EBE Reflection Paper

Medicinal product incorporating a drug delivery device component: An Industry Perspective on developing an efficient, 'End to End' Control Strategy

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Developed by the EBE Biomanufacturing Working Group and its topic group on Drug-Device Combinations (DDC).

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About EBE

The European Biopharmaceutical Enterprises (EBE) represents the voice of biopharmaceutical companies of all sizes in Europe and is a specialized group within the European Federation of Pharmaceutical Industries and Associations (EFPIA). Established in 2000, EBE is recognized as the leading biopharmaceutical association in Europe.
"Industry" mentioned in the title and throughout this paper refers to EBE member companies.

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Executive Summary

A cross-industry working group within EBE (European Biopharmaceutical Enterprises) has recently focused on EU specific topics relating to those integral combination products which are regulated as medicinal products but which contain a drug delivery device component. This paper provides an Industry perspective on the development of a control strategy to support a single integral medicinal product containing a drug delivery device component.

EMA's Quality Working Party and Biologics Working Party have communicated in a 2017 concept paper (4) their intent to develop a guideline on quality aspects of the dossier requirements for drug-device combination (DDC) products for marketing authorisation applications (MAA's), line extension applications and variations to show that the combination has been appropriately designed and controlled and can be used correctly in the intended clinical situations.

This paper outlines how existing quality guidance can be used as a framework for DDC product control strategy development and seeks to demonstrate that, if an 'end-to-end' approach to drug product control has been applied, an acceptable Pharmaceutical Quality System (PQS) is in place and an appropriate risk profile has been established, batch releases need not rely wholly on end product testing. It is acknowledged that additional guidance on quality content may be necessary, however, the adaption and integration of drug and device dossier content for DDCs should be possible with minimal disruption to existing 'best practice'.

This paper is intended as a companion piece to the EBE reflection paper: 'Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment', published in January 2018 (5).

Taken together, these two EBE Reflection Papers aim to encourage the discussion between the industry and the EMA on the identified issues.

Table of Contents

1. Introduction

In the context of the publication of the new Regulation on Medical Devices (MDR) in the European Union Official Journal, Regulation (EU) 2017/745 of the European Parliament and of the Council amending the Medicinal Product Directive (MPD, Directive 2001/83/EC) and replacing the Medical Device Directive (MDD, Directive 93/42/EEC) ((1) to (3)) the European Medicines Agency (EMA) in February 2017, initiated a call for comments on its concept paper: 'Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product, EMA/CHMP/QWP/BWP/661488/2016' ((4). The proposed guideline is intended to address instances of inconsistent and incomplete data that are currently being submitted in Module 3 (Quality) to support marketing authorisation dossiers, line extension applications and variations for medicinal products incorporating medical devices, henceforth referred to as drug-device combination, or 'DDC' products[1].

The EMA considers the proposed guideline to be a business need because there has been an increase in the marketing authorisation activity linked to DDCs. The EMA is focusing on those DDC products, e.g. pre-filled syringes, inhalers and auto-injectors, that are seen as more complex than container-closure systems, due to the associated delivery and measuring or metering function. The concern is that the added complexity leads to higher potential for medication errors or Adverse Drug Reactions (ADR's). The future EMA guideline seeks to drive consistency in Module 3 by addressing DDC product data requirements with respect to quality aspects, usability requirements and lifecycle management.

A cross-industry working group within EBE has focused on EU specific topics relating to those products which are regulated as a medicinal product that incorporates a drug delivery device component, focusing on single integral products (as defined in MDR Article 10 Chapter 1, see Section 7 'Glossary of terms and definitions).

In order to encourage dialogue between industry and the EMA on this topic, the EBE working group produced a reflection paper with themes mirroring the scope of the above mentioned EMA concept paper and also considering the potential impact of the new MDR which enters into force in May 2020. This reflection paper, 'Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment', was published in January 2018 (5).

