European Federation of Pharmaceutical Industries and Associations

EFPIA Position on Medical Calculator Qualification/Classification

September 2024 v5.0

A. Objective

The EU utilizes a risk-based approach for qualification and classification of medical calculators to allow calculators performing simple calculations to be excluded from qualification as a medical device.

B. Background

Since December 2022, the Borderline and Classification Manual (the Manual) released by the Medical Device Coordination Group (MDCG) includes a new category for "Medical calculators" (section 1.1.9.2).[1] The Manual states, "*the intended purpose of a medical calculator is to facilitate one or more (sometimes up to 400) routine medical calculations at the point of care for multiple clinical disciplines by means of an app or webpage. Calculation methods incorporated in the medical calculator are taken from or based on formulas or tables documented in research publications and (national) guidelines. Often, these calculations are relatively simple and could be done with a basic electronic calculator or even on paper (simple search). The healthcare professional that uses the medical calculator at the point of care is likely to use the outcome of the calculation in making decisions about diagnosis or treatment of a patient in a routine setting. Two examples of such medical calculations offered by this medical calculator are:*

- *calculation of stroke risk for patients with atrial fibrillation using the CHA_2DS_2-VASc Score to determine if patients need antithrombotic therapy (e.g. by prescribing anticoagulant medicine).*
- *calculation of the creatinine clearance using the Cockcroft-Gault Equation to determine the status of the kidney function. The calculated score is used to identify kidney failure and to help decide if dialysis is required."*

Both examples provided by the Manual include intended use statements for making treatment or diagnosis decisions. The Manual then goes on to essentially state that any score calculation based on a formula or complex algorithm goes beyond that of a simple search; is for the benefit of individual patients; and therefore, meets the definition of a medical device (per MDCG 2019-11)[2] in accordance with Regulation (EU) 2017/745 (Medical Device Regulation – MDR).[3] In addition, Rule 11 of Chapter III in Annex VIII of the MDR makes such medical calculators at least class IIa.

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[1] Such categories are added to the Manual based on the outcome of the Helsinki procedure, where a Competent Authority (CA) in a Member State begins a consultation with other Member State CAs and relevant stakeholders on a borderline or classification issue for a medical device.

[2] According to MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR

[3] According to EU MDR 2017/745 – Medical device classification adopts a risk-based approach following a set of Rules listed under Annex VIII. Any Medical-device software is classified under Rule 11. Based on rule 11, software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa or above.

The approach for medical calculators identified in the Manual is not consistent with a risk-based approach nor is it aligned with the regulation of these types of products in other jurisdictions:

- The IMDRF Guidance on the risk categorization of SaMD values the significance of the information provided by SaMD to healthcare decisions in the context of the state of healthcare situations and provides clear criteria that would allow the assignment of low-risk calculators to a regulatory category that does not require a conformity assessment procedure by a notified body.[4]
- US FDA exercises "enforcement discretion" for software functions that perform simple calculations routinely used in clinical practice and has exclusions/exemptions for low risk software;[5]
- UK MHRA considers calculators where the calculation/result can be easily verified unlikely to be devices; calculators linked to specific devices/drugs are likely to qualify as devices whatever the complexity of the calculation; [6]
- Health Canada considers software functions that are intended to provide a convenient way to perform various simple medical calculations, which are routinely used in clinical practice to meet one of the exclusion criteria for SaMD (software as a medical device);[7]
- TGA excludes software functions that digitalize paper based or other published clinical rules or data including simple dose calculators and Electronic Patient Records:
    - Simple calculators that use relevant published clinical standards or authoritative sources to make calculations or display calculations and outputs so they may be validated by the user, but do not control the administration of a calculated dosage
    - Electronic Patient Records (EMRs) and Electronic Health Records (EHRs) that use relevant published clinical standards or authoritative sources to make calculations or display calculations and outputs so they may be validated by the user, but do not control the administration of a calculated dosage.[8]

C. Problem Statement

We acknowledge the careful balance that must be struck related to the appropriate regulation of the broad spectrum of medical calculators, some of which have been the cause of adverse events. Yet, any regulatory framework must employ a risk-based approach in order to support innovation while also protecting patients. **In the current EU environment, developers of medical calculators face significant challenges and uncertainty introducing such technologies in the EU due to lack of a risk-based approach and misalignment with regulation of medical calculators by other stringent regulatory authorities**.

