ISSN:3007-9640 DOI: https://doi.org/10.70114/acmsr.2025.2.1.P13

The Analysis and Discussion of Risks Related to FDA Adverse Event of Continuous Glucose Monitoring System

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Abstract. Adverse events are one of the important bases for the re-evaluation of the safety and efficacy of medical devices. According to MAUDE, the U.S. Food and Drug Administration's (FDA) adverse event monitoring database, the factory-calibrated, integrated continuous glucose monitoring system (iCGM) received 130088 adverse events reports during the first half of 2023, ranking the second highest among all devices. In this paper, we conduct a multi-dimensional analysis of 130088 adverse events, summarize the main risk points of CGM products, and discuss these risk points accordingly. The analysis in this article can provide a reference for manufacturers, users, and regulators to provide risk management and control of CGM products.

Keywords: Continuous Glucose Monitoring System (CGM); Adverse Event; Regulatory Science.

1. Introduction

1.1 CGM Product Brief

At present, there are two main ways to self-monitor blood glucose in diabetic patients, traditional blood glucose monitoring (BGM) and continuous glucose monitoring (CGM). Continuous glucose monitoring can detect the patient's blood glucose level in real time, and has the ability to find hidden hyperglycemia and hypoglycemia that are not easy to be detected by traditional detection methods, which has become a new trend in blood glucose monitoring. In China, CGM products are classified as 07-04-03 according to the 2017 edition of the Classification Catalogue [1], and the management category is classified as Category III. In the United States, CGM products have a regulatory number of 862.1355 and a management category of 2, which requires marketing approval through the 510k route.

In recent years, a number of CGM manufacturers have emerged, and the number of product registrations has increased year by year. As a major market for medical devices, this paper retrieved the registration certificate information published by the State Food and Drug Administration of China and the product registration information in the United States FDA database, and Figure 1 lists the approvals of continuous glucose monitoring system (CGM) products in China and the United States in the past five years. It can be seen from the figure that the United States market is relatively mature, with an average annual number of approved products of 3-6, while the Chinese market is growing rapidly, except for 22 years of no approved products, 4 products have been approved for listing in 21 and 23 years, showing a significant increase compared with 2019 and 2020.

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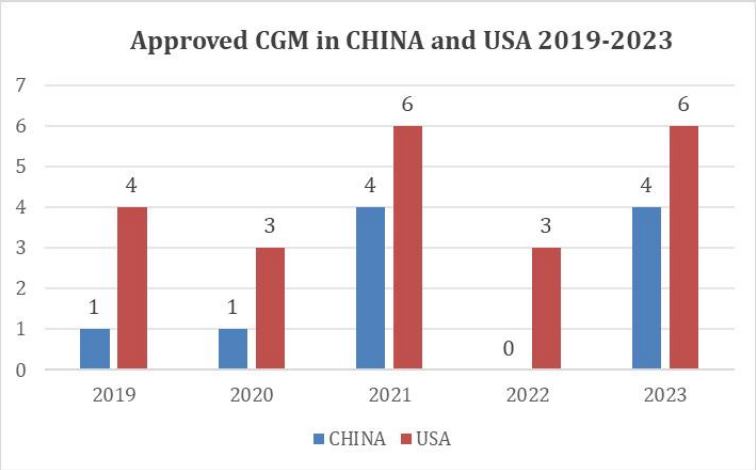

Figure. 1 Approved CGM in CHINA and USA 2019-2023

1.2 Adverse Events And Medical Devices

Adverse events are of great significance for the re-evaluation of the safety and effectiveness of medical devices. In fact, regulatory agencies around the world take AE monitoring very seriously. In China, the National Medical Products Administration (NMPA) regulates medical products, including drugs, medical devices, and cosmetics. In order to timely and effectively control the post-marketing risks of medical devices, standardize the monitoring and evaluation system of adverse events of medical devices, and clarify the requirements for post-marketing re-evaluation of medical device products, the Chinese government has implemented the Administrative Measures for the Monitoring and Re-evaluation of Adverse Events of Medical Devices (Order No. 1 of the State Administration for Market Regulation). The types of adverse event reporting units are mainly from the holders of registration certificates, medical institutions and other users and operating enterprises, and the individual reporting channels of consumers or patients are not yet open. At the same time, in 2019, China established a new "National Medical Device Adverse Event Monitoring Information System", which realizes the online filling, review, evaluation and statistics of different types of reports. Holders of registration certificates, medical institutions above the second level and operating enterprises need to register as users of the system to report adverse events of medical devices online, and monitoring agencies at all levels review the reported adverse event reports through the system. The holder of the registration certificate shall evaluate the adverse events found in the system and improve the product quality according to the evaluation results, and if it is found that there may be an unreasonable risk of endangering human health and life safety, the production and sales shall be stopped according to the circumstances; implement product recalls; disseminating risk information; Modify instructions, labels, and operating manuals; Improve production technology, design and other risk control measures, and should be announced to the public in a timely manner. In addition, China publishes the National Annual Report on Adverse Event Monitoring of Medical Devices every year to summarize the annual monitoring.