One of the topics addressed in the January 2018 EBE reflection paper was the location and extent of device and DDC product information in the quality section of the regulatory submission. Key proposals in the reflection paper include the following regarding CTD Module 3 (Quality) content for an EU MAA:

- Location of device and DDC product information in Module 3 should remain flexible. Three fundamental approaches to the distribution of information and data between 3.2.P and 3.2.R. CTD sections are described. The location of this information does not materially affect product quality; therefore, alternative approaches should be equally acceptable.
- Regardless of where device related information is located in the Module 3, industry is broadly aligned on the extent of device and DDC product information required.
- An example of Module 3 dossier content strategy was provided as part of a case study on the extent of device and DDC product information required in CTD Module 3. The case study considers a prefilled syringe assembled with a spring loaded auto-injector as an example of a well-established delivery system.

[1] This draft guideline (EMA/CHMP/QWP/BWP/259165/2019) was released by EMA, on 3 June 2019 for public consultation.

The January 2018 EBE reflection paper specifically proposed that the quality contribution for DDCs should be built around a high-level package on the manufacture and control of the drug delivery device in Module 3 that is focused on the areas listed below:

- Manufacturing and Controls
- Compatibility/interaction between the drug product and the device
- Container closure integrity
- Accuracy of dosing
- Functional performance
- Usability of the product

A DDC control strategy is linked to all the above attributes and is therefore a fundamental part of the quality section of an MAA. If it is to be successful, the EMA guidance will need to incorporate both established DDC regulatory principles and existing expectations for a medicinal product MAA.

The legal enforcement of the MDR from May 2020 will require that a notified body (NB) opinion be obtained for integral DDCs in the case where no CE certificate and/or no declaration of conformity is available. If DDC information in core Module 3 is to be presented in a more holistic fashion, with drug and device part of a combined control strategy, this raises questions about the optimum review process and the relationship between review bodies. Industry have concerns relating to the timing of NB review for the device component and the potential for duplication during competent authority review. A series of proposals to address these issues are discussed in the EBE-EFPIA reflection paper 'An Industry Perspective on Article 117 of the EU Medical Devices Regulation and the Impact on how Medicines are Assessed', published in July 2018 (6)

This paper is intended as a companion piece to the January 2018 EBE reflection paper and is a more detailed exploration of how a DDC control strategy might be developed and implemented in a regulatory context, using an example of a Pre-Filled Pen (PFP) with a sealed cartridge or prefilled syringe (PFS) as the primary container. It outlines how existing guidance can be used as a framework for DDC control strategy development and seeks to demonstrate that, if an 'end-to-end' approach to product control has been applied, an acceptable Pharmaceutical Quality System (PQS) is in place and an appropriate risk profile has been established, a reduced end product testing approach can be adopted in order to streamline batch release and to assure product quality.

2. General considerations on control strategy

For the purposes of this discussion, the term 'drug product component' refers to the drug product formulation within the primary container. The term 'assembled DDC product' refers to the assembled drug-device combination but does not include the secondary pack. The terms 'finished product', 'DDC product' and 'finished DDC product' refer to the final, secondary packaged drug-device combination.

In the EU, a drug-device combination product, within which the drug component exerts the predominant therapeutic effect, is regulated as a medicinal product. The device component is intended for delivering the drug and must be considered when developing the overall control strategy. This paper considers how existing medicinal product control strategy approaches may be adapted in order to address the fundamental concerns outlined by EMA in their 'Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product' (4). Taking a medicinal product perspective, some general control strategy considerations for DDCs are outlined in this section.

The proposed DDC standard includes considerations of appropriate medicinal product guidance e.g. ICH Quality Guidelines Q8, Q9, Q10, Q12 (Draft) as well as Medical Device standards EN/ISO 13485 and EN/ISO 14971.

As outlined in ICH Q8, the control strategy for a finished medicinal product is expected to describe and justify how in-process controls and the controls of input materials, intermediates, container closure system, and drug product components contribute to the final product quality.

