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REVIEW

Current Application of the Medical Device Single Audit Program (MDSAP) as a Global Regulatory Reliance Framework for the Inspection of Medical Devices

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Abstract
The globalization and rapid advancements in medical technologies necessitate the harmonization of international regulatory frameworks to ensure the efficient and timely clinical application of medical products, including pharmaceuticals and medical devices. Regulatory reliance, a critical component of this harmonization process, is a powerful tool that provides efficient access for economic entities and regulatory authorities, promoting predictable decision-making and accelerating approvals. The Medical Device Single Audit Program (MDSAP) serves as a regulatory reliance framework for medical device inspections. Implemented by countries including Japan, the United States, Canada, Australia, and Brazil, MDSAP allows third-party certification bodies, recognized by these regulatory authorities, to conduct audits on medical device manufacturers. The outcomes of these audits are shared with the regulatory authorities, who use them for regulatory assessments and decision-making. Since transitioning to its implementation phase in 2017, MDSAP has been widely utilized in various countries. This review provides an overview of the adoption and utilization of MDSAP in major countries, exploring the program's impact on regulatory processes and its potential as a method of regulatory reliance to facilitate timely access to effective and safe medical devices.

Keywords Medical Device Single Audit Program (MDSAP) · Regulatory reliance · The International Medical Device Regulators Forum (IMDRF) · Medical device regulation · Third-party certification bodies

Introduction

The rapid advancements and increasing globalization of medical technologies have created an urgent need for the international harmonization of regulatory frameworks. This harmonization is essential to ensure the efficient and timely clinical application of medical products, such as pharmaceuticals and medical devices. A critical component of this harmonization process is the development of frameworks for regulatory reliance, which facilitate cooperation and mutual recognition among regulatory authorities worldwide.

The International Coalition of Medicines Regulatory Authorities (ICMRA), a global organization comprising the heads of national medicines regulatory authorities, defines regulatory reliance as "a mechanism to strengthen regulatory capacity, improve health systems nationally and internationally, increase the availability of medicines, save financial resources, and use human resources more strategically" [1]. This definition underscores the importance and benefits of regulatory reliance activities. Similarly, the World Health Organization (WHO) defines regulatory reliance in its 2021 Good Reliance Practices guidance as "the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision" [2]. The WHO promotes this concept as a more efficient approach to accelerating access to effective and safe medical products.

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Regulatory reliance has been applied in many countries during the recent COVID-19 pandemic to facilitate rapid market access for urgently needed medical products. This includes pre-market assessment of the marketing application dossier and inspection of manufacturing facilities and clinical trials sites to assure conformance with regulatory requirements. Inspections by regulatory authorities on the manufacturing and quality control of medical products are essential throughout the product lifecycle to ensure their quality. From the perspective of accelerating access to effective and safe medical products, the establishment of regulatory reliance in this field is highly anticipated.

In terms of pharmaceutical inspections, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) released guidance titled "GMP INSPECTION RELIANCE" in 2018. This guidance suggests that reliance activities, including the use of GMP inspection results from other countries, could eliminate the need for on-site GMP inspections by the concerned country [3]. Discussions on the future direction of reliance in pharmaceutical inspection harmonization are already well underway [4].

For medical devices, the International Medical Device Regulatory Forum (IMDRF) developed the guidance of Medical Device Single Audit Program (MDSAP), which serves as a regulatory reliance framework for inspections of medical devices. Japan, the United States, Canada, Australia, and Brazil led the implementation of MDSAP based on the guidance.

To provide a technical perspective on how the MDSAP program operates: The manufacturer typically requests the MDSAP audit. These audits are on-site inspections, similar to those performed by regulators; however, they are conducted by a recognized third parties. The manufacturer is responsible for paying for the third-party audit, which is conducted by a certification body recognized by the regulatory authorities participating in MDSAP. The third-party auditor conducts the audit and generates the audit report and the certificate. These outcomes of the audit can be submitted either directly by the third party to the regulator or included by the manufacturer in their regulatory application. The regulatory authority then reviews the outcomes for their regulatory assessments and decision-making processes (Fig. 1). It is important to note that regulatory reliance is generally applicable when the product received by the relying country is exactly the same version as that inspected by the reference agency or recognized third party. This is particularly crucial for medical devices, which undergo rapid version upgrades and changes throughout their life cycle, often requiring subsequent regulatory filings, assessments, and potential

