Applying the Scientific Research & Development exemption afforded under Regulation (EC) No 1907/2006 Articles 56(3) and 67(1) to analytical activities using *in vitro* diagnostic (IVD) medical devices at a laboratory scale

Industry interpretation of the meaning of 'Controlled Conditions'

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Introduction

In October 2017, the European Chemicals Agency (ECHA) published guidance[1] stating that the Scientific Research and Development (SR&D) exemption as afforded under Regulation (EC) No 1907/2006 ('REACH Regulation')[2] Articles 56(3) (Authorisation) and 67(1) (Restriction) could be applied to analytical activities using *in vitro* diagnostic (IVD) medical devices, providing that these activities used volumes below one tonne/year of the Annex XIV or Annex XVII substance and were carried out under controlled conditions.

This document describes MedTech Europe's interpretation of 'controlled conditions' as used in Article 3(23) (definition of 'Scientific Research and Development') of the REACH Regulation, to promote industry alignment and help MedTech Europe members assess whether the exemption applies in a given situation.

Moreover, this position paper is intended to guide discussions with the European Commission, ECHA and potentially Member States, in an attempt to foster a common understanding of controlled conditions for the IVD sector.

ECHA guidance

ECHA have published some guidance material which has been used in this determination:

- Q&A 1442[3]
- 'Guidance on Scientific Research and Development (SR&D) and Product and Process Orientated Research and Development (PPORD)' (Version 2.1, October 2017)

While further guidance from ECHA on the interpretation of controlled conditions is not anticipated in the near future, the conditions that may be issued in relation to any Authorisations granted for analytical activities using IVDs at a laboratory scale could also be used as guidance in making this determination.

[1] ECHA, Guidance on Scientific Research and Development (SR&D) and Product and Process Orientated Research and Development (PPORD) (Version 2.1, October 2017)
[2] Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
[3] While Q&A 1442 is the most relevant, Q&As 585, 1030, and 1304 may contribute to the understanding of IVDs fitting into the definition of SR&D and the use of substances for SR&D being exempt from Authorisation if controlled conditions are met.

Volume Condition

As stated in ECHA's Q&A 1442 v1.1 of 3/10/2018:

"The use of an Annex XIV substance when it is required, on its own or in a mixture, as part of an in vitro diagnostic method (e.g. in a reagent, calibrator, control material or kit) is considered as scientific research and development and is therefore exempted from Authorisation requirements if this activity is carried out under controlled conditions and in a volume not exceeding one tonne per year and per legal entity."

However, it can be assumed that the volume is the total volume used by the end user and not just the volume supplied by one manufacturer. Therefore, it is the sole obligation of the user to monitor their annual volumes.

Controlled Conditions

Stated in ECHA's 'Guidance on Scientific Research and Development (SR&D) and Product and Process Orientated Research and Development (PPORD)' (Version 2.1, October 2017), 'controlled conditions' within the context of the REACH definition:

"[…] can be understood to mean that procedures and measures are in place to minimise[4] or control[5] exposure and potential risks from exposure of humans and the environment to the substance. This may include, for example, limitation of uses to qualified persons having access to the substance, or collection and disposal of waste. Member States may also impose specific requirements."

As indicated above, achieving 'controlled conditions' requires the implementation of procedures and/or technical measures to minimise or control human exposure or releases to the environment, throughout the substance lifecycle. The specific measures are not further defined in the regulatory guidance but can be assumed to be dependent on the substance in question, and certainly on whether it presents a human health or environmental hazard.

In the case of any substance, the implementation of Occupational Health and Safety and/or Environmental Management systems could be an important factor indicating control or minimisation of exposure. Evidence of adequate management systems can include certifications to:

- ISO 45001 or OHSAS 18001 (Occupational Health & Safety)
- ISO 14001 (Environmental Management), ISO 14004 (guidance document)

In lieu of ISO certification, institutions may demonstrate equivalency through their established internal practices, documentation and where a threshold is set, their monitoring activities.

[4] where information on the hazards is not available
[5] when the hazards are known

These management systems take into account all compliance obligations of the organisation. This includes implementation of a hierarchy of controls: Elimination, Substitution, Engineering Controls, Administrative Controls and training of employees handling the related substances. Taken together, these practices ensure procedures and technical measures are in place to achieve controlled conditions.

Examples of Controlled Conditions for Substances with Human Health Concerns

Where the Annex XIV or Annex XVII substance has an established Derived No-Effect Level (DNEL) or Derived Minimal Effect Level (DMEL), the end user must implement appropriate procedures and/or technical measures corresponding to the physicochemical properties of the substance and the hazards associated with its specific use. Where appropriate, these shall correspond to the risk management measures provided in the supplier Safety Data Sheet (SDS). Maintenance of environmental and, where appropriate, biological monitoring programmes may be considered best practice to ensure control is maintained.

