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Active versus Non-active Definition for Metered Dose Inhalers

In light of the European Medical Device Regulations (MDR), there have been general discussions across industry as to whether a standard (non- breath actuated) metered dose inhaler (MDI) could be considered 'active' or not, for the purposes of MDR.

This classification has implications on the information provided to a Notified Body (when seeking a NB Opinion) and also to the classification of any accessories associated with the MDI such as spacers due to **MDR Rule 2**: *All non-invasive devices intended for channeling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are in Class IIa: if they may be connected to an active medical device in Class IIa or a higher class.*

Generally speaking, it is the whole actuator, can and valve assembly that delivers the dose. If we take each component in isolation the functions of containing, metering and delivering the formulation (including the propellant) cannot be achieved. Therefore, the scope of this group will be to consider all parts of standard MDI (excluding any dose counter or other external electro-mechanical components attachments).

Once the EU MDR is in effect this will become a general question as industry starts to require a NBOp; therefore would be good to have industry on the same page before that.

The following reference from Medical Devices Regulation and EU medical device guidance documents (MEDDEV) provide definition of a medical device and examples of active versus non-active examples of devices. These may help in justification of whether MDIs may be an active or non-active device. However, MDIs are not considered stand-alone medical devices.

MDR definition of medical device:

(1) 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: — diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, — providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.
The following products shall also be deemed to be medical devices:
— devices for the control or support of conception;
— products specifically intended for the cleaning, disinfection or sterilization of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

MDR definition for active device (Article 2[4]):

> *'active device' means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts* by changing the density of or *converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices. Software shall also be deemed to be an active device*

MDR Annex VIII Classification of Devices: Rule 20

> *All invasive devices with respect to body orifices, other than surgically invasive devices, which are intended to administer medicinal products by inhalation are classified as class IIa, unless their mode of action has an essential impact on the efficacy and safety of the administered medicinal product or they are intended to treat life-threatening conditions, in which case they are classified as class IIb.*

The following additional guidance from the EU Medical Devices Guidance documents (MEDEV) may be useful in providing additional clarification on 'active'.

Guidance document - Field of application of directive "active implantable medical devices" - MEDDEV 2.1/2 rev.2

> *2.1.2. For the purpose of the Directive 90/385/EEC a medical device is active if it "relies for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity. This includes, for instance, devices activated by means of pressure unless this effect is achieved by energy resulting from the body of the patient. The definition implies that the function of the device involves using the source of power to perform useful work. The mere transmission of heat, light, pressure or vibration does not mean that a device is active.*

Guidance document - Classification of Medical Devices - MEDDEV 2.4/1 rev.9

> 3.1.4. Active medical devices *Any medical device operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices. Stand alone software is considered to be an active medical device.*
> The concept "*act by converting energy*" includes conversion of energy in the device and/or conversion at the interface between the device and the tissues or in the tissues.

The concept of "*significant changes*" includes changes in the nature, level and density of energy (see Rule 9). This means that for instance an electrode is not an active device under this classification system as long as the energy input is intended to be the same as the energy output. For instance, resistance in a wire that causes minor changes between input and output cannot be considered to constitute "significant change". However, electrodes used in electrosurgery for cutting tissues or cauterisation are active devices because their operation depends on energy provided by a generator and their action is achieved by conversion of energy at the interface between the device and the tissue or in the tissue.
The application of energy from the human body does not make a device "active" unless that energy is stored within the device for subsequent release. For instance, energy generated by human muscle and applied to the plunger of a syringe (thus causing a substance to be delivered to a patient) does not make this syringe an "active device". However, if a drug delivery system depends upon manual winding to preload a spring which is subsequently released to deliver a substance, then the device incorporating the spring is an "active device".
Medical devices using prestored gases and/or vacuum as a power source are regarded as active devices, *e.g.* gas mixers with anaesthesia machines and gas powered suction pumps.
Heating/cooling pads intended only to release stored thermal energy are not active devices because they do not act by conversion of energy. However, heating/cooling pads which act by chemical action (e.g. endothermic or exothermic reaction) are active devices as they are converting chemical energy into heat energy and or vice versa.

Case for the MDI being an active device:

The action of the propellent in an MDI can be interpreted as providing an energy source, i.e. when the propellant is within the canister it is in liquid form (as pressurised), containing the API(s) as either a solution or suspension and upon emission from the MDI, at room temperature and pressure, the propellant takes the form of a gas and evaporates (leaving smaller particles of active). The propellant could then be considered as the energy source for the active component(s) to move from the MDI to the patient. The density of the propellant will change from when it is in solution within the MDI to when it is emitted upon actuation.

Case for the MDI being a non-active device:

For most MDIs the patient applies force to the canister/valve/actuator combination in order to open the metering chamber to the outside atmosphere, thus allowing the metered dose to be released; as the valve stem returns to its resting position the metering chamber refills from the reservoir in the canister. Therefore, **there is no additional force beyond the one the patient (human being) is providing to operate the valve**. Once the passageway to the exterior atmosphere is enabled, the propellant, by its own nature, is changing from its liquid phase to its vapour phase (its boiling point is -26ºC).

The MDI valve, through its subcomponents, allows a metered quantity of propellant mixed with API(s) to be sampled and subsequently delivered to the patient, which requires a level of force to be applied by the patient or helper device. There are clear instructions in the leaflet that the inhaler must be on its inverted position, otherwise, the patient will not get the right dose. This means the **MDI valve uses gravity** so as to enhance the passage of the liquid propellant into its upper stem which then, **through gravity**, transitions into the actuator stem block. The, nature of the propellant itself does not guarantee that the whole content of the metering chamber will be evacuated through the upper stem when actuated on its upright position.
It is only at the point in time when the spray leaves the upper stem tip and into contact with the inner side of actuator stem block when propellant physical properties become into play and, even at this point in time, the actuator physically forces the spray to a detour (it redirects the spray onto an almost 90º shift) forcing it to get in direct contact with the atmosphere and consequently evaporate.

The actuator is the patient contact point for delivery of the medicine. It may be simple application of force by patient or may involve more complex non-user, mechanical or powered mechanism. Differences in means of application of force to activate the actuator will require separate review and assessment and may result in different conclusion on the applicability of the MDR.

In relation with the type of coating, this is a critical point during product development as the final coating selection will determine the amount of API available to be resuspended in the suspension within the container closure. Leaflet instructions suggest to shake the inhaler before using in order to ensure that the API has the chance to get resuspended in the suspension, but shaking does not introduce energy into the system.

Conclusion: Overall it is concluded that the simple application of force by the patient, the requirement to invert the MDI and use gravity lead to the delivery of the dose. Following the review of the arguments above and guidance provided in MDR definitions, MDR classification Rules and MEDDEV documents, it is concluded MDI are **non-active** devices.

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