A medicinal product control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas other elements may be managed via in-process manufacturing controls, controls for material attributes and design, or real-time release testing. The use of a risk-based approach is encouraged. This directly aligns with the principles defined in EN/ISO 14971 and how a control strategy would be approached for medical devices.

A control strategy is heavily reliant on the identification and control of those attributes that are known to be critical for drug product performance in order to meet the Quality Target Product profile (QTPP), i.e., safety, quality, efficacy, known as Critical Quality Attributes (CQAs). These principles can be extrapolated into the control of those drug-device combination (DDC) products which form a single integral product.

For a DDC, drug control and device control need to be successfully integrated to provide the control strategy for the finished product. That is not to say that the drug and device elements cannot be controlled separately, rather that the interplay between the two must be considered during the development of the overall control strategy.

ICH Q8 states that a drug product control strategy can include, but is not limited to, the following:

- Control of input material attributes based on an understanding of their impact on processability or product quality;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or product quality;
- In-process or real-time release testing in lieu of end-product testing;
- A monitoring program for verifying multivariate prediction models.

All of these aspects should be considered during device development and are managed within a suitable quality system, but it is not necessarily a requirement to present such information within Module 3.

Identification of Critical Quality Attributes related to the device component of a DDC product should comprise:

- Review of the impact of the device components on overall safety, quality and efficacy of the medicinal product.
- Consideration of Essential Requirements of Annex I to the current Medical Device Directive (to be replaced with Annex I General Safety and Performance Requirements of the Medical Device Regulation (EU) 2017/45, application date 26 May 2020)) (1)

Accordingly, potential Critical Quality Attributes for a device component are typically related to:

- Functionality and performance of the device components, when assembled into the DDC, to deliver the drug product
- Conformity to safety principles, taking account of the generally acknowledged state of the art.

Using the example of Pre-Filled Pen (PFP) with a sealed cartridge or prefilled syringe as the primary container, the potential design features linked to the device component QTPP might be summarised as follows:

- **Functionality and performance target:** effective drug delivery of intended dose, within suitable injection time, into target tissue, under normal use conditions, by intended user groups.
- **Safety target:** low risk for harm caused by device if used as intended, and acceptable risk in case of misuse or malfunction. Low risk of adverse impact of device components or assembly process to potential CQAs of drug product during its shelf-life e.g. sterility.

The key factors that influence these targets and that need consideration for development of an effective risk-based DDC control strategy are product design, material attributes, manufacturing process(es) and process design, as well as the user interface. For the device component of a DDC, these key factors are subject to 'design control'. Design controls are a component of a comprehensive quality system that ensures that the design of a device meets the intended user needs and that corresponding manufacturing processes are designed, verified, and controlled accordingly. The quality assurance process is a holistic approach that extends across the product lifecycle, from the development of device requirements through design, production, distribution, use, maintenance potentially through to obsolescence. Design control begins with development and approval of design inputs and includes the design of a device and the associated manufacturing processes. The challenge for a DDC is therefore to integrate device component design control with the overall medicinal product control strategy and quality system, taking a balanced, risk-based, approach.

Typical product and process development tasks that build the foundation for development work incorporating device elements into the DDC Control Strategy are illustrated in **Error! Reference source not found.**.