In the United States, the United States Food and Drug Administration (FDA) regulates human drugs, veterinary drugs, biological products, medical devices, food, cosmetics, radioactive products, and tobacco. Adverse event reporting is subject to the provisions of 21 CFR Subchapter H Part 803. FDA has established a database called Manufacturer and User Facility Device Experience (MAUDE) to store AE reports from manufacturers, importers, device user facilities, healthcare professionals, patients, and consumers, among others. For manufacturers, importers, and hospitals, AE reporting is mandatory as required by 21 CFR Subchapter H Part 803. Whereas, for other stakeholders, such as healthcare professionals, patients, and consumers, reporting for AEs is voluntary. AE reports were received through a safety information and adverse event reporting procedure called MEDWATH. Each year, FDA receives hundreds of thousands of Medical Device

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Reports (MDRs) of suspected device-related deaths, serious injuries, and failures. The MAUDE database is open to the public and users can search and download the data. FDA has also established a medical device recall database to store recall reports. Medical device recall reports are regulated under 21 CFR Part H Part 806. The medical device recall database is also available to the public.

2. AE Data Analysis

This article analyzes the 130088 adverse event reports of the United States Food and Drug Administration's (FDA) MAUDE database in the first half of 2023 on the factory-calibrated Integrated Continuous Glucose Monitoring System (iCGMS). Adverse event reports were analyzed from different perspectives and the main risk points of CGM products were extracted.

2.1 Word Cloud Analysis

According to the results of word cloud analysis in Figure 2, the three root words with the highest word frequency are probabl, caus, and medic, and their corresponding meanings are "probable", "cause", and "medical", respectively. It is worth noting that loss&data occurs more frequently, pointing to information and communication problems, and the results of subsequent adverse event data analysis confirm this observation. In addition, injuri&alleg's point to patient injuries and allergies also suggests that allergies to iCGMS products are a cause for concern.

Figure. 2 Word Cloud of AE Description

2.2 Patient Harm Distribution

From Figure 3, the vast majority of patients reported adverse events were asymptomatic (87.39%). The remaining 16,573 adverse events were further analyzed with different clinical symptoms, of which 14,291 were related to glycemic symptoms (accounting for 86.23% of the total number of symptoms, including 11,489 cases of hyperglycemia and 2,802 cases of hypoglycemia). For the other symptoms of 2282 patients with adverse events (Fig. 5), the top proportions were loss of consciousness (27.17%), dizziness (16.78%), foreign body sensation (15.86%), and general malaise (13.06%).

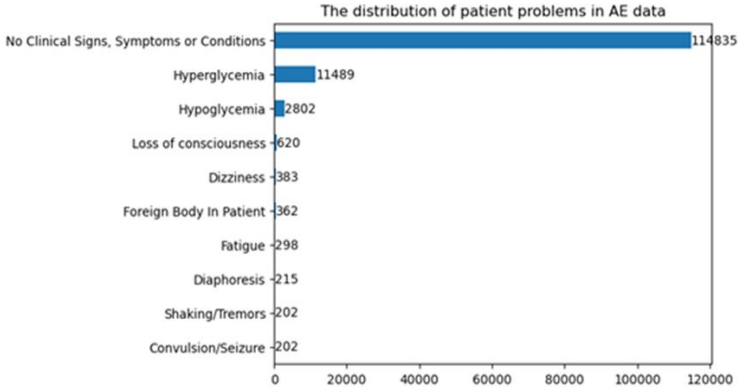

Figure. 3 Patient Harm Distribution

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2.3 Device Problem Distribution

Figure 4 details the top 10 medical device problems in the CGM system in this adverse event, with a total of 125868 cases, accounting for 96.76% of the total number of adverse events. As can be seen from the figure, wireless communication problems account for the largest proportion (54.70%). The second problem was related to the test results, accounting for 30.91% of the total number of problems, including the comprehensive problem of no output signal (16.03%), as well as the simple inaccurate reading (11.07%), incorrect reading (2.88%), and failure to read (0.93%). Finally, there are various software and hardware problems, accounting for 14.40%, including early termination (6.90%), unexpected program shutdown (2.80%), corresponding term/code unavailability (1.74%), and a small number of problems such as component disengagement (1.64%) and power connection (1.03%).

