III, regardless of whether the software is "informing," "driving," or "treating or diagnosing" the healthcare situation or condition. Thus, the MFDS approach to SaMD classification is missing an important factor that is present in the IMDRF SaMD Risk Categorization Framework ("the significance of the information provided by the SaMD to the healthcare decision")[2]. This factor is critical to include in classification decisions, as a SaMD product that provides information to a healthcare provider intended to inform his/her treatment decision for a cancer patient has a much different risk than a SaMD product used to automatically diagnose cancer in a patient.

MFDS has indicated that it is currently working on efforts to more closely align its SaMD classification approach with the IMDRF SaMD Risk Categorization Framework. APACMed encourages MFDS to pursue such an approach and ensure that both the "state of the healthcare situation or condition the SaMD is intended for" and the "significance of the information provided by the SaMD to the healthcare decision" are taken into account when making a SaMD classification determination.

Best Practice Theme 03 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 European Union, 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 functions, medical device modules are subject to medical device regulatory requirements while non-medical device modules are not.[15] In the United States, a similar concept is included in the 21st Century Cures Act legislation, stating that the US FDA shall not regulate those functions which do not meet the definition of a medical device when software has multiple functions.[16] The Agency provides further thinking in its guidance on "Multiple Function Device Products," which has broader applicability than just software.[17] In these international examples, 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 have on the medical device functions.

China

In its ***Guidelines for Technical Review of Medical Device Software (Exposure Draft, Edition II)***, NMPA does briefly describe its regulatory approach to software products that consist of both non-medical device and medical device functions:

"If the non-medical device function can be separated technically from the medical device software, that is, the modular design is adopted for the non-medical device functions, the functional modules shall not include the non-medical device functional modules. Any information on the non-medical device functional modules in the instructions for use shall be deleted or indicated."[3]

While such an approach appears to be aligned with the international best practices described above, stakeholders could benefit from more detailed guidance from NMPA with respect to software products with multiple functions. Additionally, NMPA should extend this approach to software products that consist of multiple medical device functions. Specifically, in a multiple function software product, NMPA should regulate each medical device function independently based on its intended use.

A similar approach should also be applied to SaMD that have been deployed on hardware medical

devices. In *Guidelines for Technical Review of Medical Device Software (Exposure Draft, Edition II)*, NMPA indicates that a SaMD product that runs on a medical device computing platform is considered a software component of that medical device, even if it is not essential for that device to achieve its intended use. In such instances, the software must be registered with the medical device and does not have its own registration license[3]. Such an approach is particularly burdensome for a SaMD product that is intended to operate on or with multiple different medical devices, as multiple different registration licenses must be maintained for the same software product.

For example, NMPA currently considers software that is intended to be used to remotely access medical and in vitro diagnostic devices as a software component of those devices and requires it to be registered separately with each of the devices. Such remote access software should be considered as an independent SaMD product: It has an intended use that is separate and distinct from the devices with which it interfaces, and it should therefore have its own registration license. Further, the remote access software is not a software component of the devices with which it interfaces because those devices do not rely on it to achieve their intended use and are able to operate independently without it.

This concept aligns well with IMDRF Principles. In its *Software as a Medical Device (SaMD):Key Definitions* guidance document, 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."* Further, the definition notes that *"SaMD may be interfaced with other medical devices, including hardware medical devices and other SaMD software, as well as general purpose software"* and *"SaMD may be used in combination (e.g., as a module) with other products including medical devices."* An important principle conveyed within this definition and the IMDRF guidance documents is that SaMD is location-independent. It may be deployed on a number of technology platforms, including personal computers, smart phones, the cloud, and even medical device platforms. As long as the SaMD has its own intended use that is separate and distinct from the hardware medical device on which it is deployed, it should be regulated independently and have a distinct regulatory classification and registration license[18]. This is also consistent with the international regulatory approaches to software products with multiple functions described above.

As such, we recommend that NMPA revise its approach to the regulation of SaMD that is deployed on medical device platforms and align with the IMDRF principles described above. Such SaMD should be regulated independently from the hardware medical device and according to their intended use.

