European Federation of Pharmaceutical Industries and Associations

EFPIA Reflection Paper on Integral Drug-Device Combination Product Platform Approach

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Executive Summary

This paper describes how Quality by Design[1] (QbD) principles combined with use of prior knowledge and a Design of Experiments[2] (DoE) approach may be employed to create a design space of device and drug variables that constitutes an integral drug-device platform. These ICH Q8 (R2) [1], Q9 [2] and Q10 [3] concepts based on risk management are also largely consistent with ISO14971 [4]. Once the platform design space[3] has been approved by Regulatory agencies then a new product residing within the platform design space should have a reduced or no need of review for certain nonproduct-specific data that pertains to the device constituent part.

Background

The Medical Device Regulation (MDR, 2017/745), including Article 117 [5] that amends Annex 1 of directive 2001/83/EC, is scheduled to come into force on 26 May 2021, replacing the current Medical Device Directives. The MDR Article 117 introduces a new requirement that a Notified Body Opinion (NBOp) should accompany regulatory documentation for an integral drug-device combination (iDDC) product being submitted to National Competent Authorities (NCAs) or EMA[4]. On the basis that the NBOp considers the intended use, user(s) and environment of the given medicinal product, a consequence of Article 117 is that a new Marketing Authorisation Application for an approved iDDC medicinal product, will require a NBOp to be submitted for the new product, even when a NBOp has been obtained by the Marketing Authorisation Holder (MAH) for another approved product, using the same device constituent parts.

Scope

The scope is applicable to the initial Marketing Application and post-approval changes for single use iDDC products. The focus is on iDDC products developed by the MAH using procured device

[1] Quality by Design: See ICH Q8 (R2). A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

[2] Design of Experiments: See ICH Q8 (R2). A statistical tool to optimise the experiments required to define a QbD Design Space which is defined as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality

[3] A design space as applied to a platform iDDC product.

[4] Article 117 also states that an iDDC product may have documentation that allows CE marking of the medical device constituent part. However, the CE mark cannot be affixed to the device constituent part of an iDDC under MPD labelling requirements and removal of the CE mark from the device would render the certificate void.

constituent parts. Other approaches are discussed including the 'general use approach' similar to those currently employed for CE-marking.

Although this manuscript uses prefilled syringe and pen as examples, the platform design space concept should be equally applicable to other types of iDDC product, e.g. certain single use, inhalation products that are not requiring a CE-mark.

Problem Statement

Many considerations by the Competent Authorities (CA) for an iDDC from the medicinal product perspective are now also being assessed by the Notified Bodies (NBs) but from the device safety and performance viewpoint. For example, given that a prefilled syringe has constituent parts that also form the immediate, primary packaging, container closure system, there is significant overlap of interest for the same drug/device interaction and drug delivery information by the CA and the NB. Areas that may result in duplicated review include drug-device compatibility, dose accuracy, sterility and clinical risk management. Therefore, there is a recognised overlap in responsibility and expectations by the CA and NB that has the potential for a degree of duplication in documentation submitted and reviewed for which it is desirable to reduce to the essential minimum and avoid conflicting opinion from two separate review bodies [8].

The potential for duplicate review of device information also occurs when a Marketing Application for a new iDDC medicinal product, or a variation to an existing product, introduces a device constituent part that has been previously approved in a prior product. The original iDDC product device information is then prior knowledge to the MAH, CA and potentially the NB – when the same NB is used for both iDDC products. The proposed iDDC platform device design space submission scenarios that are subject of this reflection paper can resolve this potentially duplicate review when the same device constituent part is used for different medicinal products in an iDDC product.

Stream-lining Review of iDDC Medicinal Products Using a Device Platform Approach

Regulatory efficiency could be improved by a platform approach to iDDC medicinal products that include the same device constituent part. The described platform device approach aids providing a streamlined, efficient pathway of product review by justified reuse of a NBOp, when multiple products use the same device constituent that has functionality that lies within a platform design space. The platform design space concept is described in the following section and is derived from Quality by Design, as described in ICH Q8 (R2) [1], Q9 [2] and Q10 [3], based on risk management that is consistent with ISO14971 [4]. The proposed approach is designed to reduce:

- the risk of prolonging the timeline for submission of a dossier to the CA while resolving NB concerns in issuing the NBOp.
- Duplicate/multiple review(s) by CA and NB of the same device and drug-device interaction information, thereby managing workload since the focus of review would be on the unique and different aspects of the new product.
- the potential for different questions or 'requests for further information' on the same aspect of the medicinal product by two different reviewing entities, NB and CA, leading to possible divergent assessment.