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[4] IMDRF Guidance Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations

[5] FDA Guidance for Industry and Food and Drug Administrative Staff: Policy for Device Software Functions and Mobile Medical Applications

[6] MHRA Guidance: Medical device stand-alone software including apps (including IVDMDs) v1.08

[7] Health Canada Guidance Document: Software as a Medical Device (SaMD: Definition and Classification

[8] TGA Guidance: Is My Software Regulated

The Manual does not provide examples of simple calculations that would not fall under the definition of a medical device. It also does not provide guidance for software that only calculate a dose based on approved medicinal product labels to aid the health care professional (HCP) in prescription or dispensation decisions. This could be interpreted as all software with a calculation function using a formula, table or algorithm, including those documented in research publications and (national) guidelines, are "medical devices". This type of interpretation challenges several already existing web-based solutions and mobile applications intended to help EU health care professionals more efficiently and consistently perform simple calculations, i.e., the calculations that the HCP can perform using paper, without interfering in their professional capacity.

D. Policy Proposal

Proposed policy strategy

- Establish criteria for which medical calculators can be considered to perform simple calculations
- Update of the Borderline Manual (please, see Appendix A) with examples on which medical calculators would not be considered a medical device, including an example of calculators used to help HCPs in dose calculation as part of the approved summary of product characteristics (SmPC) or "drug label";
- Update of MDCG 2019-11 to clarify that medical calculators performing simple calculations, including those used as part of SmPC for a medicine to aid HCPs, are not medical devices
- Work with MedTech Europe and other relevant stakeholders to identify alignment on the above approach

Policy position:

Criteria for simple calculations that could be done with a basic electronic calculator or even on paper and considered "simple search"

Software functions that meet at least one of the following criteria are considered "simple search" and are not subject to MDR:

1. Calculations that contain a few variables and using basic functions available on a calculator and it can be easily verified by the intended user; or
2. Digitalize paper based or other published clinical rule routinely used in clinical practice and research and it does not make treatment or diagnosis decisions that lead to an immediate or near term actions; or
3. Digitalize dosage calculation that automates the arithmetic operation for medicinal product dosage calculation according to the medicinal product SmPC to facilitate prescription and/or dispensation by HCP.

Medical Calculators Performing Simple Calculations – not subject to MDR

Example	Rationale
Software that calculates - Parkland Formula calculator for burns - Body Mass Index (BMI) - Glasgow Coma Scale Score	1. Calculations that contain a few variables and using basic functions available on a simple calculator and it can be easily verified by the intended user 2. Digitalize paper based or other published clinical rule routinely used in clinical practice and research and it does not make treatment or diagnosis decisions that lead to an immediate or near term actions
Software that calculates: - Cardiovascular disease risk according to Framingham Risk[9,10] - Creatinine Clearance (Cockcroft-Gault Equation)[11] for HCP as a look-up function* - A pneumococcal vaccination recommendation based on patient's age and risks based on existing disease or treatment patients previously accepted is converted into a digital flowchart which resides on a webpage	2. Digitalize paper based or other published clinical rule routinely used in clinical practice and research and it does not make treatment or diagnosis decisions that lead to an immediate or near term actions
Software that calculates: - Patient's weight-based loading and maintenance dose of drug per the SmPC - Based on predetermined dosage, different combination of vial strengths to minimize number of injections and/or drug waste	3. Digitalize dosage calculation that automates the arithmetic operation for medicinal product dosage calculation according to the medicinal product SmPC to facilitate prescription and/or dispensation by HCP

*Example listed in section 1.1.9.2 of the Manual.