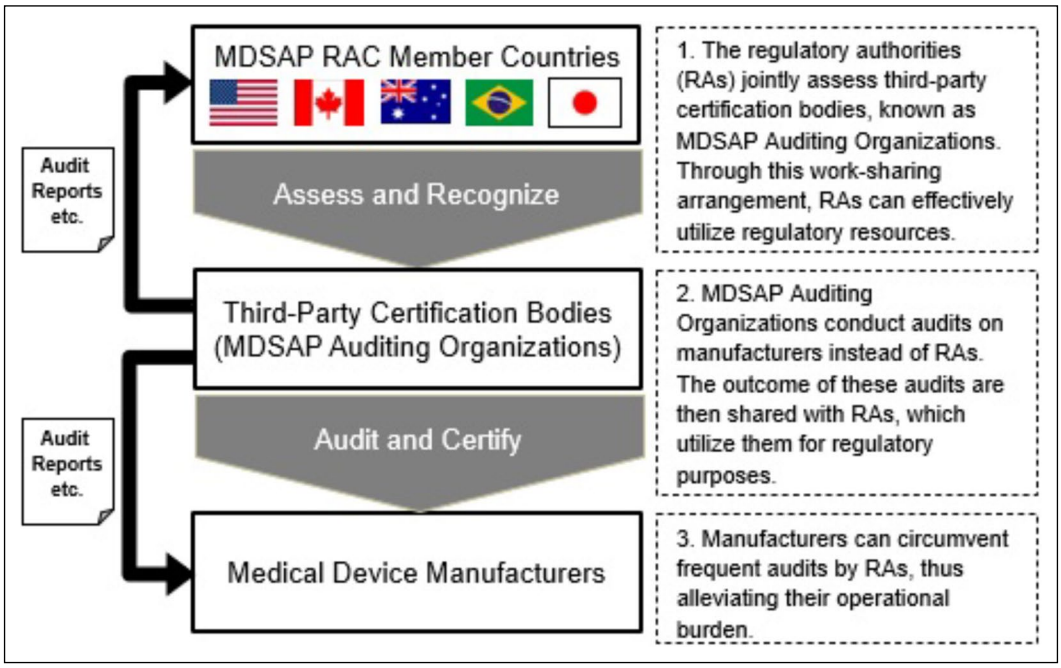

Figure 1. The Approach of MDSAP. The MDSAP involves collaboration between regulatory authorities (RAs) from member countries—United States, Canada, Australia, Brazil, and Japan. These authorities jointly assess and recognize third-party certification bodies, known as MDSAP Auditing Organizations. The MDSAP Auditing Organizations conduct audits on medical device manufacturers instead of RAs. The outcomes of these audits are then shared with the RAs for regulatory purposes. This arrangement allows manufacturers to reduce the frequency of audits by multiple RAs, thereby alleviating their operational burden while ensuring compliance with regulatory requirements.

inspections. Thus, this review typically includes confirmation of this point.

After a pilot period from 2014 to the end of 2016, the MDSAP transitioned to the implementation phase in 2017. Since then, the outcomes of MDSAP audits have been utilized for regulatory purposes in various ways. Although the utilization of the outcomes vary among countries, there have been no reports on the actual use of this program as a regulatory reliance mechanism in major countries.

In this review, we provide an overview of the adoption and utilization of MDSAP in major countries. We also discuss the factors behind the differences in the use of MDSAP among countries and evaluate the usefulness of MDSAP as a method of regulatory reliance.

Inspection Organizations for Medical Device in Different Countries

Unlike pharmaceuticals, many countries utilize third-party certification bodies instead of regulatory agencies for the inspection of medical device manufacturers. To clarify the characteristics of inspections for medical devices, we compared and categorized the inspection methods of medical device inspection organizations in major countries, particularly those participating in MDSAP (Japan, the US, Canada, Australia, and Brazil) as well as the EU, a significant medical device regulatory authority. Inspections of pharmaceutical manufacturing sites are conducted by regulatory authorities in all countries (Table 1). However, for medical devices, many countries have adopted inspections conducted by third-party certification bodies instead of regulatory authorities. Specifically, countries can be categorized into three types based on their inspection practices:

1. Regulatory Authority-led Type: In this category, regulatory authorities are the primary bodies conducting inspections. This approach is used by the US and Brazil.
2. Certification Body Co-use Type: In these countries, both regulatory authorities and certification bodies conduct inspections. Japan and Australia follow this approach.
3. Certification Body-led Type: Here, all inspections are carried out by certification bodies. This method is used by Canada and the EU

The varied use of certification bodies across countries is summarized in Table 1.