Korea

To APACMed's knowledge, MFDS has not yet described its regulatory approach to software products with multiple functions. MFDS is encouraged to leverage international best practices and publish guidance on this topic so as to ensure that, for software products with multiple functions, regulatory oversight is exercised only over those functions with an intended purpose that fulfils the medical device definition.

Best Practice Theme 04 Alternative Pathways for DH

Given the significant differences between SaMD versus traditional medical devices and IVDs, some health authorities have developed alternative SaMD regulatory approaches tailored to their unique and iterative aspects. These approaches can take a variety of forms, such as recognition and reliance models, pre-certification type programs, and predetermined change control plans, which are described in our original report[1].

China

NMPA has launched a special review procedure for innovative medical devices. This procedure gives manufacturers of innovative medical devices both process priority benefit as well as communication advantage at various stages of the registration journey. Medical devices that meet the following criteria, as per NMPA, are considered as innovative medical devices:

- Applicant legally owns the patent right in China to the product's core technology invention
- Applicant legally obtains the invention patent rights in China or has a right to use it through transfer, and the application date for the special review of the innovative medical device is no more than five years from the patent authorization notice
- The patent administration department under the state council has published the application for the core technology invention patent, and a search report is issued by the Patent Search and Consultation Center of the state intellectual property office
- The aforementioned search report states that the core technology of the product is innovative and creative
- Applicant has completed the preliminary research of the product and has a basic prototype; the research process is real, controlled, and the data are complete and traceable
- The main working principle or mechanism of the product is the first case in China
- The product performance or safety is fundamentally improved as compared with similar products, and the technology is at the international leading position with significant clinical value
- Class II or Class III products only

The benefits for medical devices designated as innovative include a prioritized and expedited review, dedicated people in charge of conducting the review, and consultancy from the Center for Medical Device Evaluation (CMDE) under the NMPA (even before registration)[19].

While NMPA's special review procedure for innovative medical devices has many benefits, it is also limited in that it is only available to applicants owning patent rights in China. Ideally, such a program would be open to all developers of innovative medical devices, regardless of patent origin. Such an approach would ultimately benefit patients, enabling them to gain access to a wider range of innovative technologies in a more expeditious manner.

Additionally, NMPA should explore more DH-specific alternative regulatory pathways that ensure device safety and effectiveness while supporting speed of innovation. For example, NMPA should consider the implementation of recognition and reliance models[1] whereby the Administration makes use of regulatory assessments from comparable regulators when conducting DH regulatory decision-making. In such a model, NMPA could leverage approvals from reference regulatory agencies (such as Singapore's HSA, US FDA, European Union Notified Bodies, Korea's MFDS, and/or Japan's MHLW) to accelerate regulatory decision-making for DH products and enable their faster introduction into the Chinese market. NMPA may also consider establishing a consortium with other Asia-Pacific regulators to collaborate on joint regulation of DH products.

NMPA is also encouraged to consider more innovative approaches to change management for DH products. Specifically, NMPA should implement predetermined change control plans, similar to the approaches that have been developed by US FDA and Japan's PMDA/MHLW[1]. In such a concept, a software developer would gain alignment with NMPA during an initial premarket submission on the scope of future software changes and how the risks associated with those changes would be controlled using a predetermined change control plan. Once the initial product is launched and the predetermined change control plan approved, the software developer could then make changes according to the predetermined change control plan without lengthy premarket reviews required. Such an approach greatly facilities the iterative nature of DH products and ensures that patients and healthcare professionals receive innovative and timely updates in a safe and effective manner.

Implementation of such novel regulatory approaches would facilitate the rapid introduction of safe and effective DH solutions in China, and create a regulatory-enabling environment that fosters the development of leading-edge technologies.

Korea

MFDS has enforced the ***Act on Nurturing Medical Device Industry and Supporting Innovative Medical Devices***, effective May 2020. The purpose of the Act is to contribute to the promotion of public health, job creation, and development of the national economy by laying the foundation for cultivation of the medical device industry. Specifically, the Act aims to encourage commercialization of innovative medical devices and Innovative Software Medical Devices, thereby strengthening the competitiveness of Korea internationally.

