Regulation of veterinary point-of-care testing in the European Union, the United States of America and Japan

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Summary

Point-of-care testing (POCT) is used to detect diseases and other conditions or to monitor therapeutic procedures. In veterinary medicine, POCT not only helps during the prevention, diagnosis and treatment of animal diseases but it also has a direct impact on human health by safeguarding food supplies and preventing zoonoses. Despite its importance, the regulation of the quality, safety and effectiveness of POCT products is rarely discussed. This review reveals that the level of regulatory surveillance of veterinary POCT products in the European Union (EU), the United States of America (USA) and Japan is strikingly different, ranging from no regulation (EU) to comprehensive regulation which is comparable to the procedures for the regulation of human *in vitro* medical devices (Japan). Details about the licensing procedures in these three locations, discussion of their strengths and weaknesses, and suggestions for possible future development of the regulation of these products are also provided.

Keywords

European Union – Japan – Point-of-care testing – Regulation – United States of America – Veterinary diagnostics.

Introduction

Point-of-care testing (POCT), based on the *in vitro* analysis of biological specimens, is routinely used to detect diseases, monitor therapeutic procedures and provide prognosis (1). This broad term encompasses the use of diagnostic products ranging from simple non-active consumables (e.g. lateral flow tests) to sophisticated benchtop instruments (e.g. haematology analysers). In small animal practices, POCT provides data for immediate medical decisions to improve patient outcome, increase owner satisfaction and also maximise clinic profitability (2). In livestock management, POCT analysis (of milk etc.) is often used in line with the principles of precision farming to control health and welfare of the animals effectively or to facilitate breeding by detecting oestrous cycle, pregnancy or fertility problems (3, 4).

Veterinary POCT may also directly influence human health by safeguarding food supplies and enabling timely detection, prevention and control of zoonoses outbreaks. In fact, the majority of emerging human pathogens are zoonotic in origin (5) and their uncontrolled spread may have devastating impacts on global health and economy, as seen recently during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic (6). In this scenario, the role of veterinary POCT is not in the identification of new zoonotic diseases but in the early detection of already known infectious agents. Veterinary POCT can also be used for first-line testing of biological samples from livestock and wildlife before their transfer to centralised laboratory facilities (7). The effectiveness of this approach was well illustrated during the latter stages of the Global Rinderpest Eradication Programme (GREP). Additionally, such decentralised POCT can decrease economic losses by reducing the unnecessary slaughter of uninfected animals in situations where rapid action is needed to prevent the spread of disease (8, 9).

To ensure the above-mentioned functions, the data gained by POCT must be sufficiently reliable (10). Each POCT product has its limitations in terms of sensitivity and specificity but these limitations must be duly determined by the manufacturer and must correspond to the intended use of the product. There are several global guidelines available addressing the quality of veterinary diagnostics. First, veterinary laboratories can implement International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) 17025, which specifies general requirements for the competence, impartiality and consistent operation of analytical laboratories. Second, the World Organisation for Animal Health (OIE), an intergovernmental organisation with 182 Members, has developed two approaches to facilitate the regulation of veterinary diagnostics. Most importantly, it publishes the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*) and the *Manual of Diagnostic Tests for Aquatic Animals* (*Aquatic Manual*) which provide internationally agreed standards, guidelines and recommendations for the use of diagnostic laboratory methods and veterinary diagnostic kits analysing samples from terrestrial and aquatic animals, respectively (11, 12). Additionally, the OIE maintains a register of diagnostic kits with validated 'fitness for purpose', i.e. kits with proven performance (13). Fourteen kits are currently registered but nearly all of them have been designed for laboratory use. Specific guidelines for POCT would be beneficial to support the decentralised use of these rapid tests and methods by laypersons and untrained veterinary professionals in an uncontrolled environment (farms, households and small animal practices).

