EVALUATION OF PRIMARY FUNCTIONS

The concept of primary functions was first introduced in the 2022 revision of ISO 11608, *Needle-based injection systems for medical use – Requirements and test methods:* Part 1. Primary functions are defined in the ISO 11608-1 standard as a "function or operation of the needle-based injection system, which, if it does not perform to specifications during use, would directly result in a failure to accurately deliver the medicinal product via the correct route and/or directly result in unacceptable harm to the patient." Determination of primary functions should focus on "top level" characteristics of the device and be guided by risk analysis. Characterization of non-functions, such as biocompatibility, pyrogenicity, among others, are also required to be addressed, but do not qualify as primary functions. Once primary functions are identified, those identified functions are subject to significant preconditioning prior to evaluation to ensure they meet all required specifications.

The final decision and justification for the requirement in the context of the intended use will be the responsibility of applicant. West Pharmaceutical Services has compiled the following table as recommended primary functions, with stated rationale, for West's SmartDose® on-body delivery systems (OBDSs).

PRIMARY FUNCTION	(A) ACCURATE DELIVERY OF THE MEDICINAL PRODUCT VIA THE CORRECT ROUTE (Detail directly from ISO 11608:2022, Part 1)	(B) UNACCEPTABLE HARM TO THE PATIENT	PRIMARY FUNCTION (Y/N)	RATIONALE
DOSE VOLUME ACCURACY	Failure to meet dose accuracy requirements is a failure to accurately deliver the medicinal product via the correct route	No need to assess under criteria (B) as dose accuracy is always a primary function	Y	Defined as "Difference between the intended dose and the delivered dose" per ISO 11608-1 section 3.7 Dose volume outside the specifications (underdose) may result in failure to achieve the therapeutic effect. Overdosing is not a risk since cartridge is prefilled to a desired volume and OBDS/cartridge is single use. Primary function based on criteria (A). Dose accuracy is specified in ISO 11608:2022 as always, a primary function for needle-based injection systems, including OBDS Designated as a primary function based on criteria (A) and/or (B)
DOSE DELIVERY TIME	Failure of the injection time specification could potentially impact accurate delivery of the medicinal product via the correct route due to user actions (e.g. removing the NIS from injection site before observing the end of dosing indicators)	Failure to meet injection time specification may result in unacceptable harm to the patient (e.g. due to patient tolerability, medication error due to premature removal)	Y	Defined as "Measure of the total time over which the total dose volume is delivered" per ISO 11608-6 section 3.4. Dose delivery time is an automated function. Delivery time exceeding the specifications may result in either the termination of the dose delivery (through the software) or the user prematurely removing OBDS, leading to underdose. Additionally, if the delivery time is longer than specified, the software will terminate delivery resulting in a potential underdose, even if patient does not remove device prematurely. Shorter than specified delivery time may lead to patient discomfort Designated as a primary function based on criteria (A) and/or (B)

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DOSE COMPLETION INDICATION (USER INTERFACE)	End of dose indication, whether active (audible) or passive (visual) by definition is feedback on the status of the delivery and as such does not directly impact accurate delivery of the medicinal product via the correct route	However, as this NIS function is also a user interface, the failure of this function could result in the user removing the injector from the injection site before the dose is delivered, potentially impacting accurate delivery of the medicinal product via the correct route This could implicate an unacceptable harm to the patient (e.g., due to premature removal from the injection site leading to underdosing and/or a medication error or leaving the device on for longer than intended)	Y	The OBDS provides audio/visual notification at the end of dose completion so that the user can confirm the dose delivery and remove the OBDS. If Dose Completion Notification is not received after successful dose delivery, the user can assume unsuccessful delivery, which can affect the therapeutic outcome. This NIS function is also a user interface, the failure of this function could result in the user removing the injector from the injection site before the dose is delivered, potentially impacting accurate delivery of the medicinal product via the correct route. This could implicate unacceptable harm to the patient (e.g., premature removal from the injection site leading to underdosing and/or a medication error or leaving the device on for longer than intended Designated as a primary function based on criteria (A) and/or (B)
ADHESION TACK FORCE	Inadequate adhesion could cause the device to detach from the body leading to a disruption of the injection delivery	Adhesion that is too strong could cause tissue trauma, creating unacceptable harm to the patient	Y	The failure of device remaining adhered on the body can result in device falling, which can lead to underdose. Adhesion that is too strong could cause tissue trauma, creating unacceptable harm to the patient Designated as a primary function based on criteria (A) and/or (B)
BUTTON ACTIVATION FORCE	Activation force is a specification that is defined by the limits of user capabilities and would directly impact the accurate delivery of the medicinal product if the user cannot trigger the automated delivery mechanism. This would be considered a primary function under (A)	Failure to meet activation force specifications could delay the delivery of the intended dose, potentially resulting in unacceptable harm to the patient and/or medication error	Y	The button activation by the user is required to be able to initiate the automated drug delivery. If the button activation force is too high, the user may not be able to initiate the dose delivery. Too low a button activation force can lead to premature initiation of drug delivery and potentially affect the correct route of medicinal product (Criteria A) Designated as a primary function based on criteria (A) and/or (B)
EXTENDED NEEDLE LENGTH	Injection could be completed outside of target injection site and impact the correct delivery	Injection could be completed outside of target injection site and cause pain and create unacceptable harm to the patient	Y	If the extended needle length is outside of the specifications, the medication may not be injected into subcutaneous tissue, which can lead to failure to achieve the therapeutic effect Primary function based on criteria (A) and/or (B)

West's SmartDose® drug delivery platform is not independently cleared or approved by any Regulatory Body for general healthcare professional or patient use, nor is it available for general commercial purchase. Its distribution and use are subject to applicable regulatory requirements for clinical investigation, and for marketing authorization, as used in combination with a specific drug or biological product. Each component of a combination product is subject to the requirements established by the Regulatory Body for that component (drug, biologic or device). The regulatory process can be more complicated for combination products including an evaluation of the product characteristics, delivery system and its functionality, as well as the potential for undesirable interactions between the drug or biologic and the delivery system. As a result, we note that the SmartDose® drug delivery platform's compatibility with any particular drug or biologic must be confirmed, and its ability to achieve the desired patient benefits must also be confirmed, on a case-by-case basis in a manner sufficient to meet Regulatory Body requirements.