Actual Use of MDSAP and Inspection Methods in Different Countries

Next, we compared the main inspection methods and the current utilization of MDSAP in each country (Table 2).

United States

US medical device regulation was first introduced in 1976 through amendments to laws governing medical-related products by Congress [5]. As this framework was derived from pharmaceutical regulation, inspection organizations are the regulatory authority, the U.S. FDA (Table 2). The US mentions in the MDSAP Q&A that it uses MDSAP for routine inspections conducted on a risk basis as a substitute. In 2019, it was reported that there were a total of 2144 inspections of products by USFDA. Of these, 1,153 were routine on-site inspections by USFDA personnel and 991 were inspections in which MDSAP reports were used in lieu of on-site inspections [6]. This means that 46% of the USFDA inspections utilized MDSAP reports rather than USFDA on-site inspections.

Table 1. Comparison of Inspection Organizations for GMP Inspections and QMS Inspections.

	Country or Region					
	US	Brazil	Japan	Australia	Canada	EU
Pharmaceutical GMP Inspection	Pharmaceutical GMP inspections are conducted by the respective regulatory authorities in each country					
Medical Device QMS Inspection	Regulatory authority	Regulatory authority	Regulatory authority and certification body	Regulatory authority and certification body	Certification body	Certification body

Table 2. Main Inspection Methods in Major Countries and the Utilization of MDSAP.

Country or Region	Types of Inspection Organizations	Main Inspection Methods*	Methods of Utilizing MDSAP	The Utilization rate of MDSAP that is made Public
US	Regulatory authority-led type: the inspections are conducted by the U.S. FDA	On-site inspection	MDSAP audit reports are accepted by the U.S. FDA as substitutes for FDA routine inspections[a]	46%[b]
Brazil	Regulatory authority-led type: the inspections are conducted by ANVISA	On-site inspection	MDSAP audit reports can be used by ANVISA to grant or bi-annually renew GMP Certificates for class III or IV medical devices in Brazil, replacing ANVISA inspections[a]	55%[c]
Japan	Certification body co-use type: the inspections are conducted by PMDA and certification bodies	On-site inspection and desktop inspection	MDSAP audit reports can be used to exempt a manufacturing site from on-site inspections for new and periodic inspections[a]	33%[d]
Australia	Certification body co-use type: the inspections are conducted by TGA and certification bodies	On-site inspection and desktop inspection	MDSAP audit reports and certificates are used to assess medical device compliance, unless exceptions or policies apply[a]	NA
Canada	Certification body-led type: the inspections are conducted by certification bodies	On-site inspection	MDSAP certification is required for all Class II, III, and IV medical devices[a]	100%
EU	Certification body-led type: the inspections are conducted by certification bodies	On-site inspection	MDSAP audit reports are utilized at the discretion of EU certification bodies as part of the surveillance audits, thereby streamlining the regulatory process[e]	NA

*On-site inspection: A form of inspection where the inspection organization listed in the table conducts the inspection on site. Desktop inspection: A form of inspection conducted by the inspection organization listed in the table, based on documents provided by the facility being inspected.

[a]MDSAP, Medical Device Single Audit Program Frequently Asked Questions, https://www.fda.gov/media/161094/download?attachment.

[b]US FDA, Use of MDSAP—Regulatory Updates (US FDA), https://www.fda.gov/media/140215/download?attachment.

[c]ANVISA, Regulatory Updates: Brazil, https://www.fda.gov/media/146222/download?attachment.

[d]PMDA, Acceptance Result of the Outcome of the MDSAP Audit, https://www.pmda.go.jp/files/000263159.pdf.

[e]Medical Device Coordination Group, MDCG 2020–14 Guidance for notified bodies on the use of MDSAP audit reports in the context of surveillance audits carried out under the Medical Devices Regulation (MDR)/In Vitro Diagnostic medical devices Regulation (IVDR), https://health.ec.europa.eu/system/files/2020-08/md_2020-14-guidance-mdsap_en_0.pdf.

Brazil

The inspection organization in Brazil is ANVISA (Table 2). Medical devices are classified from Class I to IV, with Brazilian GMP Certificates required for Class III and IV devices, necessitating an ANVISA inspection for issuance. However, if an MDSAP report is submitted and deemed appropriate, the inspection can be exempted. In 2020, Brazil reported that about 55% of Brazilian GMP certificates were issued using MDSAP reports [7].