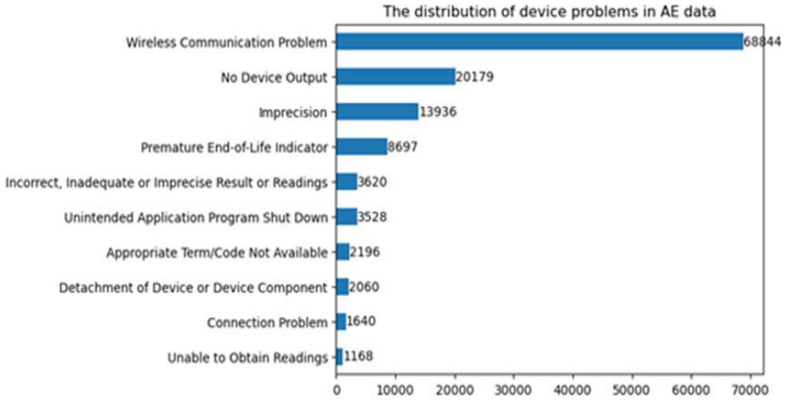

Figure. 4 Device Problem Distribution

2.4 The Correlation Between Patient Harm and Device Problem

The relationship matrix analysis was performed on the clinical symptoms and device problems of patients in adverse events of the CGM system (Fig. 5). Inaccuracies in test results were evident in a wide range of symptoms, most notably in hyperglycemia and hypoglycemia, followed by incorrect or no readings in hyperglycemia and hypoglycemia, and foreign body sensation in the presence of component detachment. At the same time, the biggest wireless communication problem with the instrument is not obvious in the patient's symptoms.

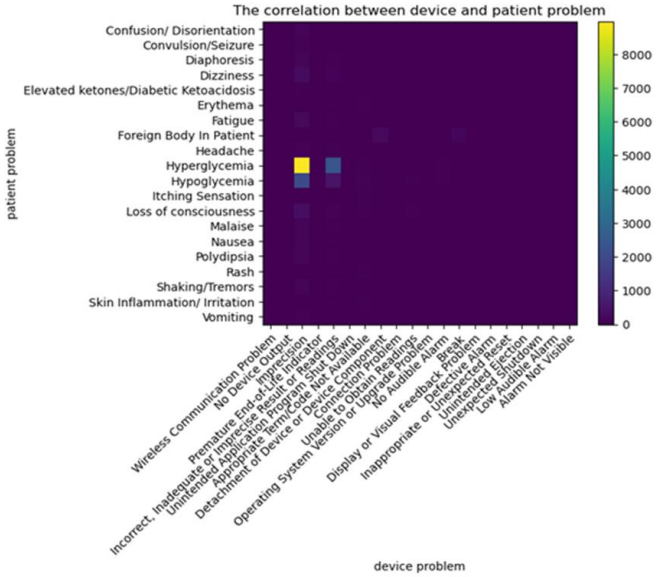

Figure. 5 The Correlation Between Patient Harm and Device Problem

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2.5 AE Data of China

In addition to the FDA adverse event analysis, this article supplements this article by analyzing 10 cases of CGM-related adverse events in Fujian Province, China from 2019 to March 2024 in China, which are reported from users, operating enterprises, and holders such as medical institutions. Device issues are shown in Table 1 below

Table 1. Summary of AE in Fujian Province

Event Description	Count
Inaccurate display	3
Connection failure	3
Operational failure	1
Dilapidation	1
Monitor fall off	1
Sensor placement fail	1

3. Results And Discussion

3.1 Wireless Connection Problem

According to the analysis of device problems above, wireless transmission problems account for the largest proportion, and the specific causes of wireless transmission are not clear in the data set, but according to the experience of previous reviews, radio frequency interference, software design problems, network security problems, etc., may lead to wireless connection errors.

In terms of RF interference, manufacturers can refer to some international industry standards, such as AAMI TIR69:2017/(R)2020 Risk Management of RF Wireless Coexistence for Medical Devices and Systems[2], which provides requirements and guidelines for RF wireless coexistence and risk management for medical devices. In addition, the FDA has issued a guideline entitled "Radio Frequency Wireless Technology in Medical Devices"[3], the current version of which was published in 2013. Medical devices that use RF wireless technology should be evaluated for their ability to function properly in a shared electromagnetic environment. The evaluation should be carried out in detail with a detailed analysis of the parameters of the device function, wireless function, wireless technology, and wireless technology. Based on risk analysis, coexistence testing is performed according to the test plan according to the risk category (high risk, medium risk, low risk, no significant risk). The test plan should specify the test indicators, reception criteria, test methods, test recording events, the electromagnetic environment in which the device is expected to be used, and the unexpected signals used during the test. Test metrics include, but are not limited to, throughput, latency, bit/number packet error rate, and availability.