In human medicine, products used for POCT are regarded as *in vitro* diagnostic (IVD) medical devices. These devices are subject to comprehensive regulation in all developed countries such as the European Union (EU), the United States of America (USA), Japan, Australia and Canada (14) and some form of regulatory oversight is applied in most countries worldwide (15). The degree of regulation varies greatly among the different locations and depending on the risk class of the product (14, 16). Regulations typically apply to the entire product's lifecycle to ensure its quality. They affect development

(e.g. design, transfer to production), pre-market (e.g. labelling, advertisement) and post-market (e.g. vigilance, post-market surveillance, disposal) activities. Given that the variety and complexity of regulatory processes may limit the availability of products on the market, several organisations such as the World Health Organization (WHO) and the International Medical Device Regulators Forum (IMDRF) strive for their international harmonisation (13, 17).

Despite equivalent roles of human and veterinary POCT products, the regulatory status of the latter is far less clear and rarely discussed. The relevant sources are scarce and, if available, they focus on the international harmonisation and licensing procedures of laboratory diagnostic methods rather than on POCT (10). Yet these products are widely available to end-users such as farmers, veterinarians and animal owners, and are therefore increasingly important in current veterinary practice.

This article aims to provide an insight into the regulation of these POCT products in the EU, the USA and Japan. These three locations are among the founding members of relevant international regulatory groups such as the Veterinary International Conference on Harmonization (VICH) (18) and the IMDRF (19). As such, they significantly influence global regulation and present a role model for other states. The USA, the EU and Japan are also the biggest producers of medical devices, together accounting for more than 85% of the world's market (20). The quality of their products directly influences users all over the world. The presented comparison should not only provide useful information for veterinarians, animal owners, manufacturers and policymakers but also initiate discussion about the regulation of these products.

European Union

Currently, there is no harmonised EU legislation on veterinary POCT products (21). However, in common with all products marketed in the EU and not regulated by dedicated legal acts, veterinary POCT products must comply with Directive 85/374/EEC on product liability

and Directive 2001/95/EC on general product safety. In addition, POCT products using electrical energy (e.g. blood chemistry analysers) are further subject to Directive 2014/30/EU on electromagnetic compatibility and Directive 2014/35/EU for low voltage instruments. Given that none of these directives has been designed to evaluate the specific properties of veterinary POCT products, some EU member states have adopted national laws to ensure their safety and performance while others (e.g. Belgium and Italy) have no specialised rules that cover these products. This lack of a harmonised approach leads to different scopes of regulation and unequal legal requirements among EU member states and creates barriers within the single market. More details of national approaches are outlined below.

Veterinary POCT kits (sets of reagents) are subject to national regulation in several EU countries. The subject of these regulations may be further specified as intended to test tissues and body liquids of food-producing animals (Bulgaria) (22), manufactured from or with the aid of microorganisms or parasites (the Netherlands) (23), used for serological diagnosis of animal diseases (Romania) (24) or designed to detect infectious diseases, biological impurities and residues of prohibited substances in animal tissues and animal products (Poland) (25). Each country then applies its national legislation to grant marketing approval. The marketing applications include administrative data, product description, summary of analytical performance and instructions for use in the local language. In addition, product samples need sometimes to be provided for local testing by national reference laboratories.

In other EU countries, veterinary POCT products and their accessories are divided into different legal categories based on their risk potential. In Germany, substances for veterinary diagnostics may be subject to German drug law and classified as 'fictitious' medicinal products (26). These IVD products for animals (e.g. reagents for enzyme assays, electrolyte analysis or clinical haematology) are perceived as low risk and can be marketed freely provided that they have been manufactured under the Good Manufacturing Practice (GMP)

standards. Those POCT products that are produced with the use of epizootic pathogens or biochemical or biotechnological procedures are regulated by the German Animal Health Act (27). In cases where these tests are used to diagnose epizootic diseases, the Friedrich-Loeffler-Institut (FLI) has jurisdiction over these products and issues product licences that are required to market these tests in Germany. All regulated POCT products are subject to post-market surveillance.

Few EU countries regulate both veterinary POCT kits and diagnostic instruments. In Spain, POCT kits and instruments are treated equally (28). In the Czech Republic, diagnostic instruments are subject to notification while POCT kits require official approval (29). Basic data about the applicant, product and manufacturing site must always be provided. In the case of POCT kits, the adherence to GMP principles is also reviewed. Products are then entered into a corresponding national database and can be placed on the Czech market. A similar approach is adopted in Slovakia (30) and partially also in Croatia (31).

