# **Framework discussion document - veterinary in-vitro Diagnostics**

## Issue summary

AnimalhealthEurope needs to develop an industry position on the harmonisation of regulatory control of in vitro diagnostics (**IVDs**) in the EU.

## Background to the issue

* IVDs is a growing segment within the product portfolios of AnimalhealthEurope member companies (several have acquired diagnostic companies); it is a growing market in both the companion animal and the livestock sectors.
* **There currently is no European legislation regulating diagnostics in the animal health sector.**
* Member companies [will] expect AnimalhealthEurope to address issues related to the regulation of IVDs; an EU association already exists ‘Diagnostics for animals’ (run by SIMV); AhE activities should complement and not duplicate D4A activities.
* 5 member associations represent veterinary diagnostics: BfT (Germany) SIMV (France), Veterindustria (Spain), POLPROWET (Poland) and AISA (Italy ).
* Currently only 4 EU member states (Germany, France, Poland and Spain) have legislation governing the regulation of selected (DE, FR; POL) or all (ES) veterinary IVDs.
* IVD covers a range of disparate products, and different regulatory approaches may be required for each category (e.g. lab tests vs point of care (POC) tests; assays vs instrumentation; notifiable diseases vs other diseases)
* EU Regulations govern the regulation of IVDs (and medical devices) in the human health sector
  + [Regulation 2017/745](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745) of 5 April 2017 on medical devices
  + [Regulation 2017/746](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0746) of 5 April 2017 on in vitro diagnostic medical devices
* The issue of EU legislation to govern the regulation of veterinary IVDs arises periodically within the EU institutions, most recently during the review of the VMP legislation.
* The Portuguese presidency (1H 2021) has voiced the idea again and may put forward a proposal. This is likely to be supported (e.g. by Italy, Belgium, and Greece ministries); also supported by industry in Portugal, Germany (partly), France, Spain, Italy (see [Annex 1](#_Annex_1:_CNA)).
* Results of Italian survey among the EU authorities (presented at HMA in Malta in 2017):
  + 51% of respondents did not regulate veterinary diagnostic products
  + 71% of respondents thought that veterinary medical devices and IVDs should be regulated
* CEN has proposed to establish a technical committee for AH to develop EU harmonised standards for the quality control of diagnostic reagents (see [Annex 2](#_Annex_2:_Proposal))
* There is a risk that rules developed for the human health sector are applied to animal health and are not appropriate.
* AnimalhealthEurope needs to be prepared; global alignment on basic principles is desirable (see HealthforAnimals: “Diagnostics: Plotting a forward-looking regulatory path” Dr 1, March 2021)
* The diagnostics sector is rapidly evolving with new biomarkers and new technologies, including digital technologies, advancing the areas of point-of-care tests and precision livestock farming. A portion of diagnostic work currently carried out at central veterinary laboratories will increasingly migrate to POC testing.

## Scope and definitions

The **scope** of this AnimalhealthEurope activity should be veterinary IVDs. Digital tools connected with precision livestock farming and animal health monitoring should be a separate topic.

**IVDs** are typically testing of biological samples from individual animals with the purpose of detection of a biomarker to diagnose a disease or indicate the health status of an animal. The products can range from supply of reagents (for laboratory analysis systems) to self-contained POC devices. Other definitions in human IVD Regulation - see [Annex 3](#_Annex_3:_summary).

**Regulatory control** can be defined as any method of controlling the quality of product in the marketplace, ranging from self-regulation, to legally binding standards with self-compliance, certification bodies (with/without independent audit) and to legally binding standards with government agency assessed compliance (registration/licence).

## Current activities and next steps

* CNA survey to map which countries in the EU have specific legislation covering veterinary IVDs (done - see [Annex 1](#Annex1) for a summary)
* Analyse the current legislation for the human health sector “medical devices” and “IVD medical devices” ([Annex 3](#_Annex_3:_summary)) and the current veterinary IVD legislation in DE, ES and POL ([Annex 4](#_Annex_4:_National)). Evaluate the positives and negatives, and lessons that can be drawn.
* Assess whether the veterinary sector would also benefit from a harmonised EU set of rules for IVDs, and for each category of IVDs, what level of regulatory control would be suitable.
* Prepare a proposed position paper on a “fit-for-purpose” regulatory system for AH IVDs and circulate internally for comment.