Thereby, the platform design space approach may provide a mechanism, aligned with Article 117, to accelerate iDDC product approval; resulting in improved patient access to important medicines.

Considerations in Defining an Integral Drug-Device Combination Product Platform

Currently there is no unified understanding of a platform device suitable for the varied perspectives of the MAH, NB and CA. In designing a definition, a working assumption is that a device platform is a family of one or more qualified device configurations that can be used for a range of medicinal product, falling within bracketed parameters or attributes for the product characteristics. The design space for an integral drug-device combination product platformincorporates device characteristics, which are transferable across products and user populations, with defined use and intended purpose (e.g. subcutaneous or intravenous injection). The goal of a platform approach to iDDC medicinal product review by a CA is to obtain a NBOp that may be usable in the MA for any new product that is justified to lie within the platform design space with minimal to no additional NB review.
The platform design space would be described or defined by a set of variable, discrete and unchanged characteristics. Table 1 provides for three Case Studies with a non-exhaustive list of potential iDDC platform device characteristics, indicating the variable and set parameters within their respective device platforms.

The platform design space may be of 1, 2, 3 or more dimensions, in which each dimension is a measurable variable across the platform. From Table 1, *Case Study A* has a single dimension variable for viscosity since in this case rheological behaviour is directly resulting from varying protein concentration and the temperature range for which the iDDC product is intended for use, and the medicinal product formulation that has the potential impact on device performance. These parameters are reflected by a change in extrusion force require to expel the medicinal product from the device constituent part. *Case Studies B and C* have two varying dimensions for viscosity and delivered volume. Using bracketing and matrixing, the limits of each dimension are characterised according to the requirements for a medicinal product and for the functioning administration device system, including the intended user populations, physical and chemical characteristics of the medicinal product that have potential to impact device performance. As the number of variables in a platform increases, tools such as DoE can be employed to reduce the number of different iDDC product configurations that require characterisation such that not every range requires testing at each extreme. The characterised ranges across the variables (dimensions) describes the platform design space similar to the ‘design space’ of ICH Q8 (R2).

Table 1. Example Variable and Non-variable Device Characteristics as Applied to Three Case Study Integral Drug-Device Product Platforms

Design characteristics relevant to administration	**Case Study A** *(PFS – different products of differing protein concentration and formulation)*	**Case Study B** *(PFS – different products of differing protein concentration, formulation and fill volume)*	**Case Study C** *(Prefilled Pen – different products of differing protein concentration, formulation and fill volume)*
Intended Purpose	S/C injection	S/C injection	S/C injection
Patient population	Adult	Adult	Adult
User	HCP	HCP, home use	HCP, home use, self-administration[b]
Device risk class	IIa	IIa	IIa
Primary container closure system	1. Type 1A glass syringe barrel with elastomer stopper and needle guard, stainless steel needle length **are constant.** 2. Needle gauge or needle internal diameter **may vary**[d]	1. Type 1A glass syringe barrel with elastomer stopper and needle guard, stainless steel needle length **are constant.** 2. Needle gauge or needle internal diameter **may vary**[d]	1. Type 1A glass syringe barrel with elastomer stopper, stainless steel needle length and elastomer needle guard **are constant.** 2. Needle gauge or needle internal diameter **may vary** [d]
Secondary device constituent parts impacting User Interface	Plunger rod is **constant**	Plunger rods may vary in colour to distinguish different strengths.[b, c]	Pen front and rear sub-assemblies may vary in colour to distinguish products or strength. [b, c]
Secondary device constituent parts not impacting the User	-	-	1. Springs of differing strength [d] 2. Plunger rod length
Delivered volume	1 mL	0.3 – 2.0 mL[a]	0.3 – 2.0 mL[a]
Protein Concentration	1.0 – 150.0 mg/mL[a]	1.0 – 150.0 mg/mL[a]	1.0 – 150.0 mg/mL[a]
Viscosity	1 – 16 cP[a]	1 – 16 cP[a]	1 – 16 cP[a]
Injection Time	< 15 s	< 15 s	< 15 s
Storage temperature	2 - 8°C	2 - 8°C	2 - 8°C

[a] Variable characteristic

[b] Non-bracketed characteristic; examples provided are user population and colour as discrete variables characterised for the platform configurations

c If only the pigment used has changed and biocompatibility is demonstrated for a series of different colours, the colours may be justified as not being a substantial change in the iDDC and within the device platform may not be considered as a platform variable.