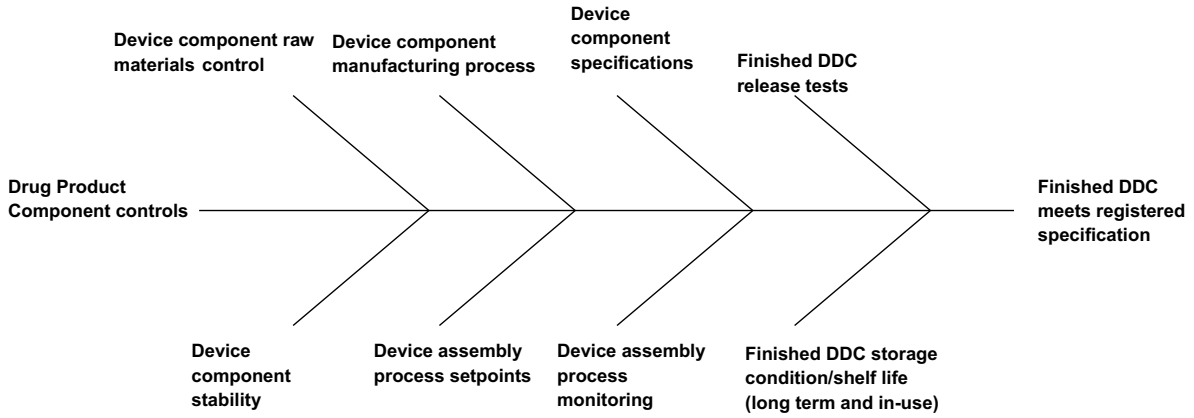
Table 1: Foundation for the development of the control strategy for a DDC product

Key Factors relating to device functionality and safety	Development Tasks	Output of Product and Process Development	Control Strategy Development	
			If product attributes are impacted by	Potential control measures
Product Design (device component)	Design and Development Process including Design Risk Assessments	Design Verification (Did we get the design right?) Compatibility and stability evaluation for DDC product. In-use stability assessment of DDC product	Design	design specifications/drawings
			Quality of raw materials	materials specifications and supplier controls device components expiry and recommended storage conditions
			In-use / use environment	product labelling (primary and secondary)
Manufacturing Processes and Process Design	Process Development including Process Risk Assessments	Process Validation	Manufacturing process of subassemblies and components	subassembly process monitoring and process setpoints IPC subassembly testing
			Manufacturing process of DDC product	process monitoring and process setpoints IPC release testing
User Interface	Human Factor and Usability Evaluations, Use Risk Assessments,	Design Validation (did we design the right device?) by Human Factors Studies and risk analysis.	User	Instructions for Use (IFU) and product labelling (primary and secondary)

With the above in mind, a hypothetical DDC product control strategy might be visually represented as shown in Figure 1 below.

This example assumes that the drug product component is a discrete entity, e.g. a sealed cartridge, around which the device component is assembled, resulting in the finished DDC product.

Figure 1: Example potential elements of the control strategy for a DDC product



As described in ICH Q10, which is itself based on established GMP and ISO standards, a control strategy is a component of a broader Pharmaceutical Quality System (PQS). With regard to Module 3, existing medicinal product CTD guidance does not require the PQS to be disclosed in detail; this is instead subject to regulatory inspection. By analogy, for a DDC, the industry proposal is that the critical device elements identified during control strategy development should be highlighted and discussed in the regulatory dossier but the wider device component quality system should not be a mandatory part of Module 3. A more detailed discussion of the development and implementation of a risk-based control strategy for a DDC product with a discrete drug product component - a Pre-Filled Pen (PFP) with a sealed cartridge or prefilled syringe as the primary container - is contained in Section 3 of this paper.

For an example of a DDC Module 3 dossier content strategy, see the reflection paper, 'Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment', January 2018 (5) .

3. Establishing an appropriate control strategy for a drug-device combination product

Since an integrated DDC control strategy is intended to be part of a medicinal product CTD Module 3 (Quality), this section primarily uses ICH medicinal product terminology and seeks to exemplify how these principles might be adapted to include relevant elements of the already well-established 'best practice' for device component design and development. The example detailed below is purely for illustration and should not be regarded as definitive.

It must be noted that there is some divergence across industry, particularly with regard to risk assessment. Although risk assessment principles are agreed and documented in ICH guidance and ISO standards, different companies may use different internal processes and terminology.