## Human legislation on IVDs

A comprehensive system of certification through MS registered notified bodies, a certification mark on the packaging, comprehensive set of manufacturer obligations (including pharmacovigilance), a traceability system using unique ID numbers, a EUDRAMED database containing: a) registration of devices (b) the UDI-database (c) registration of economic operators (d) notified bodies and issued certificates (e) clinical investigations; (f) vigilance and post-market surveillance.

## EU legislation

There is no EU legislation specifically on Veterinary IVDs; but products need to comply with:

* Directive 85/374/EEC on product liability
* Directive 2001/95/EC on general product safety

There is also a raft of EU legislation governing the safety of electrical/electronic equipment. This is discussed later.

## National legislation on veterinary IVDs

See Annex 4 for Germany, Poland and Spain (France tbc)

## CEN Technical Committee on Animal Health [diagnostics]

AnimalhealthEurope should develop a close working relationship with this new committee. This might be a good strategic move with a view to our global harmonisation/regulatory convergence goals.

Manufacturing quality oversight is an important aspect of safety and quality for diagnostics (e.g. compliance with ISO certification), and should be separated from regulatory approval of a safe and efficacious product.

## Industry preferences

* Some members support to have a regulated market and for diagnostics to meet a minimum standard (e.g. CE label / quality stamp on it that it works).
* A legislative framework would help to clean up the market and could deliver other benefits (such technical data protection promoting investment and innovation).
* A harmonised approach at EU level, adapted to the needs of the veterinary sector and not ‘highest-denominator’ or human copy-cat, and flexible enough to allow for technological advancements.
* Some members do not want additional regulatory control at EU level (but it may be coming)
* Close alignment of approach with that of HealthforAnimals is important, e.g. elaboration of definitions, impact/risk categories, differentiated approach, etc.

## Potential position statements / principles concerning veterinary IVDs

* The goal of the EU legislation should be to promote the access to care, sustainability, compliance and improved animal care that diagnostics can promote.
* The level of regulatory control should be proportionate and reflect the potential impact on animal health or public health (e.g. notifiable diseases, zoonotic diseases) and should follow the “Better Regulation” principles.
* There should be differentiation between types of tests following an impact/risk assessment. For example, qualitative tests and quantitative tests; predictive and monitoring and confirmatory diagnostics; laboratory systems+reagents and POCs; biomarkers for disease and biomarkers for health status.
* Consideration needs to be given whether there is a need to differentiate between companion animals and food-producing animals separately, or between the level of training and education of the owners (for example, the owner capability and type of samples needed (faeces, blood, milk))
* The legislation should include definitions and set out a framework (rather than details) for requirements according to what the inputs are (biological samples, electronic data, etc.), the outputs (qualitative or quantitative measure, specific diagnosis, etc.) and how the data is used (by a veterinarian, to flag risk, by an animal caretaker, etc.).
* A suitable transition period will be required for IVDs already on the EU market
* Approaches need to appropriately consider the investments that companies make, taking into consideration the intellectual property of companies.
* The animal and human diagnostics sectors are different. Applying human health diagnostics rules to the animal diagnostics sector, is not always appropriate.
  + This distinction is important for business and scientific reasons, and the argumentation needs to be expanded. For example:
    - Validation occurs in animal species itself reducing the need for redundant type testing/regulation
    - Stricter regulations increase burden/costs creating barriers to entry

## Instruments and electrical equipment safety compliance

Currently the scope of this discussion paper has been limited to veterinary IVDs. While “tests” in general may not require marketing authorizations, electrical equipment is currently covered under the EU legislation (see list). Currently, these instrument compliance regulations do not distinguish between animal health or human health, and we are not aware of any reason why they should do. Human operator safety applies equally for both sectors.

However, further reflection might be needed on whether to include the aspect of instrument certifications within AnimalhealthEurope reflections and whether there is a need, on some particular points, to have more specific veterinary sector legislation on electrical instrument compliance, to ensure the requirements are not overly burdensome?