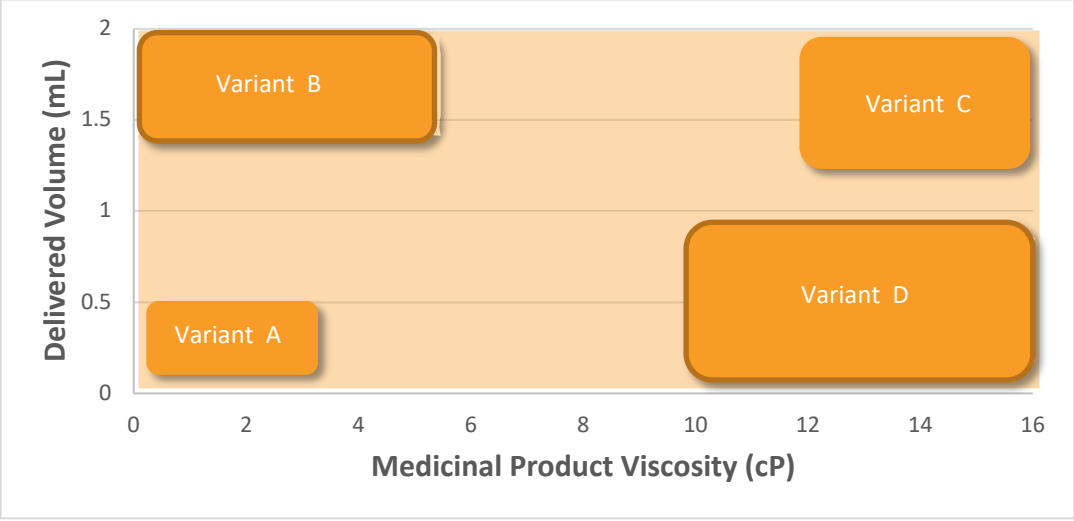
[d] Needle gauge (internal and/or external bore diameter) and/or springs may be changed to accommodate differences in medicinal product viscosity to maintain iDDC performance for break loose and extrusion forces, and injection time.

Figure 1 is an illustration for an iDDC platform design space for two variables (dimensions) of viscosity and fill volume. The Variants A to D represent the iDDC configurations that have been characterised to bracket ranges of injection volume and viscosity using a representative medicinal product or surrogate solution, as indicated by the dark blue boxed areas. The different sizes of the dark blue boxes reflect different ranges that were characterised for each configuration. The illustration has an underlying assumption of a linear response for the rate of delivered volume and the medicinal product viscosity, represented by the rectangular platform design space.

The configurations used to define the platform design space would include any device design changes used to mitigate the impact of e.g. the protein concentration (or surrogate solution) differences, for example use of different internal needle bore and/or different spring strengths to mitigate impact of viscosity changes on the iDDC performance such as injection time.

Any iDDC medicinal product that lies within the bounds of the design space area (light blue area that designates the acceptable ranges for the platform variables) and meets criteria of the design characteristics, would be considered as covered by the drug/device data that defines the platform device technical dossier and hence that the NBOp for the platform would apply for that iDDC product. It is thereby implied the that iDDC product data that are required to demonstrate compliance with the applicable GSPRs as described in Annex I of the MDR, lie within the platform design space. In this example both extremes for two variables are characterised; however, use of DoE, or other models, may reduce the number of required configurations to be characterised as the number of variables increases.

Figure 1: Illustration of a Two-Dimensional Platform Design Space



The needle bore diameter and injection time, along with delivered volume and viscosity, are all inter-related within the platform design space and these relationships should also be understood. Therefore, similar illustrations could be created for the other dimensions in the platform e.g. viscosity vs injection time, injection time vs delivered volume, in a multidimensional space. Case Study C, the PFP iDDC product, adds a further dimension with changes in spring strength.

Whereas medicinal product viscosity and deliverable volume are continuous variables, many device constituent part variables may be discrete e.g. inner needle bore diameter would only be available from Suppliers in a limited number of sizes (often referred to as regular and thin-walled). The platform owner could factor in different needle diameters across the viscosity range by understanding the relationship between the impacted variables with supportive experimental data across the claimed ranges of the platform design space.