The following criteria are used to determine if a manufacturer may be designated as an "Innovative software medical device company":

- Excellence in human and material input resources, such as securing research personnel in the medical devices sector and preparation of production facilities
- Excellence in research and development activities, with mid- to long-term investment plans
- Technical and economic excellence of the medical devices' research and development outcome, and contribution to the improvement of public health
- Corporate social responsibilities and ethics, such as compliance with sales and distribution activities

Innovative software devices are eligible to go through an innovative review process including modular review (the applicants can apply for review/approval at the beginning of the product planning stage instead of applying after completing their development and verification) and priority review (innovative software devices are placed higher in priority than other medical/software devices in the review process).

A major advantage of the innovative software medical device pathway is exemption from certain submission documentation requirements. Example exemptions that may be granted by MFDS, upon assessment of the product as well as company's operations, include documentation exemptions related to manufacturing and the manufacturing certificate. In the instance that there are no standards or specifications for the manufacturing of the innovative software medical device, MFDS may provide permission by setting the standards as presented by the applicants themselves. Innovative software medical device manufacturers only need to get approval of changes for innovative

SaMD when there are major changes (e.g., changes of intended use and operational principles) which are designated and notified by MFDS, otherwise, these should be regularly reported to the minister in the same manner as minor changes. Also, innovative software medical device manufacturers conducting a clinical trial must only get approval by an Institutional Review Board (IRB) instead of the minister.

Other benefits of the innovative software medical device pathway include preferential treatment related to national research and development projects, tax relief at the state and local level, research facility construction exemptions, reimbursement of clinical trials, and MFDS' support for the promotion of the use of the innovative software medical devices. MFDS also has a comprehensive center for consultancy, such as for queries related to import/export requirements[20].

While Korea's *Act on Nurturing Medical Device Industry and Supporting Innovative Medical Devices* has many benefits, it is also limited in that it is targeted to only those manufacturers that have mid to long-term R&D investment plans in Korea. Ideally, such a program would be equally applicable to both developers with and without R&D investment plans in Korea, as both groups have the capability of bringing innovative software medical devices to market. Such an approach would ultimately benefit patients, enabling them to gain access to a wider range of innovative technologies in a more expeditious manner. We also recommend expanding the scope of this particular program to include all innovative digital health solutions.

Similar to NMPA, MFDS should as well explore more DH-specific alternative regulatory pathways that ensure device safety and effectiveness while supporting speed of innovation. Such approaches may include recognition and reliance models and predetermined change control plans.

With respect to recognition and reliance models,[1] MFDS should consider making use of regulatory assessments from comparable regulators when conducting DH regulatory decision-making. In such a model, MFDS could leverage approvals from reference regulatory agencies (such as Singapore's HSA, US FDA, European Union Notified Bodies, China's NMPA, and/or Japan's MHLW) to accelerate regulatory decision-making for DH products and enable their faster introduction into the Korean market. MFDS may also consider establishing a consortium with other Asia-Pacific regulators to collaborate on joint regulation of DH products.

MFDS is also encouraged to consider more innovative approaches to change management for DH products. Specifically, MFDS should implement predetermined change control plans, similar to the approaches that have been developed by US FDA and Japan's PMDA/MHLW[1]. In such a concept, a software developer would gain alignment with MFDS during an initial premarket submission on the scope of future software changes and how the risks associated with those changes would be controlled using a predetermined change control plan. Once the initial product is launched and the predetermined change control plan approved, the software developer could then make changes according to the predetermined change control plan without lengthy premarket reviews required. Such an approach greatly facilities the iterative nature of DH products and ensures that patients and healthcare professionals receive innovative and timely updates in a safe and effective manner.

Implementation of these novel regulatory approaches would facilitate the rapid introduction of safe and effective DH solutions in Korea, and create a regulatory-enabling environment that fosters the development of leading-edge technologies.