In terms of cybersecurity, in 2022, the Center for Medical Device Evaluation of the NMPA issued the Guidelines for the Review of Cybersecurity Registration of Medical Devices (2022 Revised Edition)[4], which put forward specific requirements for the cybersecurity of medical devices to ensure the safety and effectiveness of product cybersecurity. The United States Food and Drug Administration's (FDA) guidance on cybersecurity currently in effect mainly includes three parts, namely, premarket cybersecurity design, identification and document submission, post-market cybersecurity management, and cybersecurity considerations for OTS software [5,6,7]. These guidelines provide comprehensive coverage of the cybersecurity management requirements for pre- and post-market products. In March 2024, the FDA released a draft of the revised cybersecurity guidance, which is called "Select Updates for the Premarket Cybersecurity Guidance: Section 524B of the FD&C Act"[8], in which the main change is the addition of a new proposal for cyber devices to meet the FD&C Act 524B(b) to submit cyber security information. The draft content will be added to Chapter 7 of the Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions [9] to support the obligations under section

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524B of the FD&C Act. Under the framework of the EU Medical Device Regulation (MDR), the Medical Device Coordination Group (MDCG) has also issued the "MDCG2019-16 Rev.1 Guidance on Cybersecurity for Medical Devices" [10], which elaborates on the specific requirements of the European market in terms of cybersecurity design, production, instruction manual preparation, and aftermarket adverse event handling at the system level. At the same time, the International Medical Device Regulatory Forum (IMDRF), as the leading body to coordinate the regulatory requirements of various regulatory agencies around the world, has also issued three guiding technical documents on the principles and practices of medical device cybersecurity, aiming to unify and improve the management level of global medical device cybersecurity.

Based on the experience of previous reviews, the cyber security problems of CGM products are relatively high, which deserves more attention from manufacturers and regulators. With the development of cloud computing technology, more and more CGMs use cloud computing to store and transmit health data, and manufacturers should refer to the Guidelines for the Registration and Review of Medical Device Software (2022 Revised Edition) issued by the State Food and Drug Administration to prepare corresponding research materials. In addition, the rights and responsibilities of data management should be clarified to ensure that the data custodian has the corresponding medical data management qualifications, and if the data is stored outside the hospital, it should be clarified whether the institution has the health data management qualifications. In addition, if data export is involved, it shall comply with the requirements of relevant national laws and departmental rules.

3.2 Monitoring Accuracy

Through the comprehensive analysis of the results, it was found that the inaccuracy of CGM test results was a common problem in adverse events, especially in patients with abnormal symptoms of hyperglycemia or hypoglycemia. In this case, there is often a mismatch between the patient's own symptoms and the CGM blood glucose monitoring value, so it is especially prudent to monitor blood glucose in patients with acute and critical illness in the case of stress hyperglycemia, asymptomatic hypoglycemia, and large fluctuations in blood glucose. This is also reflected in the study of the use of CGM in critically ill patients, which showed that the accuracy of CGM in the range of low glycemic values was poor by statistical analysis of blood glucose and fingerstick blood glucose values in 1504 groups of 52 patients [11].

In addition, for the problem of inaccurate test results, not only the sensitivity of the device sensor, but also the situation of the subject should be taken into account. Patients requiring glucose monitoring are often treated with exogenous interfering agents such as acetaminophen, ascorbic acid, aspirin, ibuprofen, hydroxyurea, and others [12]. In addition, for CGM systems that measure blood glucose in interstitial fluid through sensors, endogenous interferences such as uric acid, such as uric acid, and even human muscle mass, may affect the accuracy of the monitoring results [3].

4. Conclusion

Post-market data of medical devices is of great significance to control product risks and ensure product safety and effectiveness. Taking real-world data such as post-listing adverse events, recalls, and customer complaints as the basis for regulatory decision-making, conducting in-depth analysis of these data, and taking the analysis conclusions as input for the formulation and revision of relevant guidelines and standards, and taking the main risk points as the focus of technical review, can greatly improve the efficiency of supervision, enhance the targeting of supervision, and help enterprises form a closed loop of risk.

In this article, we delved into the adverse event data of CGM from FDA’s MAUDE database. We analyzed the data from different aspects and gained some insights, including the main types of device errors that led to adverse events. According to data retrieval and analysis, CGM products show a high incidence of adverse events, so continuous tracking and analysis of adverse events is

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particularly important to improve product design, control major risks, and improve product safety and effectiveness. Future work includes continuous follow-up of adverse events of CGM products in major countries and simultaneous analysis of adverse event data, which may be considered for inclusion in more countries such as the European Union and Australia databases.

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