* Directive 2006/95/EC on electrical equipment designed for use within certain voltage limits
* Directive 2011/65/EU on RoHS (restriction of hazardous substances in electrical equipment)
* Directive 2012/19/EU on WEEE (waste electrical and electronic equipment)
* Directive 2014/30/EU on electromagnetic compatibility products use electrical energy
* Directive 2014/53/EU on making available on the market of radio equipment

# **Annex 1: CNA SURVEY: Mapping national approaches to the regulation of veterinary medical devices and in-vitro diagnostics**

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## Summary of results

N= 10 (Nordics counted as 1) - 10 replies, representing 14 MSs (Nordics = 4 MSs)

|  |  |
| --- | --- |
| 1. Does your **association** **scope** include medical devices and in-vitro diagnostics within its activities?   YES = Germany France Poland Spain Italy |  |
| 1. Does your government apply the ‘human’ **medical devices** legislation to veterinary medical devices? (Regulation (EU) 2017/745   YES = NORDICS |  |
| 1. Does your government apply the ‘human’ **in vitro diagnostic** medical devices legislation to veterinary in vitro diagnostics (IVDs)? (Regulation (EU) 2017/746)   YES = NORDICS |  |
| 1. Is there **other national legislation** covering veterinary medical devices and in-vitro diagnostics.   YES = Germany France Poland Spain |  |
| 1. Does your **government** believe there is a **need for EU legislation** covering veterinary MDs and veterinary IVDs?   YES = Portugal, Italy, Belgium, Greece |  |
| 1. Does your **membership** believe there is a **need for EU legislation** covering veterinary MDs and veterinary IVDs?   YES = Portugal, *Germany (partly*), France, Spain, Italy |  |
| 1. Is this an **important issue** for (a) your government and (b) your membership?   YES = Germany France Spain Italy |  |

# **Annex 2: Proposal for the creation of a new CEN technical committee - ANIMAL HEALTH**

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## 3-1 Scope

### It includes:

✓ **Guidelines** for implementation of diagnostic methods and quality control of diagnostic reagents;

✓ **Data management** and analytical technologies used for diagnostic methods.

### It excludes:

✓ Terminology and methods for specific disease diagnosis already covered by OIE and EURLs;

✓ Standards on primary production in microbiology of the food chain

## 3-2 Work program

* **Biological reagents performance control**

➔ The objective is to propose a standardised control of diagnostic reagents (immunology and molecular biology) used in the animal health diagnostic sector.

* **Dematerialised data exchange system in laboratory analysis**

➔ The objective is to ensure the management of information resulting from

analysis, testing and diagnosis in animal health.

* **Other deliverables could be developed later on, upon decision by the new TC.**

This could include specific requirements and recommendations for the implementation of diagnostics based on:

* + Cell cultures;
  + Molecular methods;
  + Immunological techniques;
  + Mass spectrometry (MALDI-TOF);
  + Any other relevant technologies fully in the scope of the Technical Committee.

Other topics…

* + A list of the relevant analytical methods recognised as appropriate for the EU context,
  + Analytical methods for animal diseases not covered by EURLs nor OIE.

## 3-3 Links with existing documents and standards

### In OIE:

* + Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)
  + Manual of Diagnostic Tests for Aquatic Animals (Aquatic Manual)

### In UN/CEFACT:

* + Electronic Laboratory Observation Reporting (eLabs)

### In CEN/ISO:

* EN ISO/IEC 17025 - General requirements for the competence of testing and calibration labs
* EN ISO 22117 - Microbiology of food chain - Specific requirements and guidance for proficiency testing by interlaboratory comparison
* EN ISO 19036 - Microbiology of food chain - Guidelines for the estimation of measurement uncertainty for quantitative determinations
* EN ISO 22174 - Microbiology of food - Polymerase chain reaction (PCR) for the detection of food-borne pathogens - General requirements and definitions
* In CEN: No standard identified on biological reagents control and data exchange system

# **Annex 3: summary of REGULATION (EU) 2017/746 on human IVDs**

## Scope:

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in vitro diagnostic medical devices for human use and accessories for such devices

## Definitions

‘in vitro diagnostic medical device’ means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

1. concerning a physiological or pathological process or state, or congenital physical or mental impairments, or the predisposition to a medical condition or a disease.
2. to predict treatment response or reactions or to define or monitoring therapeutic measures.
3. Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices.