Best Practice Theme 05 Pre-Submission Consultation (PSC)

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 or sponsors of DH solutions to seek innovation support during a pre-submission phase in order to expedite patient access to the solution in a safe and effective manner. Manufacturers or sponsors can consult the regulatory authority on requirements during the DH solution development phase and seek feedback on dossier completeness before submission. For novel DH solutions which do not fit naturally into current regulatory systems, PSC is crucial to expedite registration and facilitate early patient access. NMPA China and MFDS Korea have implemented PSC mechanisms. However, in Korea, the mechanisms put in place for pre-submission consultations and pre-review are only available for innovative, newly-developed, or scarce medical devices. Given the constantly evolving and changing digital health regulatory landscape, stakeholders could benefit from an expansion of these mechanisms to include all DH solutions and not just innovative, newly developed, or scarce medical devices. MFDS Korea also has an additional scheme, called "Approval Helper for Novel Medical Devices", that is only applicable to newly developed medical devices, and, similarly, stakeholders could benefit from a scope expansion of this program to include DH solutions as well[21].

Best Practice Theme 06 Frameworks for AI/ML

As AI/ML-enabled DH solutions become more prevalent, it is important that regulators implement novel regulatory approaches, particularly with respect to change management, that foster innovation and enable safe and effective AI/ML solutions and their modifications to reach patients and healthcare professionals in an expeditious manner.

China

Over the last several years, NMPA has been very active in evolving its framework for the regulation of medical devices that leverage AI, working on a number of initiatives through the Artificial Intelligent Medical Device Innovation and Cooperation Platform (http://aimd.org.cn/zzjg). The Administration has also issued a number of different guidance documents. For example, in 2019, NMPA published *Review Key Points and Relevant Instructions of Aided Decision-Making Medical Device Software Using Deep Learning Techniques* to describe development, validation, and lifecycle management activities that deep learning medical device developers should take into account[22]. In 2020, NMPA published a number of AI-related proposals, issuing draft versions of *Artificial intelligence medical device – Quality requirements and evaluation – Part 1: Terminology*[23] *and Artificial intelligence medical device – Quality requirements and evaluation – Part 2: General requirements for data sets*[24]. Moreover, NMPA proposed an AI-based medical device standards system, consisting of 24 standards to address topics ranging from risk management to model training and verification to development infrastructure and environment[25]. Most recently in 2021, the NMPA issued various AI-focused guidance documents, such as *Guidelines for Review of Artificial Intelligence Medical Device Registration (Exposure Draft)* that provides an overview of the general requirements that should be taken into account for the lifecycle management of AI medical devices and describes the content that should be included within their registration documentation[26]. NMPA also recently finalized *Guidelines for the Classification and Definition of AI-based SaMD* in which it describes its approach to the classification of AI-SaMD products.

Specifically, this finalized document states the following with respect to classification of AI-based SaMD:

"For the AI-based SaMD with low-maturity algorithm in medical application (which means that it has not been marketed or its safety and effectiveness have not been fully verified), it shall be regulated as a Class III medical device if used for assisting in decision making, such as providing focus characteristic recognition, lesion nature judgment and determination, medication guidance, treatment plan formulation and other clinical diagnosis and treatment suggestions; and it shall be regulated as a Class II medical device if not used for assisting in decision making, such as providing clinical reference information through data processing and measurement.

For the AI-based SaMD with high-maturity algorithm in medical application (which means that its safety and effectiveness have been fully verified), it shall be regulated according to the management category in the prevailing 'Classification Catalogue of Medical Devices,' classification and definition documents, etc."[4]

This text appears to imply that, when an AI-based SaMD demonstrates sufficient safety and effectiveness, it will be classified based on its intended use in a manner similar to other SaMD products. This aligns well with international regulatory best practices whereby AI-based SaMD is simply considered as a subset of SaMD and is therefore classified in the same manner, based on its intended use. APACMed encourages NMPA to continue to follow this approach for the classification of AI-based SaMD and refrain from adding classification burdens to such devices simply because they leverage AI.