3.1 Quality target product profile and risk assessment

Critical Quality Attributes and their corresponding acceptance criteria are established by translating the identified Product Quality Attributes identified by risk assessment to potentially impact on product quality, safety or efficacy, into measurable technical product requirements. Standards such as ISO and pharmacopoeias provide expectations that are widely accepted across jurisdictions and should be applied when appropriate. Although ICH described risk-based approaches are rapidly gaining traction across the biopharmaceutical industry, conventional approaches remain acceptable as would hybrid approaches. Nonetheless, this section focuses on the principles of risk-based assessments and their application to determine a control strategy for a DDC product.

Initially a medicinal product under design should have a Quality Target Product Profile (QTPP) as its basis. The feasibility of the QTPP may be supported by prior knowledge of related product modalities, their attributes and their manufacture. The QTPP needs to balance the highest possible level of product quality with the ability to consistently manufacture, while allowing for transfer of the process to other sites and accommodate process changes through improvements as well as facility fit. This profile should be refined as new information becomes available through product development.

The target product profile serves as a starting point for an assessment of product quality attributes (referred to herein as a Product Quality Attribute Assessment, PQAA) which establishes the impact of identified drug, device and drug device combination attributes on product quality, patient safety, drug efficacy and device functionality. The assessment uses both product-specific knowledge and prior knowledge from appropriately similar molecules and should be reviewed regularly through the product development and lifecycle to assimilate new knowledge that may alter the final risk assessment (see below discussion of the risk assessment, herein referred to as a Product Quality Risk Assessment or PQRA) for the attribute and hence its control strategy. The PQAA is a measure of the severity or criticality of the attribute on patient safety and product efficacy and may be impacted by any device component. Typically, a product attribute is assessed for its impact on the intended product potency, immunogenicity, toxicity and PK/PD (bioavailability). Risks of potential impact are evaluated to provide an overall Severity or Criticality score for the attribute (other terms for the potential impact to quality, safety or efficacy may be used; for the purpose of this document, 'Severity' will be used). The Sponsor selects and justifies the threshold of Severity where a product attribute may be determined as a Critical Quality Attribute (CQA).
The acceptable level of CQAs typically have justified pass/fail acceptance criteria regardless of their point of control in the product or batch lifecycle.

A Product Quality Risk Assessment (PQRA) may be performed to determine an appropriate control strategy for each product attribute that avoids redundant testing and reduces the risk of impact for the attribute to an acceptable level. This approach is aligned with the MDR Annex I requirements to 'eliminate or reduce risks as far as possible through safe design and manufacture'. One commonly used procedure to perform the risk assessment incorporates the manufacturing and assembly processes into consideration by taking the Severity score and combining with the attribute Occurrence and Detection (S x O x D) scores using impact matrices. Occurrence evaluates the probability that the attribute exceeds the prescribed limits and is a measure of attribute frequency as influenced by any critical process parameters (CPPs) identified in process characterisation studies. Other means to form a risk assessment of product attributes may be equally valid. The "S x O x D" approach is outlined as an example methodology. Note that for a DDC product, most, if not all, process parameters (PPs), for a well-designed and controlled process, have no practically meaningful impact on product quality. The justification for 'no practically meaningful impact' would be case-by-case and the responsibility of the Sponsor. Detection evaluates the points in the manufacturing process, product development and stability at which the attribute is monitored, as well as the sensitivity of the method. These three interacting risk parameters can be adjusted to obtain the optimal control strategy for that product attribute. Care should be taken for any interacting product attributes such that a holistic attribute approach is also advised in addition to individual product attribute evaluations.

3.2 Implementation: from risk assessments to controls

A conventional control strategy would employ end-product release testing for all CQAs. Using the risk-based PQRA approach, or equivalent, it is possible to move many product attributes, that are conventionally controlled by release testing against the specifications, to upstream manufacturing in-process controls. Indeed, when supported by data, including prior knowledge, the risk associated with some attributes is low enough that they can be removed from routine control (non-routine control such as for product comparability exercises or at process validation is still recommended).