Japan

Japan's QMS inspections are conducted by PMDA, and certification bodies recognized by the Japanese government (Table 2). While PMDA primarily conducts inspections for high-risk Class III and IV medical devices, low-risk Class II device inspections are performed by certification bodies. PMDA and the certification bodies, based on a risk-based approach, may conduct on-site inspections as deemed necessary. However, when MDSAP audit reports are available, the results are accepted by the regulatory authority, and on-site inspections are replaced with desktop inspections. Since 2017, Japan has utilized MDSAP, with about one-third of inspection applications to PMDA using MDSAP recently, especially for foreign inspections, suggesting its use as a substitute for on-site inspections for high-risk medical devices manufactured in foreign countries (Figs. 2, 3).

Australia

Australia has an inspection scheme that uses certification bodies in addition to the regulatory authority's inspections (Table 2). Australia uses MDSAP reports as evidence of conformity to pre-market and post-market regulatory requirements. When appropriate, the use of MDSAP reports and certificates can exempt the inspection conducted by the authority.

Canada

Canada's inspection organization is the MDSAP Auditing Organizations, certification bodies that conduct MDSAP audits (Table 2). Since January 1, 2019, the Canadian Health Ministry has mandated manufacturers of Class II and above medical devices to obtain MDSAP certification, as required by Canadian law (Medical Devices Regulations, SOR/98-282), making the utilization rate 100%.

European Union

The inspection organizations in the EU are certification bodies recognized by the EU (Table 2). In 2020, the EU

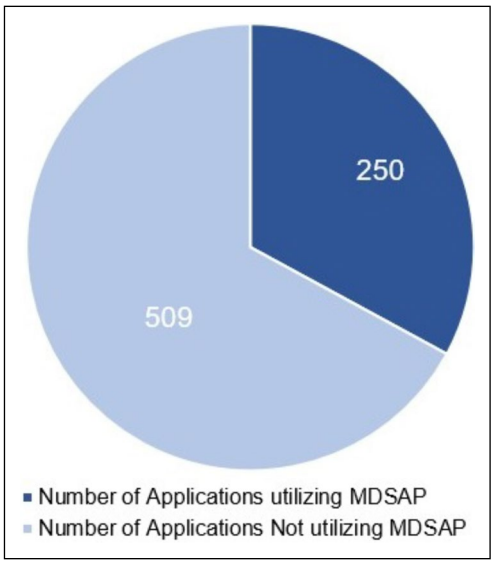

Figure 2. Number of Applications Utilizing MDSAP in QMS Conformity Inspection Applications to PMDA (Fiscal Year 2022) [8]. This pie chart shows the distribution of Quality Management System (QMS) conformity inspection applications submitted to PMDA in fiscal year 2022. Of the total 759 applications, 250 utilized MDSAP for their QMS conformity inspections, while 509 did not. This distribution underscores the extent to which manufacturers and regulators are adopting MDSAP to streamline regulatory processes and ensure compliance with PMDA requirements.

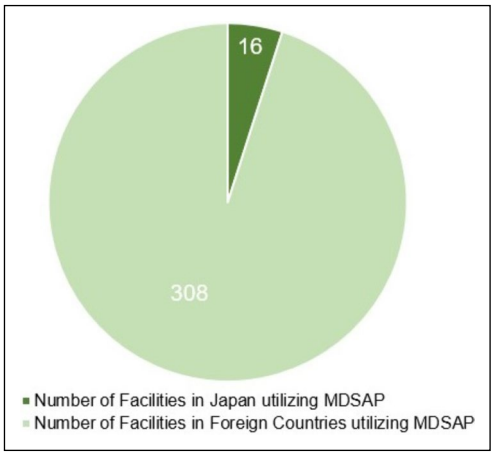

Figure 3. Number of Japanese and Foreign Facilities in Applications Utilizing MDSAP to PMDA (Fiscal Year 2022) [8]. This pie chart illustrates the number of facilities in Japan and foreign countries that utilized MDSAP in their QMS conformity inspection applications submitted to PMDA in fiscal year 2022. Out of a total of 324 facilities, 16 were in Japan and 308 were in foreign countries. This data highlights that the number of foreign facilities utilizing MDSAP is overwhelmingly higher than those in Japan.

issued MDCG 2020–14, which clarifies the policy for using MDSAP reports within the EU inspection scheme [9]. According to this guidance, EU certification bodies are recommended to streamline parts of their own inspections by

using MDSAP reports, but only in surveillance inspections (periodic sampling inspections conducted after the initial certification). The extent to which MDSAP is utilized is left to the discretion of the certification bodies, and the extent of MDSAP's use in the EU is unclear.