A key aspect to consider in the definition of an iDDC platform is that surrogate solutions may be used, when appropriate and justified, to characterise and define the platform design space. Indeed, the use of appropriate surrogate solutions is acceptable in ISO 11608-1 *Needle-based injection systems for medical use* [6]. Use of a surrogate solution is necessary when an iDDC system is designed with the intent of creating a platform using that same basic system for multiple, different medicinal products.

Uncertainties Remain in Interpretation of Medical Device Regulation and the EMA Guidance.

This section describes the flexibilities that should be available to the MAH in the use of prior NBOp assessments for the review and approval of new iDDC products that fit a described device platform. Article 117 of the MDR has introduced uncertainty whether an iDDC product-specific NBOp is the expectation. Whilst the NBOp against Annex I requirements is issued in the context of the medicinal product; options are considered here in view of the interpretation of Article 117 for reuse of a NBOp across different medicinal products or a general-use platform NBOp and still meet the expectation of Article 117.

Reuse of a General-Purpose Platform Notified Body Opinion or Product-specific Notified Body Opinion.

The platform device case studies that are outlined in this paper can have two different regulatory submission scenarios depending on different interpretations of the legal framework set up by Article 117 that ask the following question:

Can a platform or general purpose NBOp that is not specific to a particular Medicinal Product be justified, within the current EU legal framework, for use in different iDDC Medicinal Product applications?

Similarly, can a NBOp specific to iDDC Product 1 be reused by the Applicant in the Marketing Application for iDDC Product 2, again, on the basis that the device and drug-device information for iDDC product 1 is transferable across products as prior knowledge?

The EFPIA member companies' position, as illustrated in Figure 2A, is that device documentation can be submitted to the NB for an assessment, and that the resulting platform NBOp could then be included in multiple Marketing Authorisation submissions to the CA without requiring further NB evaluation when the new iDDC medicinal product device performance parameters are bracketed (or matrixed) within the previously assessed product. The device documentation may describe a platform device using a set of appropriately justified surrogate solution (e.g. a solution containing excipients bridging ranges of e.g. viscosity and buffer concentration, pH etc) to characterise the platform design space. The platform technical dossier could be evaluated by a NB as a general use platform iDDC system (Figure 2A) that can be reused for other iDDC products whose device performance parameters lie within the platform design space.

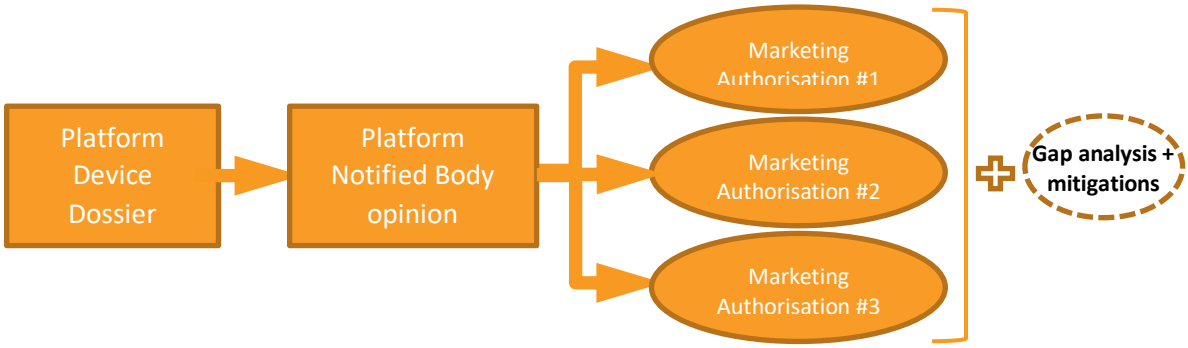
Alternatively, as outlined in Figure 2B, a NBOp could be obtained for iDDC Product 1 and that NBOp reused by the Applicant for subsequent, applicable iDDC Product Marketing Applications that employ the same device system. In effect, the NBOp for iDDC product #1 with the risk assessment mitigations addressing product-specific drug and drug/device information acts as the general-purpose platform NBOp. The mitigations would be expected to be more extensive to reuse a product-specific NBOp than to use a platform NBOp.