In its finalized "Deep Learning" and draft "*Guidelines for Review of Artificial Intelligence Medical Device Registration*" guidance documents, NMPA provides some useful design, validation, and lifecycle management considerations for AI-based medical device developers. However, these guidance documents do not consider nor promote unique regulatory approaches to change management for AI-based medical devices. Specifically, the guidance documents require developers of AI-based medical devices to follow routine regulatory approaches when implementing

major software updates, requiring the submission of an application for approval prior to change implementation. Further, any data-driven software update (such as increased training data) that leads to a statistically significant improvement in performance is considered a major software update. These regulatory change management requirements severely hamper the iterative aspects of AI solutions by requiring developers to go through lengthy review processes prior to implementing beneficial software changes. Innovative regulatory pathways, such as predetermined change control plans that promote the implementation of significant changes to AI-based medical devices in an expeditious, safe, and effective manner, are not considered nor proposed in the guidance documents. As such, it is recommended that NMPA reconsider its approach to change management for AI-based medical devices and implement innovative regulatory pathways that enable their iterative aspects.

Lastly, NMPA runs the risk of over-burdening developers of AI-based medical device products through its proposed issuance of 24 AI-related standards. Many of the proposed topics, such as cybersecurity, risk management, and software development and lifecycle processes, are already addressed by existing, internationally recognized, and technology-agnostic standards. As such, NMPA should combine standards topics where feasible and discuss nuances specific to AI-based medical devices in the context of existing standards, in order to avoid duplication and potential conflicting requirements.

Korea

MFDS has published guidance documents related to AI-based medical devices, such as ***Guideline on Review and Approval of Artificial Intelligence (AI) and Big Data Based Medical Device***[7] ***and Guideline for Evaluation of Artificial Intelligence (AI)-based Medical Device.***[27] In its "Big Data" guidance, MFDS indicates that AI-based medical devices are regulated in relation to their intended use and are classified in the same manner as other medical devices. The guidance also provides an overview of submission and version control requirements for AI-based medical devices. MFDS' "Evaluation" guidance focuses on the fact that AI-based medical devices may be able to leverage retrospective data in clinical study designs in order to reach more timely and cost-effective decisions regarding clinical performance. The guidance describes important considerations for such "retrospective clinical trials" and provides criteria and methods for evaluation efficacy.

MFDS has adopted a risk-based approach to the regulation of AI-based medical devices that focuses on intended use when determining regulatory requirements (such as classification). This aligns well with international best practices and fosters innovation of these technologies by not creating any unnecessary or overly-burdensome regulatory barriers. Further, MFDS is one of the few regulatory authorities that has published guidance related to the use of retrospective data in clinical evaluations of AI-based medical devices. Such guidance provides effective support to developers working to navigate the clinical study landscape and will enable innovative AI-based medical devices to reach patients and healthcare professionals in a more timely and efficient manner.

MFDS has also described an approach to change management for AI-based medical devices that is more progressive than those methods employed by many regulators in the APAC region. Specifically, in its "Big Data" guidance, MFDS indicates that training data changes leading to performance improvements are exempt from change approval when the developer establishes a change management policy focused on maintaining the quality and performance of the product. This enables AI-based medical device developers to regularly update device performance through expanded training data sets without the need to undergo lengthy regulatory review processes. MFDS is encouraged to consider even more progressive approaches to change management, such as predetermined change control plans that enable major changes to be implemented post-market when a developer has an established protocol in place. Such approaches will further contribute to innovation of AI-based medical devices in Korea, and will ensure that innovative, safe, and effective changes reach patients and healthcare professionals in a timelier manner.

Use Cases

InferVision and VUNO Inc. are two DH developers that have navigated the regulatory approval processes in China and Korea, respectively. Below, we review their experiences and identify their key success factors.

China

InferVision is a pioneer in the application of AI and deep learning for healthcare purposes. Its goal is to employ advanced deep learning technologies to create value for patients, providers, and payers, as well as to provide high-quality medical services to billions of lives worldwide. InferVision AI solutions assist radiologists in detecting abnormalities in imaging data and offer quantitative analytics for optimal decision-making and treatment. They integrate state-of-the-art deep learning algorithms trained on hundreds of thousands of curated datasets to identify critical features and patterns from medical images. Infervision has a global footprint – its AI solutions are currently empowering over 400 medical institutions across North America, Europe, and APAC.