Examples of Controlled Conditions for Substances with Environmental Concerns

When a substance is used in a process where waste is generated, complying with the EU level Waste Framework Directive (EU) 2018/851[6] and local regulatory requirements for waste management is essential. Where the waste is classified as hazardous it shall be sent for incineration or other appropriate disposal method to demonstrate an adequate level of control. Furthermore, supposing a substance is used in a process where wastewater is generated, the EU level Urban Waste Water Directive 91/271/EEC[7], the Water Framework Directive 2000/60/EC[8] as well as local regulatory requirements for wastewater management must be complied with; this may result in the operator being granted consent to discharge to wastewater treatment plants by an authority. This may demonstrate an adequate level of control for that substance. When a substance has a defined Predicted No-Effect Concentration (PNEC), maintaining discharge or environmental emissions limits beneath that value would be considered controlled.

Additional Considerations for Substances Defined as 'Non-Threshold'

Special consideration must be taken where a substance has been added to Annex XIV or Annex XVII without a defined threshold concentration, e.g. a DNEL, DMEL or PNEC, where defining a specific level of control may be more challenging.

In preamble (70) of the REACH Regulation, referring to Authorisations which may be granted for a substance for which it is not possible to establish a safe level of exposure (a non-threshold substance):

"measures should always be taken to minimise, as far as technically and practically possible, exposure and emissions with a view to minimising the likelihood of adverse effects. Measures to ensure adequate control should be identified in any Chemical Safety Report. These measures should be applied and, where appropriate, recommended to other actors down the supply chain."

[6] Directive (EU) 2018/851 of the European Parliament and of the Council of 30 May 2018 amending Directive 2008/98/EC on waste
[7] Council Directive 91/271/EEC of 21 May 1991 concerning urban waste water treatment
[8] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy

When identifying the appropriate controlled conditions for non-threshold substances, it is recommended that an assessment be made and documented in regard to the specific substance, how it is used and taking into account any exposure or emissions pertaining to that use. Measures taken to minimise could include the following risk management measures for example (non-exhaustive list):

- Engineering controls such as Local Exhaust Ventilation (e.g. enclosure of the process, fume cupboards, dust extraction system etc.), access control for places of use and storage, also secondary containment systems for liquid substance storage and waste containers.
- Administrative controls such as maintenance scheduling, safe system of work procedures, spill response teams, substance-specific training, processes for waste segregation and transfer, regular communications, cleaning procedures, health surveillance and air monitoring programmes.
- Personal protective equipment such as safety gloves, eye protection, plastic aprons, liquid-proof boots and protective clothing. Also, respiratory protection such as full or half-face filtered masks, compressed air-fed apparatus and associated fit-testing programmes.
- At a minimum, meeting the specific local regulatory requirements in place to achieve an adequate level of control for that substance and any control recommendations specified by the supplier based on their knowledge of the substance.

Communicating SR&D Exemption Conditions

Transparent communication regarding presence of the Annex XIV or Annex XVII substance and appropriate risk management measures are fundamentally necessary elements in enabling users to meet their requirements for controlled conditions. This shall consider point of sale communications, to ensure downstream users are equipped to meet their obligations for SR&D uses.

Existing regulations cover the range of obligations for hazard communication. As it pertains to scientific research and development activities:

1. Title IV of REACH sets forth duties to communicate across the supply chain via Safety Data Sheets (SDSs) and how to communicate where an SDS is not required, e.g. for articles. This includes not only substance identification, but also hazard classification, risk management measures and recommendations for disposal.

2. Annex I of Regulation (EU) 2017/746 (In Vitro Diagnostic Medical Device Regulation)[9] sets forth the requirements for information that must be included in the Instructions for Use (IFU) of the product:

   20.4.1. (h): *"a description of the reagents and any limitation upon their use (e.g. suitable for a dedicated instrument only) and the composition of the reagent product by nature and amount or*

[9] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices

concentration of the active ingredient(s) of the reagent(s) or kit as well as a statement, where appropriate, that the device contains other ingredients which might influence the measurement;"

20.4.1. (n): *"information that allows the user to be informed of any warnings, precautions, measures to be taken and limitations of use regarding the device. That information shall cover, where appropriate:*

[…]

(iv) precautions related to materials incorporated into the device that contain or consist of CMR substances, or endocrine disrupting substances or that could result in sensitisation or an allergic reaction by the patient or user,"

20.4.1. (ac): *"warnings or precautions to be taken in order to facilitate the safe disposal of the device, its accessories, and the consumables used with it, if any. This information shall cover, where appropriate:*

[…]

(ii) environmental hazards such as batteries or materials that emit potentially hazardous levels of radiation;"[10]

This communication may be done via a Safety Data Sheet (SDS) and/or inclusion in the Instructions for Use (IFU) for the IVD or other equivalent means.

[10] This is interpreted to mean any environmental hazard.

About MedTech Europe

MedTech Europe is the European trade association for the medical technology industry including diagnostics, medical devices and digital health. Our members are national, European and multinational companies as well as a network of national medical technology associations who research, develop, manufacture, distribute and supply health-related technologies, services and solutions.

For more information, visit www.medtecheurope.org.

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