These scenarios assume certain similarities in the medicine itself and intended use/users, relating to the GSPRs, that may (if needed) be justified by the Sponsor to assess the applicability of the transferred ('reused') NBOp. Since the device constituent part of the iDDC product has been previously approved by the EMA, it is assumed that there would not be any device-related deficiencies in the gap analysis. However, a risk assessment should be performed with mitigations as part of the CTD submission package to the CA. For both Figure 2 scenarios, if suitably justified by the Applicant, there may be no further review required by the NB since all device design and performance information for the device constituent is either unchanged and would have been previously reviewed by the NB or is bracketed by the previously reviewed general use platform device data. The MAH would only need to justify the applicability of the prior NBOp to the CA in terms of using the device with the particular drug in the new drug-device combination product and address any residual risks. For example, the MAH would justify how the drug-specific platform iDDC data brackets the specific medicinal product information for compliance to the applicable GSPRs, and non-exhaustively for:

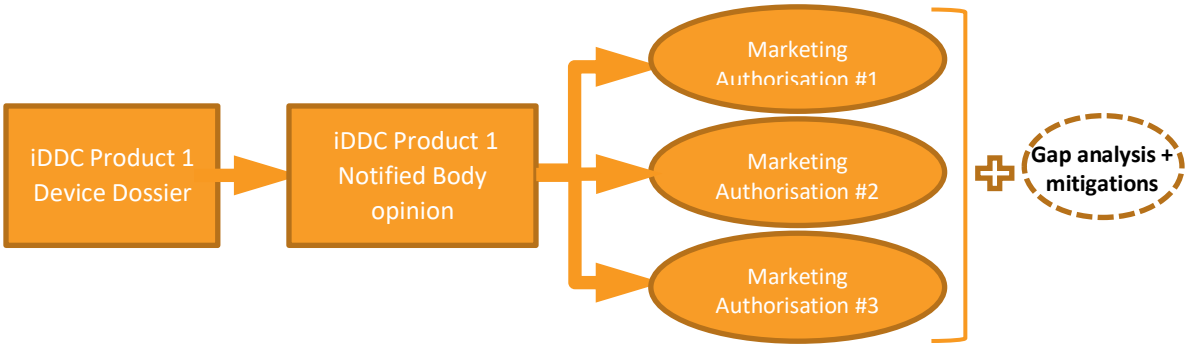
- the drug product indication,
- drug-device interactions,
- drug compatibility,
- use-related risk assessments for the drug constituent part,
- a summary of the human factors validation study for the new combination product,
- appropriate drug product labelling and the drug specific Instructions For Use.

Figure 2: Proposed Streamlined Integral Drug Device Combination Product Review Process by Reusing a Pre-existing Notified Body Opinion for Different Marketing Applications

A) Use of a Platform Device NBOp



B) Reuse of a Product-specific NBOp

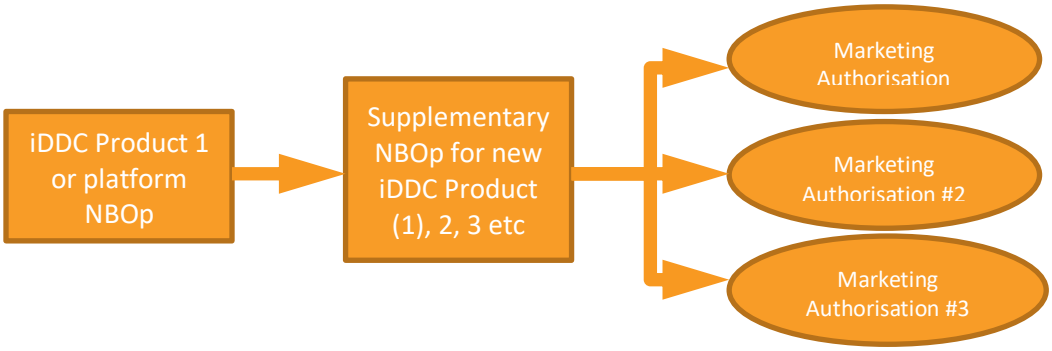


A device platform may be introduced in an initial MA or post-approval by variation or extension application. A device platform may also evolve and increase in complexity post-approval to e.g. introduce a paediatric population into the product label, adding a PFS safety device or ergonomic hand grip, adding a new strength, etc.

3.2. Use of a Supplementary Notified Body Opinion

Should Article 117 be interpreted as not supporting the transfer of a Product 1 NBOp for use with Product 2, or the use of a drug agnostic, general purpose or platform NBOp; then the Applicant may request from the NB, a supplementary NBOp that is specific to the new medicinal product and refers to prior NB assessments for the platform iDDC configurations that constitute the device technical dossier or to a general use platform NBOp (Figure 3). A review of the device technical documentation for the GSPRs is then warranted, that focusses on the new medicinal product specific data. Review of the remaining GSPR data, that are covered by the prior NBOp, can then be abbreviated and based on the prior knowledge held by the NB, resulting in a greatly reduced timeframe to obtain the product-specific NBOp. Any identified gaps specific to the new drug may be resolved by the MAH by providing information or the gap included in a risk assessment with proposed mitigations to the CA. Unless a system of mutual agreement across the NBs is created then this approach restricts the MAH to the use of the same NB for the supplementary NBOp as used for the prior general purpose or product-specific opinions.