One of InferVision's products, the InferRead Lung CT.AI (Figure 1), is 510(k)-cleared by the US FDA, CE-marked in Europe, and approved by the NMPA to assist radiologists with their chest Computed Tomography (CT) image analyses. It is capable of identifying various types of lung nodules, providing quantification for each lesion, and generating radiological reports. The application has been trained with hundreds of thousands of exams to ensure its accuracy, robustness, and generalizability. Validated through retrospective, Multi-Reader Multi-Case (MRMC) studies, InferRead Lung CT.AI has shown to reduce exam reading time and missed nodules for radiologists. The software is compatible with legacy systems and accepts chest CT images from PACS, RIS, or directly from a CT scanner. InferRead Lung CT.AI is the first approved AI-based medical solution targeted for the lung in both China and the US.

The InferVision team are optimistic about the wave of DH innovation expected in the next 3-5 years and the level of public-private collaboration around the evolving regulations. Greater consistency, as well as alignment to international standards like IMDRF, are needed and in progress. The NMPA take the MRMC approach very seriously as a mechanism to ensure robustness of the algorithms and to reduce safety risks. A recommendation for NMPA from the InferVision team, is to develop a separate submission channel dedicated to software so as clearly separate DH solutions from the mix of submissions in the traditional medical device queue.