Other definitions cover: ‘device for self-testing’; ‘device for near-patient testing’; ‘companion diagnostic’ to a medicinal product; ‘generic device group’; ‘single-use device’; ‘kit’ - a set of components packaged together.

## General obligations of manufacturers:

* IVDs must be designed and manufactured in accordance with this Regulation;
* implement and maintain a system for risk management;
* conduct a **performance evaluation and** draw up an **EU declaration of conformity** (see below);
* draw up and keep up to date the technical documentation for those IVDs; keep the technical documentation for 10 years; provide to competent authority on request
* affix the **CE marking of conformity** (see below);
* comply with the obligations of the Unique Device Identification (**UDI) system** (see below);
* ensure that procedures are in place to keep series production in conformity with this Regulation;
* establish, keep up to date and continually improve a **quality management system**;
* implement and keep up to date the **post-market surveillance** system; have a system for recording and **reporting of incidents** and **field safety** corrective actions; if necessary, immediately take the necessary **corrective action**; immediately inform the competent authorities of new **risks**; provide sufficient financial coverage in respect of **liability**.
* Manufacturers shall have at least one **person responsible for regulatory compliance**
* Register in an electronic system run by the EC to obtain their **registration number**

General obligations of importers and distributors also specified

## EU declaration of conformity:

Shall state that the requirements specified in this Regulation have been fulfilled; the manufacturer shall continuously update it; shall, as a minimum, contain the information set out in Annex; by drawing up the EU declaration of conformity, the manufacturer shall assume responsibility for compliance with this Regulation and all other Union legislation applicable to the device.

## ‘UDI system’ - identification and traceability of devices

* Identification within the supply chain; operators to achieve an appropriate level of traceability:
* A Unique Device Identification system (**‘UDI system’)** must be on the label & packaging; establishment of an E-system for UDI (‘UDI database’); to be used for reporting serious incidents
* The EC shall set up and manage an UDI database to validate, collate, process and publish info
* The manufacturer shall assign an **UDI device identifier** to the device and add it to the **UDI D-B**.
* The notified body shall include a reference to the Basic UDI-DI on the certificate issued
* The Commission shall run a database to create the **single registration number** of manufacturers
* **Registration of** manufacturers/ importers - shall submit the required information to the D-B; the competent authority shall verify the data and obtain a single registration number (‘SRN’) from the D-B and issue it to the manufacturer;
* **European database on medical devices** (Eudamed): EC shall set up, maintain and manage ‘Eudamed’ containing D-Bs (a) registration of devices (b) the UDI-database (c) registration of economic operators (d) notified bodies and on certificates (e) clinical investigations; (f) vigilance and post-market surveillance; (g) market surveillance.

## CE marking of conformity:

Devices, in conformity with the requirements of this Regulation shall bear the CE marking of conformity; followed by the ID number of the notified body responsible for the conformity.

## Notified Bodies

* MSs that designate a notified body, to carry out **conformity assessment** activities shall appoint an ‘**authority responsible for notified bodies’ (ARNB)**
* **Requirements relating to notified bodies**: as designated in accordance with this Regulation.
* **Monitoring** and re-assessment of notified bodies; **Review** of notified body assessment of technical documentation and clinical evaluation documentation; **Challenge** to the competence of notified bodies (NBs); **Peer review** system; **Coordination** of notified bodies

## Application by conformity assessment bodies for designation:

Conformity assessment bodies shall submit an application for designation to the authority responsible for notified bodies (ARNB). The application is assessed by ARNB and this is peer reviewed by joint assessment team (JAT) of 3 experts (1 = EC); ARNB to conduct an on-site audit.

## Classification and Conformity Assessment

* Devices shall be **divided into classes** A, B, C and D, taking into account the intended purpose of the devices and their inherent risks; dispute resolution mechanism;
* **Conformity assessment procedures**: manufacturers undertake an assessment of the conformity of the device, in accordance with the applicable conformity assessment procedures (which vary depending on the classification/risk)
* **Certificates of conformity**: are issued by the notified bodies in accordance with Annexes IX to X
* The notified body shall notify the NCA of certificates it has granted to class D devices
* **IVD in combination with a medicine**: Before it can issue a CE certificate, the notified body must seek a scientific opinion from the EMA (if CP) or a NCA on the suitability of the companion diagnostic to the medicine concerned

## CLINICAL EVIDENCE, PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

**Performance evaluation** and clinical evidence: Confirmation of safety and performance requirements shall be based on scientific validity, analytical and clinical performance data providing sufficient clinical evidence, including if applicable relevant data in ‘Annex III’.