Utilization of MDSAP by Type

MDSAP is utilized by regulatory authorities in various countries and regions either as a substitute for existing inspection methods or as an inspection method itself, with diverse applications. Regulatory authorities leverage MDSAP based on their existing inspection strategies, considering their human and budgetary resources. According to the findings in "Actual Use of MDSAP and Inspection Methods in Different Countries" section, medical device regulatory authorities can be broadly categorized into three types: regulatory authority-led, certification body co-use, and certification body-led types. This section discusses the MDSAP utilization situation for each type.

Characteristics of Regulatory Authority-led Type Authorities

Regulatory authorities classified in the regulatory authority-led type, such as the US and Brazil, do not adopt inspections or desktop inspections conducted by certification bodies other than MDSAP Auditing Organizations. These authorities primarily conduct on-site inspections themselves or through MDSAP Auditing Organizations. On-site inspections are considered to have higher reliability, which is a priority for these authorities. These regulatory bodies have relatively high utilization rates of MDSAP, flexibly alternating between on-site inspections and MDSAP audits.

Characteristics of Certification Body Co-use Type Authorities

Regulatory authorities classified in this type, such as Japan and Australia, adopt both on-site and desktop inspections. They also implement inspections conducted by certification bodies, aiming for a diverse set of inspection methods. MDSAP is utilized as one of the inspection methods, with Japan showing a utilization rate of approximately 33%. Compared to regulatory authority-led authorities, the relatively lower utilization rate might be because desktop inspections are adopted as substitutes for on-site inspections, leaving less room for MDSAP utilization. However, the fact that there is still about a 30% utilization rate suggests that MDSAP offers benefits not found in other inspection methods (see "Characteristics of Certification Body Co-use Type Authorities" section for the benefits of MDSAP).

Characteristics of Certification Body-led Type Authorities

Authorities classified in this type, such as Canada and the EU, exclusively use certification bodies for inspections. These authorities aim for more efficient inspections by leveraging the resources of certification bodies. They conduct inspections utilizing MDSAP, but their methods of utilization significantly differ. Canada, as a member of the MDSAP Regulatory Authority Council (RAC), directly conducts assessments and recognitions of MDSAP Auditing Organizations, and has adopted MDSAP audits as its sole inspection method. In contrast, QMS inspections in the EU are conducted by certification bodies recognized by the EU. These EU certification bodies are recommended to utilize MDSAP audit reports to exempt certain procedures during their routine sampling inspections, referred to as surveillance audits. The extent of MDSAP utilization in the EU may reflect differences in the assessment and reliability of the certification bodies.

Characteristics and Usefulness of MDSAP as an Inspection Method

Inspection strategies for medical devices significantly vary by country. MDSAP is actively utilized alongside existing inspection methods, complementing the inspection strategies of various countries. This section clarifies the characteristics of MDSAP by comparing and organizing the advantages and disadvantages of on-site inspections, desktop inspections, and MDSAP audits, while evaluating its usefulness (see Table 3).

On-site inspections conducted by a single authority are unsuitable for covering many facilities due to the cost, and desktop inspections depend on the reliability of the documents submitted by the entity under inspection (Table 3). On the other hand, MDSAP is characterized as a low-cost inspection method that can achieve results with reliability equivalent to on-site inspections conducted by regulatory authorities and is applicable to a wide range of facilities. In Japan, MDSAP is extensively utilized for inspections of foreign manufacturing sites (Fig. 3), suggesting its use to obtain more reliable results for high-risk medical devices at a lower cost than on-site inspections and more reliable than desktop inspections.

In MDSAP RAC member countries, where efforts have been made to ensure the reliability of MDSAP Auditing Organizations, the program is valued as a compensatory measure that addresses the deficiencies of on-site and desktop inspections. Therefore, it is highly utilized as a supplement to each country's primary inspection methods.

Table 3. Comparison of Advantages and Disadvantages by Inspection Method.