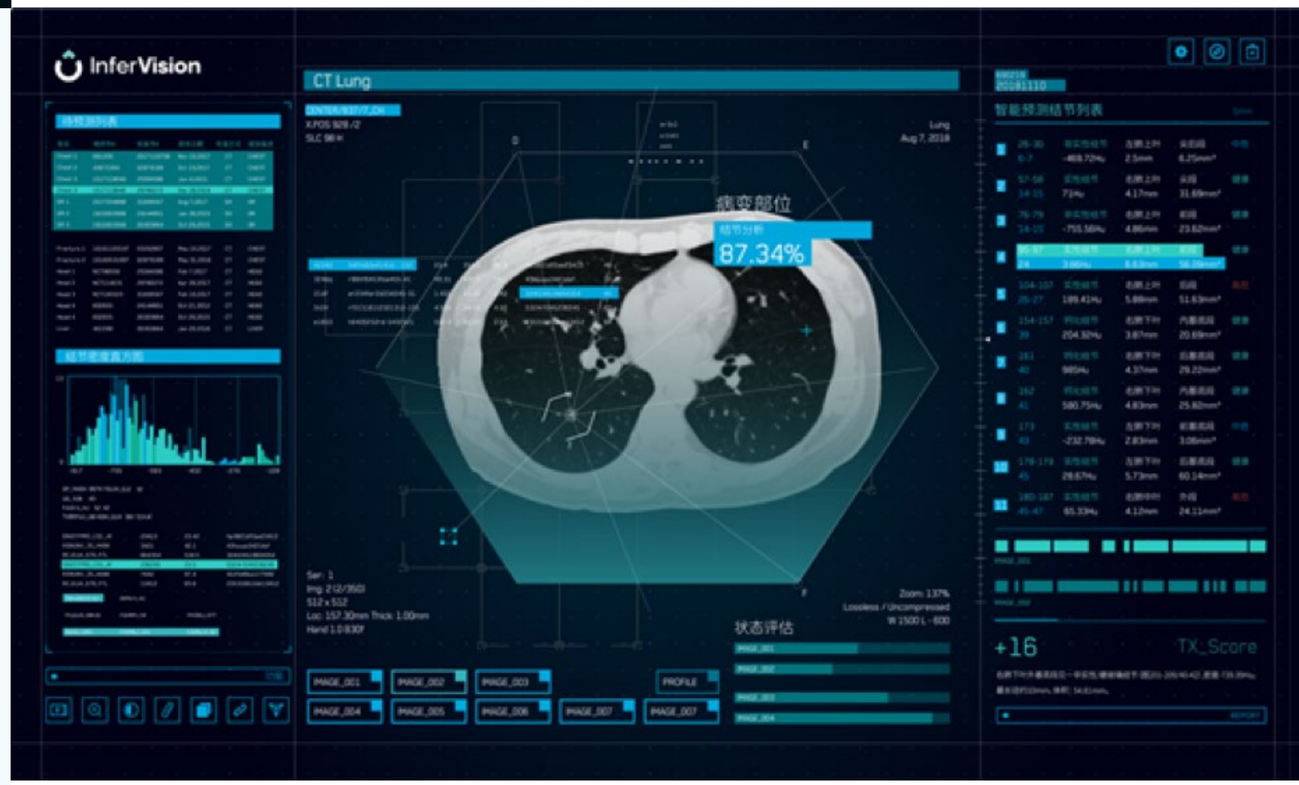

Figure 1 – InferVision's InferRead Lung CT.AI

Korea

VUNO Inc. is a Korean AI medical imaging company that delivers innovative standalone, cloud-based, and integrated deep learning applications to significantly improve physician workflow while enhancing patient care. Founded in 2014, VUNO and its team of deep learning engineers, software developers, medical doctors, regulatory affairs specialists, and other professionals experienced in product commercialization work together with the best-known medical institutions and companies in Korea to develop and commercialize medical AI software based on diverse medical data.

From imaging modalities, including X-rays and CT scans, to bio signal monitoring systems, VUNO provides a diverse array of DH solutions that quantify and analyze data to diagnose diseases. VUNO Med®-BoneAge™ (Figure 2), Korea's first approved medical AI product, is the first in a series of VUNO DH solutions across diverse medical fields.

[Product Screen] [Bone Age Report]

Figure 2 – VUNO's Med®- BoneAge™

VUNO Med-BoneAge assists bone age assessments based on a child's hand X-ray image, reducing reading time and significantly improving accuracy. Its innovative User Interface (UI) enhances user convenience and works in conjunction with PACS to provide optimized service for the reading site. For better communication between the patient and physicians, a customized report of bone age assessment is automatically generated. The comprehensive report enhances the patient's satisfaction and engagement levels.

VUNO Med-BoneAge is registered as Class II device in Korea, is CE-marked in Europe, and has been approved by Japan's PMDA. Its stated intended use is to assist trained radiologists and other healthcare professionals with an analyzed reference image that determines bone age through the Greulich-Pyle (GP) and Tanner-Whitehouse (TW) methods. The intended use population is children and adolescents below 19 years of age having medical conditions that require the determination of bone age.

VUNO was recognized as an innovative medical device company by MFDS and therefore experienced a reduction in registration submission documentation requirements. The company benefitted from MFDS' modular review process, which is aligned to the stage of solution development and therefore reduces registration timelines. The VUNO team believe MFDS is moving in the right direction by establishing such pathways for expedited review, which allow greater access to DH solutions that, in turn, provide patients with better health outcomes and higher quality of life. VUNO also noted that as the number of innovative medical devices increase in Korea, MFDS is taking multiple actions to optimally regulate and support SaMD products. There have been steps taken to lower the regulatory hurdles, such as introduction of the modular review process / rolling review to reduce the registration timeline, and the optional application of the clinical trials due to changes in equivalence standards.

Best Practices Framework

APACMed is encouraged by the efforts undertaken by APAC regulators to advance DH regulatory frameworks across the region. Based on a comprehensive assessment of the considerations described within this paper, we outline below an actionable path forward that regulators, including NMPA and MFDS, should apply when implementing fit-for-purpose, risk-based DH regulatory frameworks. Implementation of these actions will enable safe, effective, and timely delivery of innovative DH solutions that will benefit patients and healthcare professionals.

01 Fundamental principles for a DH-focused regulatory framework:

- Implement a clearly described approach to software qualification (i.e. determining when software is a SaMD) that aligns with international best practices, and whereby the regulator only has oversight over those software functions with a medical device intended use.
- Establish a classification method specific to SaMD that is based on IMDRF's N12 SaMD Risk Categorization Framework and specifically takes into account both the "state of healthcare situation" and "significance of information provided by the SaMD" in the classification decision.
- For software products with multiple functions, implement policies by which regulators only exercise regulatory oversight over those functions with a medical device intended use.