Figure 3: Proposed Use of a Supplementary NBOp



Use of the CE-marking Approach

A nonintegral device, developed for co-packaging with a medicinal product, or provided separately, requires a CE mark to indicate compliance to the medical device legislation. Many CE marked devices, for example, a syringe intended to be filled with a medicinal product from a vial, are not developed for any specific product and are for 'general use'. Typically, the GSPRs for the CE mark of 'general use' medical devices (in particular GSPR 10.3 for an administration device compatibility with a medicinal product), are satisfied using solutions such as saline or water to replace the product or even air, according to the specific device and GSPR being tested. Usage of such solutions need to be suitably comparable to the medicinal product properties relevant to the specific GSPR test and justified with data. Therefore, the NBs are familiar with assessing device performance in the absence of any specific medicinal product.

Similarly, the described platform device design space approach that complies to the GSPRs using appropriate surrogate solutions and generating a general use platform NBOp, has strong similarities to the conformity assessment process for application of a CE mark. Hence, it could be helpful to consider the principles of 'general use' for the device constituent parts of an iDDC product. A significant difference between a CE mark approach and the platform device design space approach is that the platform would be justified as applicable to each Medicinal Product for which it is used in combination. Thereby, risks associated with medicinal product – device interactions and other concerns specific to the applicable GSPRs for the new combination in the platform are addressed in the Marketing Authorisation and provides assurance of iDDC product safety and performance.

Post-approval Considerations

A general-use platform device design space NBOp, product specific NBOp or product-specific supplementary NBOp used to support a platform device design space could be updated post-approval by, for example:

1. Extending the range for a variable
2. Introducing a new variable into the platform

The evaluation by the Applicant to determine if the change is substantial or non-substantial should follow the recommendations of EFPIA [7] in which the above examples would likely be considered as substantial. Therefore, these examples would both require submission of new iDDC characterisation data based on the applicable GSPRs, risk assessment etc (according to the change(s)) to the NB for a new NBOp and to the EMA/NCA with updated CTD sections, as appropriate.

Non-substantial changes to the device constituent part of a platform iDDC may include minor changes in design that have no impact on iDDC performance or user interface but may be intended to improve a potential failure mode. As discussed in the EFPIA position paper [7], non-substantial changes should not require any update to the platform NBOp.

Conclusions

The implementation of the Medical Device Regulation (MDR, 2017/745) that introduces Article 117, and the requirement for a NBOp for iDDC medicinal product submissions, risks redundant review and divergent opinion for device information presented to the CA and NB when the same or very similar device constituent parts are used for different medicinal products. This reflection paper describes how review of different medicinal products using device systems of the same fundamental type can be streamlined using a platform device approach. A NBOp could be envisioned that employs the principles of QbD and DoE to bracket in a matrix of product attribute variables, a device platform design space. Any iDDC product within the platform design space can reuse that NBOp for multiple,

regulatory submissions when applicable. Currently there is legal uncertainty over the reuse of a NBOp. If determined by the legal authorities that a single NBOp cannot be reused, then a supplementary NBOp could be obtained from the same NB that issued the relevant NBOp for the platform, requiring minimal review by the NB.
The described concepts are outlined in ICH guidelines Q8(R2), Q9 and Q10 and it is notable that ICH Q9 guideline on pharmaceutical quality risk management is about to begin a revision that is expected to result in closer alignment with the ISO standard for medical device risk management, ISO14971, for iDDC products.

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Abbreviations

CA	Competent Authority
DoE	Design of Experiments
EMA	European Medicines Agency
GSPR	General safety and Performance Requirements
HCP	Healthcare Practitioner
ICH	International Council for Harmonisation
iDDC	Integral Drug Device Combination
ISO	International Organisation for Standardisation
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MDR	Medical Device Regulation
NB	Notified Body
NBOp	Notified Body Opinion
NCA	National Competent Authority
PFS	Pre-filled Syringe
QbD	Quality by Design
S/C	Subcutaneous

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