These examples illustrate the complexity of the regulatory environment in the EU. Given that the national regulatory requirements may be difficult to find, the European Medicines Agency (EMA) recommends contacting the national competent authority before marketing a product (32).

It is worth noting here that the EU has recently adopted new legislation to regulate POCT products for human use (16). The Regulation (EU) 2017/746 on IVD medical devices should guarantee improved safety, quality and performance of these products by increasing regulatory requirements (33). However, no efforts were made to adopt even a basic level of regulation of veterinary POCT products at the EU level (10).

United States of America

In the USA, veterinary and human medical devices are both defined by the Federal Food, Drug, and Cosmetic Act (FD&C Act), paragraph 321h (34). Veterinary medical devices, including POCT products, fall

under the jurisdiction of the United States Food and Drug Administration (FDA), whose Center for Veterinary Medicine (CVM) maintains regulatory oversight and can take an action if a product is adulterated or misbranded. Although manufacturers and distributors may request a review of their product labelling and promotional literature, veterinary POCT products are not subject to any compulsory pre-market clearance. All issues are addressed late in the post-marketing phase, which is in direct contrast with the comprehensive pre-market control of POCT products for human use (35). While product manufacturers are exempt from compulsory post-marketing reports, veterinarians and animal owners are encouraged to report suspected adverse events and thus contribute to safety monitoring. Adverse events associated with these veterinary POCT products are processed by the CVM under the FD&C Act and published on openFDA.gov (36).

Veterinary POCT kits for the detection of animal diseases or immunological status are further regarded as veterinary biological products. The authority for their regulation is provided by the Virus-Serum-Toxin Act (VSTA) and detailed in Title 9, Code of Federal Regulation (CFR), Parts 101–124 (37, 38). Jurisdiction over these products is held by the Center for Veterinary Biologics (CVB) of the United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS).

The safety, purity, potency and efficacy of veterinary biological products are ensured by a system of licences (38). Generally, only licensed products may reach the USA market. The product licensing has two levels depending on the intended use of the product (37). All diagnostic kits are subject to primary evaluation of sensitivity, specificity and reproducibility, which includes testing of proficiency panels in multiple laboratories to demonstrate interlaboratory equivalence. Additionally, POCT kits used during official control and/or eradication programmes are further subject to a secondary evaluation, which is more rigorous and involves extensive field tests of characterised animal populations (e.g. infected herds or herds imported from high-risk areas). Furthermore, the sale and distribution

of these products may be controlled by CVB and limited to APHIS-approved laboratories. In the post-marketing phase, the submission of test results for each batch produced is required (36). Only batches with satisfactory results are approved for marketing.

The CVB also issues establishment licences for USA based manufacturers. The proposed manufacturing and testing facilities must meet the requirements outlined in the VSTA (38). Licences are not issued for foreign establishments. Foreign manufacturers have to appoint a USA based representative that is required to obtain the permit for distribution and sale and bears legal responsibility for imported products. These products must meet the same licensing requirements as those produced domestically.

Since 2018, licence and permit holders are also obliged to maintain a registry of all adverse events, e.g. product failures that hinder the discovery of the correct diagnosis, which are possibly related to their veterinary biological products (37, 38). Adverse events need to be reported to the CVB in an expedited manner or within 90 days depending on their seriousness.

Japan

The basis of the regulation of human and veterinary medical devices in Japan is specified by the Pharmaceutical and Medical Devices Act (PMD Act) (39). The Ministry of Agriculture, Forestry and Fisheries (MAFF) holds jurisdiction over affairs concerning veterinary medical devices, including POCT, and releases legally binding Ministerial Ordinances which further specify details of their regulation. The regulation has a broad scope and includes all kinds of veterinary POCT products regardless of their design and target analyte. Analogically, the Ministry of Health, Labour and Welfare is in charge of human POCT.