02 Pathways to enable 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 through the development of expedited review pathways that can be leveraged by all SaMD developers and the endorsement of predetermined change control plans.
- Implement risk-based regulatory approaches that enable the innovative and iterative aspects of AI-based SaMD solutions.

03 Opportunities for convergence and collaboration:

- Support DH regulatory global convergence through the recognition and adoption of international guidance documents and standards, such as those developed by IMDRF and ISO.
- Foster greater collaboration with software developers through pre-submission consultations.
- Partner with industry through trade associations, private-public consortia, and other fora to share best practices and evolve the DH regulatory landscape together.

Bibliography

1. "Digital Health Regulation in Asia-Pacific: Overview and Best Practices". APACMed: Jan 2021.
2. "Software as a Medical Device: Possible Frameworks for Risk Categorization and Corresponding Frameworks". IMDRF: Sep 2014.
3. "Guideline for Technical Review of Medical Device Software (Exposure Draft, Edition II)". NMPA, June 2020.
4. "Guidelines for the Classification and Definition of AI-based SaMD". NMPA, Notice No. 47: Jul 2021.
5. "Guidelines for Technical Review of Mobile Medical Device Registration." CFDA: January, 2018.
6. "Determination of Medical Device Eligibility for Products in the Border Area Between Medical Devices and Industrial Products." KFDA, 2010.
7. "Guideline on Review and Approval of Artificial Intelligence (AI) and Big Data-Based Medical Devices (For Industry)". MFDS: Nov 2020.
8. "Rules for Classification of Medical Devices". CFDA, Decree No. 15: Jul 2015.
9. "The Catalog of Chinese Medical Device Classification". NMPA: Aug 2018.
10. "Guidelines on Classification and Definition of Aided Medical Decision-Making Software (Exposure Draft)." NMPA: June 2021.
11. "Principles of Medical Devices Classification". GHTF: Jun 2006.
12. "Medical Device Act". MFDS: Mar 2016.
13. "Regulation on Medical Device Codes and Classification". MFDS, Notice No. 2020-103: Oct 2020.
14. "Act on In Vitro Diagnostic Medical Devices". MFDS, Notice No. 2020-34: May 2020.
15. "Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 - IVDR". Medical Device Coordination Group (MDCG): Oct 2019.
16. "21st Century Cures Act". United States Law: Dec 2016.
17. "Multiple Function Device Products: Policy and Considerations". US FDA: Jul 2020.
18. "Software as a Medical Device (SaMD): Key Definitions". IMDRF: Dec 2013.
19. "Trial Procedures for Special Examination of Innovative Medical Devices (Special Procedures". CFDA No. 13, Revised Order 83: Feb 2014.
20. "Act to Nurture Medical Device Industry and to Support Innovative Medical Devices". MFDS: May 2020.
21. "2019 Medical Device Approval Report". MFDS, Innovative Convergence Product Support Department: Jul 2020.
22. "Review Key Points and Relevant Instructions of Aided Decision-Making Medical Device Software Using Deep Learning Techniques." NMPA: June 2019.
23. "Artificial intelligence medical device – Quality requirements and evaluation – Part 1: Terminology (Exposure Draft)". NMPA: June 2020.
24. "Artificial intelligence medical device – Quality requirements and evaluation – Part 2: General requirements for datasets (Exposure Draft)". NMPA: June 2020.
25. "Technical Jurisdiction Unit for the Standardization of Artificial Intelligence Medical Devices. Planning for Standards During the '14th Five-Year Plan Period' (Draft for Comments)". NMPA: Oct 2020.
26. "Guidelines for Review of Artificial Intelligence Medical Device Registration (Exposure Draft)." NMPA: June 2021.
27. "Guideline for Evaluation of Artificial Intelligence (AI)-based Medical Device". MFDS: Dec 2017.

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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.