Critical process parameters (CPPs) that may potentially impact product quality during assembly of drug product with device components need to be controlled to assure low risk to patient safety and product efficacy. For example, a typically controlled parameter for biological products is light intensity exposure, during drug product manufacture including assembly with device components. Light exposure can modify biological products through e.g. methionine or tryptophan oxidation or cross-linking, and such degradation pathways need to be well characterised. Under controlled manufacturing conditions, the physical assembly of drug product with device components is generally determined as low risk impact to CQAs such as container/closure integrity. Given control of light during the entire drug product manufacturing process, the remaining risks are typically determined to be sufficiently low as not to require routine control.

Process validation or qualification has occasionally been requested by regulatory agencies for drug/device assembly at time of Marketing Application review. In the January 2018 EBE reflection paper, it was proposed by industry that PFP assembly process performance qualification (PPQ) shall be completed prior to marketing authorization but not included as a standard part of Module 3 in the Marketing Application. A summary of the PPQ approach in the dossier is recommended but this is regarded as supporting information. Design of drug product presentations that include administration devices is typically completed late in the overall product development process, after development of the drug in its primary container closure system. Therefore, PPQ runs for DDC assembly at commercial sites can be on the critical path for patient access to new drugs. In consideration of the low risk associated with controlled, automated or semi-automated assembly of a pre-filled syringe or cartridge into pen or autoinjector sub-assemblies, that is frequently considered by regulatory agencies as functional secondary packaging, it is considered justifiable that assembly PPQ is concurrent with Marketing Authorisation review, prior to launch.

A DDC product manufacturer may prefer to test selected device or DDC product attributes during the assembly process. However, with adequate characterisation of device and DDC product with verification on e.g. three batches' attributes with samples representing commercial finished DDC product, the level of in process controls for non-CQAs may be reduced.

Demonstration that the device components are compatible with the drug is a key area of a DDC product control strategy that is required in Module 3 and concerns characterisation of all potential impacts the device may have on the drug over the product lifecycle from manufacture through storage and transport, to drug delivery. During development, it is recommended that relevant aspects of drug product quality are investigated before and after delivery from the device.

Quality attributes for a DDC product may thus be divided into three broad groups:

(1) Quality attributes determined during drug product component manufacture.

Active Pharmaceutical Ingredient (API) synthesis (chemical or biotechnological), harvest (cell-derived recombinant products) and/or purification, formulation and filling into the immediate container are all manufacturing steps where the attribute level has the potential to be 'fixed', prior to the addition of device components. In a DDC product Module 3, the drug product component content would be presented in the established format for a drug product control strategy. Note: Control of drug product component CQAs is not the focus of this paper and will not be explored in detail here.

(2) Quality attributes that are solely related to device component design and quality.

e.g. cap removal force, injection depth, activation force. These design attributes are critical to the performance of the finished DDC product but may be controlled independently of the drug product component. The potential risks associated with these design attributes are managed as part of the design controls process. During this process, design verification and validation tests will be performed to ensure that they meet the pre-specified design specifications and the intended user needs and manufacturing controls will be implemented, where appropriate, to ensure acceptable product quality. Further, certain device design attributes may be tested and controlled by the device components manufacturer and accepted by the DDC product manufacturer on the basis of the supplier documentation e.g. dimensions, spring force (for a mechanical autoinjector or pen). Therefore, although they may have potential for a significant severity rating, these attributes can often be concluded to be of low risk and removed from routine end product control.

(3) Quality attributes which are influenced by both the drug product component and the device component of the DDC product.

This includes drug-device compatibility as well as some attributes that may need to be verified after assembly as end-product DDC product performance tests, e.g. deliverable volume and mechanically controlled injection time. These combined drug-device attributes have a potential impact on product quality and/or efficacy and the interplay between the drug and device components must be understood to facilitate control and avoid unnecessary batch rejection.