Three different steps are required to market POCT products (and medical devices in general) in Japan (39). Each company has to *1)* register its manufacturing plant by the local prefecture (Japanese manufacturers) or by the corresponding ministry (foreign

manufacturers), *2)* appoint a marketing authorisation holder (MAH), who obtains the manufacturing/marketing licence to demonstrate the sufficiency of their quality systems, and *3)* obtain a product approval for each marketed device.

The procedures for the registration of manufacturing site and MAH appointment are identical for both veterinary and human POCT products. For product approval itself, separate systems apply. Human POCT is divided into three classes based on the 'diagnostic' risk (40). Generally, the devices belonging to the lowest risk class I can be marketed based on self-certification, class II devices require certification by one of the designated third parties and class III devices need to obtain ministerial approval. During this most demanding form of approval, the design, specification, active ingredients, assay procedure, instructions for use, performance, method of manufacturing, proposed storage, shelf life and other related characteristics of the product are evaluated by the Pharmaceuticals and Medical Devices Agency (PMDA). If all requirements are met, the ministry grants product approval. The entire process may take up to 12 months, excluding the time needed for correction of documentation by the applicant.

Contrary to this, there is no third-party certification for veterinary POCT and these products are therefore divided into two classes only. Products that meet the calibration standards set by ministerial notice no. 794 of 2017 can be marketed after notification of the competent authority, which is the National Veterinary Assay Laboratory (NVAL). The process is comparable to the self-certification of human class I products. However, the list of calibration standards is still rather limited and fewer than 50 products have been cleared via this pathway so far. The majority of veterinary POCT products, including all biological products (e.g. those used to diagnose infectious diseases), therefore require ministerial approval. This procedure is equivalent to the clearance process of human class III devices and represents the most demanding form of product approval.

In the post-marketing phase, on-site inspections to verify compliance with GMP are scheduled every five years (41). The updating process usually takes at least three months. The device approval itself does not expire.

Discussion

Timely and accurate detection of animal diseases is crucial for animal health management, sustainable food production and prevention of zoonoses (4, 9, 42). The development of affordable and easy to use POCT products is one of the important tasks of current veterinary medicine. Their use in an uncontrolled environment by untrained personnel places high demands on POCT characteristics, requiring clear instructions, simple operation and maintenance, unambiguous interpretation, robust performance, and wide transport and storage conditions.

In the case of human POCT products, the above-mentioned characteristics are tightly regulated by competent national authorities. Indeed, approximately 30% of all countries worldwide have some form of regulation concerning IVD medical devices for human use (15). Among them, the EU, the USA and Japan represent locations with high regulatory standards that try to harmonise their legal requirements for healthcare products, including human medical devices (19) and human and veterinary medicinal products (18, 43). Nevertheless, their approaches to the regulation of veterinary POCT products are strikingly different (Table I).

Table I

Comparison of the regulatory system of veterinary point-of-care testing in the European Union, the United States of America and Japan

	Regulated products	Requirements		Manufacturing approval	Competent authority	Note
		pre-market	post-market			
EU	EU level: POCT using electrical energy (e.g. biochemistry analysers)	CE mark	–	–	Decentralised (local/national authority)	Compliance with electromagnetic compatibility and low voltage directives is required
	National level: from 'none' to 'all POCT' (depends on the EU country)	see Note	see Note	see Note	National authority	If the EU country regulates veterinary POCT, specific requirements are set at national level
USA	All POCT	–	–	–	CVM (FDA)	CVM can take action if a product is misbranded, adulterated or unsafe
	Veterinary biological products (e.g. diagnostic kits)	Product licence	Reporting of adverse events; reporting of test results for each batch	Establishment licence	CVB (USDA-APHIS)	Products are classified based on their intended use
Japan	Low-risk POCT (with established calibration standards)	Notification	Good Vigilance Practice (all products)	Manufacturing plant registration + manufacturing licence	NVAL (MAFF)	Requirements are similar to human POCT from risk classes I and III, respectively (e.g. compulsory adherence to GMP)
	High-risk POCT (all other products)	Ministry approval	Good Post-marketing Study Practice (selected products)			