[9] D'Agostino RB, Sr. Vasan RS, Pencina M.J, Wolf PA, Cobain M, Massaro JM, Kannel WB. (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 117(6): 743–753

[10] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. (1998) Prediction of coronary heart disease using risk factor categories. Circulation; 97(18):1837-47

[11] Cockcroft, D.W. and M.H. Gault. Prediction of creatinine clearance from serum creatinine. Nephron. 1976. 16(1):31-41

Complex Medical Calculation – remains subject to MDR

A complex medical calculator could be considered any medical calculator that does not meet any of the criteria necessary for a simple calculation. Examples of complex medical calculators that are subject to MDR are provided below:

A. Calculators that calculate a disease risk for patients to determine a treatment or diagnosis decision that is not based on well-established and routinely used national/international guidelines and the calculation cannot be easily verified by the intended user.
B. Calculators that calculate a dosage for a patient in which the calculation does not have HCP oversight or the calculation cannot be easily verified by the intended user
C. Calculators that calculate a dosage which is directly administered to a patient (i.e. closed loop automatic insulin delivery system) without HCP intervention.

Example	**Rational**
Digital health technology (app) that calculates: Insulin dosage for titration of insulin, based on an initial dosage defined by the HCP. Dosage adjustment depends on the average blood glucose values during consecutive days	The dose calculator (app) calculates/determines the dose adjustment and provides the patient with a recommended dose value. The patient afterwards will inject himself according to the recommendation.

Appendix A: Suggested EFPIA Redline of MDCG Borderline Manual (pg 14-15)

1.1.9.2 Medical calculators

Background:

The intended purpose of a medical calculator is to facilitate one or more (sometimes up to 400) routine medical calculations at the point of care for multiple clinical disciplines by means of an app or webpage.

Calculation methods incorporated in the medical calculator are taken from or based on formulas or tables documented in research publications and (national) guidelines. Often, these calculations are relatively simple and could be done with a basic electronic calculator or even on paper (simple search). Medical calculators can include digitization of paper-based or other published clinical rules, which are routinely used in clinical practice and research, or may provide calculations consistent with the label of an approved medicinal product. These calculation functions are simple and are not subject to MDR. Other medical calculators may perform more complex calculations, be intended for use in the diagnosis or treatment of individual patients, or directly control the dosage of medicinal product (i.e. continuous glucose monitor).

Typically, the healthcare professional enters several patient-specific variables after which the ~~app~~ calculator provides an output. This output can span a range of uses and provide varying levels of transparency and impacts to the healthcare decision being made. Some calculators do not have a medical purpose or have output that provide minimal risk to patients. Software functions that meet at least one of the following criteria are considered simple and are not subject to MDR:

1. Calculations that contain a few variables and using basic functions available on a calculator and it can be easily verified by the intended user; or
2. Digitalize paper based or other published clinical rule routinely used in clinical practice and research and it does not make treatment or diagnosis decisions that lead to an immediate or near term actions; or
3. Digitalize dosage calculation that automates the arithmetic operation for medicinal product dosage calculation according to the medicinal product SmPC to facilitate prescription and/or dispensation by HCP.

Calculators performing simple calculations do not qualify as medical devices.

In contrast, **medical calculators** that are subject to medical device regulation under MDR are those **that perform more complex calculations** which are not transparent to the HCP and in which the medical purpose of the calculator is intended for medical treatment or diagnosis decisions. Examples of complex medical calculators that are subject to MDR are provided below:

A. Calculators that calculate a disease risk for patients to determine a treatment or diagnosis decision that is not based on well-established and routinely used national/international guidelines and the calculation is not transparent to the HCP.
B. Calculators that calculate a dosage for a patient in which the calculation does not have HCP oversight or transparency of the variables used in the calculation or where the dosage calculated is not part of an approved medicinal product label.
C. Calculators that calculate a dosage which is directly administered to a patient (i.e. continuous glucose monitor) without HCP intervention.

Outcome

Simple calculators that meet at least one of the three criteria listed above fit under “simple search” per MDCG 2019-11 (Step 3) and are not considered medical device software (MDSW) as the primary intent of these calculators is the matching or retrieval of information.

Any calculation not meeting the criteria of “simple calculation” can be considered “complex calculation” and an action on data beyond the use of simple search as referenced in qualification decision step 3 of MDCG 2019-11 (“Decision steps for qualification of software as MDSW”). If the calculation is for the benefit of individual patients, per decision step 4 of guidance MDCG 2019-11, and meets the definition of a medical device, it will be subject to MDR.