For a hypothetical Pre-Filled Pen (PFP), with a sealed cartridge or prefilled syringe as the primary container that follows a standard manufacturing process (1. Formulate drug product; 2. Fill cartridge/syringe; 3. Assembly and packaging of pre-filled pen) and focusing on the QTPP aspects of functionality and safety, the following critical quality attributes should be considered.

Drug product component quality

- Many potential drug product CQAs are controlled during drug product formulation, during immediate packaging and/or release testing of the pre-filled primary container. When the device assembly process and product understanding conclude that there is low risk of

impacting a CQA, that attribute need not be re-tested on the finished DDC. Examples of drug product component CQAs unaffected by device components include identity (active ingredient) and manufacturing process impurities, for example, residual solvents.

Delivered dose: accuracy and uniformity of dosage units

- The volume of drug delivered by the DDC product corresponds to the dose administered and, therefore, is typically described as a DDC performance CQA and included on the release specification.
- The drug product component also has a potential input to the delivered volume. Although quality attributes are fixed during drug product component manufacture, there may be a downstream impact on the delivered dose due to e.g. content uniformity of the input formulation. For example, it may be necessary to adjust the target fill weight based on the concentration of the formulated drug product.
- Delivered dose can be controlled by a combination of delivered (extractable) volume and assay (potency) tests or by a delivered dose test. Delivered volume may be monitored for the filled container closure (intermediate) for use in stability testing at time zero, in addition to monitoring of the finished DDC product. Under some circumstances, delivered volume and Uniformity of Dosage may be determined as an in-process control from fill weight as part of Real Time Release Testing. Control based primarily on fill weight may not be acceptable in all cases, e.g. suspension formulations; the choice of the most appropriate technique is part of control strategy development.

Microbiological quality

- Bioburden/endotoxins are often routinely monitored at the filled immediate container closure system step; these safety CQAs are linked to control of bioburden/endotoxins for input excipients and drug substance/API as well as the drug product manufacturing process and method of sterilisation or aseptic processing.
- The sterility of the entire fluid path should be included in the risk assessment, including the needle.
- It must be demonstrated that primary container closure integrity is maintained after finished DDC product assembly. Typically, demonstration of CCI does not require routine testing but is performed to qualify the assembly process and reported in 3.2.P.2.5 (*Microbiological Attributes*). Note that during medicinal product stability testing the compendial Sterility test may be replaced with a Container Closure integrity test.
- If the finished DDC product cannot be terminally sterilized, the sterility of the needle in a prefilled pen is typically assured by the use of sterile syringes with staked in needle for which the needle is encased in an elastomer needle shield. The needle with shield is assembled into the device sub-assemblies without exposing the needle. Sterility may be assured on the basis of the supplier documentation.

Appearance

- In addition to the simple description of the product, for a DDC it would be appropriate to consider particulates. See Mathonet et al 2016 (7) for a discussion on the control of visible particles for drug product contained within a device that does not allow easy removal of the immediate container.
- Consider the potential for needle blockage due to evaporation of solvent, e.g. drug product precipitate visible on needle

- Criteria for Appearance of a DDC product should include detection of visible damage has occurred during assembly. This visual inspection would typically occur during DDC product assembly as well as part of the release specification.