CE: European Conformity
CVB: Center for Veterinary Biologics (USA)
CVM: Center for Veterinary Medicine (USA)
EU: European Union
FDA: Food and Drug Administration (USA)
GMP: Good Manufacturing Practice
MAFF: Ministry of Agriculture, Forestry and Fisheries (Japan)
NVAL: National Veterinary Assay Laboratory (Japan)
POCT: Point-of-care testing
USDA-APHIS: United States Department of Agriculture Animal and Plant Health Inspection Service
USA: United States of America

The EU does not regulate veterinary POCT products at the union level. The lack of harmonisation requires member states to rely fully on their national legislation, which compromises the marketing of existing veterinary products and hinders coordinated development of new products at EU scale (42). The introduction of unified EU regulation was discussed many years ago (32). However, the expected level of such regulation remains unclear because the legal control of the most closely related products (i.e. human IVD devices and veterinary medicinal products) is in a transition phase. Whereas human IVD devices are facing stricter regulations to improve their general safety and performance (44), the administrative burden for veterinary medicinal products has been reduced to strengthen innovation and increase product availability (45).

In the USA, veterinary POCT products are divided into two legal categories based on their target analyte. Those classified as veterinary biologics are considered higher risk and require pre-market approval (37). The remaining POCT products are regarded as veterinary medical devices and are subject to post-marketing surveillance only (34). In both cases, the requirements for placing the product on the US market are clearly defined by law and may be enforced by one of the competent authorities.

Finally, Japan is the only location that regulates human and veterinary POCT products in a similar manner (39). Information about the practical impact of such regulation on the quality and availability of veterinary POCT products is anecdotal. Nevertheless, the abundantly available data on the regulation of human medical devices show that Japanese approval processes are among the most demanding globally (46). This leads to many years of delay for the registration of new products and consequently to limited access to cutting edge technologies and to reduced product availability when compared with the EU and the USA. Foreign manufacturers may even be forced to maintain obsolete product lines to serve the Japanese market.

In contrast to human POCT products, veterinary POCT is divided into only two risk classes in Japan. The vast majority of these products

need to be cleared by ministerial approval, corresponding to the most stringent approval procedure of class III human devices. This means that numerous veterinary POCT products are subject to substantially more rigorous regulation than their human analogues. This issue is illustrated by the activities of the Japan Analytical Instruments Manufacturers' Association (JAIMA), which strives to achieve the deregulation of veterinary IVD in order to establish a proper market offer (47), and by official efforts to import veterinary IVD from the EU to fill their shortage in Japan (48).

The right approach towards the regulation of veterinary POCT products is difficult to determine. Although it seems attractive to adopt the existing regulations for human POCT, it should be noted that the global market for veterinary POCT products is considerably smaller (US$1.4 billion *versus* 29.5 billion) and further fragmented by animal species (49, 50). Therefore, all regulatory efforts should still support the development of new products. A simple risk-based approach to veterinary POCT products requiring pre-market approval of higher-risk products and post-marketing surveillance only for lower-risk products may be sufficient to regulate the safety and effectivity of veterinary POCT products without compromising their availability. Of the three locations studied, such regulation was found only in the USA.

Conclusion

Veterinary POCT products play an increasingly vital role in everyday veterinary practice. Although their quality is crucial for obtaining the correct diagnosis, their legal status is rarely discussed. From the regulatory perspective, veterinary POCT products are mostly regarded as veterinary medical devices for IVD. Compared with human IVD devices, their regulation is less consistent and lacks any form of international harmonisation. The national approaches of the EU, the USA and Japan differ in the scope of the regulated products as well as in the degree of regulatory surveillance. The complexity of the regulatory environment is especially apparent when comparing the EU, which needs to be viewed as 27 individual states rather than a

single market, and Japan, whose legal requirements on veterinary POCT products equal or even exceed the requirements placed on analogous human POCT products. On the other hand, the structured risk-based approach of the USA could serve as an example for the above-mentioned locations and also for other countries worldwide.

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