## POST-MARKET SURVEILLANCE, VIGILANCE AND MARKET SURVEILLANCE

Manufacturers shall establish, document, implement, and maintain a **post-market surveillance system** in a manner that is proportionate to the risk class.

# **Annex 4:** **National legislation on veterinary IVDs**

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## Spain

All diagnostics are regulated in Spain. The rules have been recently reviewed with the publication of a new [Royal Decree](https://www.boe.es/diario_boe/txt.php?id=BOE-A-2020-11424). In summary:

Diagnostic reagents for animal diseases must be authorised by the Ministry of Agriculture and need a registration number prior to commercialisation.

* Besides, diagnostics reagents for notifiable animal diseases must be tested in an official laboratory prior to authorisation.
* The Company marketing diagnostics for animal diseases have to be registered too.
* A communication to the Ministry of Agriculture if needed in the case of diagnostics for physiological parameters such as glucometer, etc. (responsible declaration)

Some diagnostics, such as tuberculin, must be registered as veterinary medicines.

### Regulatory requirements

Before marketing, all products, manufacturers, and importers must be authorized by the competent authority. The required data are mainly administrative. Technical documentation is relatively limited and does not have a prescribed format, the authority does not require samples of the product and does not perform their testing. Free sale certificates issued by foreign countries may be recognized provided that they were based on a sufficient pre-market control. All forms and instructions are in Spanish and are available online.

All products must be listed in a register of approved products which currently contains approximately 2,400 items.

## Germany

### Legal framework

Selected veterinary IVDs are subject to specific national regulation. IVDs are divided into 2 groups based on their design and origin. The remaining products (e.g. electromedical devices such as blood biochemistry analysers) are only subject to general legislation such as the Animal Protection Act or Product Safety Act. Regulated products are:

A. **Diagnostic substances** and reagents that were not manufactured using pathogens or biotechnologically (e.g. reagents for enzyme assays, electrolyte analysis, or clinical haematology) classify as “fictitious” medicinal products. They are subject to the **German Medicinal Products Act** and fall under the jurisdiction of Federal Office of Consumer Protection and Food Safety.

B. **Diagnostic products** that were manufactured with the help of pathogens, biochemical, or biotechnological procedures, or chemical synthesis. Of these, only products diagnosing selected epizootic diseases are further regulated. They fall under the jurisdiction of the Friedrich Loeffler Institute.

### Regulatory requirements

A. “Fictitious” medicinal products are perceived as low risk. They are privileged compared to regular medicinal products and can be marketed freely provided that they have been manufactured under the GMP standards.

B. Diagnostic products - of these, only products intended for the diagnosis of notifiable (35 high risk diseases) or reportable (23 diseases of lower risk) animal diseases are further regulated.

Compliant products are entered on the [list](https://www.fli.de/fileadmin/FLI/Service/Zulassungsstelle/englisch/02_e_Zul_Mittel.pdf) of approved products which is available online and currently contains approximately 270 items.

## Poland

In Poland, only selected veterinary IVDs are regulated, as defined by the Animal Health Act 2004 (“in vitro test and reagents for the diagnosis of infectious animal diseases, including zoonoses, residues of prohibited substances and biological impurities in animal issues and products of animal origin”).

### Regulatory requirements

All abovementioned diagnostic products are regulated in the same manner. Before marketing, a favourable opinion of the National Veterinary Research Institute must be obtained (20). The application shall contain the name and address of the applicant, the commercial and technical name of the product, its intended use, packaging and package insert in Polish, information about product testing, and a sample of the product. The review of the application takes up to 60 days and the applicant is obliged to pay a fee. The opinion is valid for 5 years. Besides this regular process, the Minister of Agriculture can authorize the use of products without a proper review if their use is necessary for important public interest or to save the life or health of animals.

All approved products must be listed in a publicly available database of veterinary diagnostic products which currently contains ~300 products with valid registration.

During the post-marketing phase, all changes to the product must be reported to the National Veterinary Research Institute 60 days before the planned change is made.

## France

tbd