Inspection Method	Reliability	Cost	Advantages and Disadvantages
On-site inspection	It is the most reliable because it provides direct information from the facility	In addition to travel expenses for visiting the manufacturing site, it is necessary to allocate inspection man-days, resulting in high administrative costs	Although it is highly reliable, the high administrative costs limit the facilities to which it can be applied
Desktop inspection	It relies on documents provided by the facility being inspected. Therefore, its reliability is inferior to On-site inspections and MDSAP inspections	Since there is no need to go to the site directly, the administrative costs are low	While administrative costs are low, reliability depends on information provided by the entity under inspection. Therefore, careful consideration is required when applying this to high-risk medical devices
Inspection conducted under MDSAP	When the reliability of a certification body can be directly confirmed, the results of audits conducted under MDSAP are guaranteed to have a level of trustworthiness equivalent to an on-site inspection by national authorities	Inspections of manufacturing sites are conducted by certification bodies. Although there is a certain cost for assessing the certification bodies, the administrative costs are moderate because the number of entities being assessed is limited. Additionally, the costs associated with the assessments are apportioned among the MDSAP participating countries	The reliability is comparable to on-site inspections conducted by national authorities, but the administrative costs are kept low. Since the inspections are carried out by certification bodies, they can be applied to a wide range of manufacturing sites, offering high-cost performance

However, as suggested by the case of the EU, which does not directly engage in activities to ensure the reliability of MDSAP Auditing Organizations, the current utilization might be limited in countries not performing such activities. While MDSAP's use has advanced in major countries, its usefulness as a regulatory reliance method could spread further as more countries engage in activities to ensure the reliability of MDSAP Auditing Organizations.

Conclusions

A fundamental premise for advancing regulatory reliance is the trustworthiness of the information used. In the pharmaceutical sector, PIC/S has proposed capability verification for developing trust relationships through initiatives like the Joint Inspection Program to facilitate reliance between countries [3].

Conversely, in the medical device sector, not all countries use governmental agencies for inspections; some utilize certification bodies as inspection authorities, and some cannot allocate resources for on-site inspections. Therefore, it appears challenging to pursue reliance in the medical device sector through an approach that presupposes on-site inspections by regulatory authorities, such as joint inspection programs discussed in the pharmaceutical sector. In MDSAP, participating countries jointly assess the capabilities and reliability of certification bodies and utilize the outcomes. Within the medical device sector, it has been observed that MDSAP is actively adopted as a method complementing other inspection techniques like on-site and desktop inspections in major countries as part of the reliance framework.

MDSAP transitioned from its pilot phase to the operational phase in 2017 and has been gradually expanding its membership since then. As of May 2024, in addition to the RAC members that discuss the operation of MDSAP, WHO, the EU, Singapore, and the UK participate as official observers who join assessments of MDSAP certification bodies and related meetings, supporting MDSAP activities. In 2019, the creation of Affiliate Membership formally recognized countries that use MDSAP, with Argentina, Israel, Mexico, South Korea, and Taiwan registered as such members as of May 2024. In January 2023, MDSAP RAC released guidance titled "MDSAP Roles and Responsibilities," which made public the membership acceptance criteria for RAC members, official observers, and Affiliate Members [10]. For instance, this guidance specifies that becoming a member of the RAC, which discusses MDSAP's operation, requires signing a Confidentiality Agreement (CA) with all other RAC member countries. Japan, for example, has signed a CA with all RAC member countries (Table 4). Establishing a CA is not an overnight process but requires building trust relationships and track records through years of

Table 4. Status of confidentiality Agreements Between Japan and the Other RAC Member Countries.[a]

Country Name	Date of Signature to the Confidentiality Agreement
US	15 Sep. 2004
Canada	9 Oct. 2009
Australia	6 Sep. 2011
Brazil	26 Nov. 2012

[a]PMDA, Bilateral Cooperation, https://www.pmda.go.jp/english/int-activities/bilateral/0003.html

bilateral exchanges. It is hoped that the number of countries involved in MDSAP will expand with the cooperation of various nations.

The advancement of regulatory use of MDSAP is expected to facilitate the acceleration of market access and the realization of efficient regulation, which are the goals of reliance. The future development of MDSAP warrants close attention.

Author Contributions

KI and TK contributed to the conception, design of the work, analysis and interpretation of data for the work, drafting and revising of the manuscript. MK contributed to the interpretation of data for the work and revising of the manuscript.

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Data Availability

No datasets were generated or analysed during the current study.

Declarations

Conflict of interest

The authors declare no competing interests.

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