Device component function

- Device functionality for the final assembled DDC product must be controlled but it may be justified not to include all performance tests at end-product release testing.
- Device component and sub-assembly functionality, once confirmed in device verification to appropriate standards (e.g. ISO), are typically managed at device component or sub-assembly procurement through supplier testing and documentation.
- For device component release, acceptance quality limits (AQL) may be defined. The AQL is driven and justified by risk assessment which focuses on risk to patient, taking into account the severity of harms. Batch testing is based on statistically driven sampling procedures and statistical evaluation of test results in order to assure the defect rate does not exceed the limits as pre-defined per AQL. The applied principles are based on widely recognized standards for quality management, e.g. ISO norms, specifically DIN ISO 2859-1, although other statistical sampling guideline/methodologies may apply.
- AQL limits combine the probability of occurrence of the hazard and the harm and the severity of that harm, as recommended in EN/ISO 14971. AQL limits which might be revised based on updated risk assessment are handled in the PQS, and are not described in the dossier or subject to regulatory reporting.
- Although injection time is often ranked as a CQA, given demonstrated control of flow rate and/or sufficient experience with a product-specific DDC product, this attribute may be removed from routine testing. In addition to affecting the user experience, injection time can determine the flow rate of the drug product component and can potentially impact product quality. Notable is the impact flow rate could have on glass syringes that required a layer of silicone oil as a lubricant for a consistent break-loose force (force needed to start the plunger stopper moving to expel the drug from the syringe) and a smooth glide force of the plunger stopper. The silicone layer can shear from the syringe wall and form droplets that are detected as subvisible particles by conventional light obscuration assay. These silicone particles can be distinguished by their morphology from protein aggregate particles by microscopic flow imaging methods. Literature, company experience and data, and long history of the use of glass syringes to administer drugs, demonstrate that silicone particles at levels introduced into patients using glass syringe primary containers present negligible risk. Therefore, silicone content is not typically described as a CQA but should be characterised.

Biocompatibility of device components

- The finished DDC is assessed as part of device verification and summarised in the appropriate CTD sections but biocompatibility is not required as a routine release test because it is determined by fixed material properties. Biocompatibility for routine release may therefore be supported by upstream control of device component procurement and supplier certification.

Drug-device compatibility, including Extractables and Leachables (E&L)

- The main risk sources are primary container and drug product manufacturing equipment but any product contact components must be assessed and data provided.
- Considerations need to be taken for the potential of leaching from colourants, plasticisers, other device resin additives, adhesives or label inks.

- E&L risk from device components or sub-assemblies should be considered but can often be managed by the control of input materials. Typically, the solid-state contact between the device and the product immediate container has a minimal surface area. Volatile agents e.g. from plastic resin or adhesives, require special consideration especially if the immediate container is gas-permeable e.g. resin.
- If E&Ls are present at undesirable levels and cannot be removed by manufacturing changes, toxicological qualification may be required. Some E&Ls could react with or catalyse drug product degradation so may need to be monitored on long term stability.

An 'end-to-end' control strategy also needs to consider long term stability of the drug product and of the device. For DDC products, this includes the stability of the final assembled product and the relationship between the stability of the drug component and device component to the final product described. Therefore, the derivation of the shelf-life for the final DDC product from the drug shelf-life and the device expiry should be clearly described in the Drug CTD section 3.2.P.8.1 (Stability Summary and Conclusion). Typically, the device or device component expiries would be determined through accelerated aging studies and reported in the device verification section in Module 3.

The DDC product shelf-life is commonly the shortest of the claimed drug shelf-life and the device expiry. The date of expiration for the drug product or device is normally calculated from their respective date of manufacture. Therefore, the time a device has been stored in a warehouse should be considered.

When deriving shelf life, it is assumed that the stability of device components would usually follow a first order Arrhenius rate of decay that allows extrapolation of accelerated stability data. It must be acknowledged that the degradation of some drug or device components may be more complex and require further investigation. Nevertheless, linear decay is often used as a worst-case extrapolation given product quality attribute prior knowledge. Extrapolated stability data are required to ensure the quality, safety and efficacy of the product over the stated shelf-life and can be built into the release criteria for stability-indicating CQA. When the decay of a product quality attribute (PQA) is significant the determination of a separate stability specification for that attribute may be justified when data supports the acceptance limit to remain safe and efficacy is retained.

Error! Reference source not found. illustrates the potential controls for a Pre-Filled Pen (PFP) that is mechanically (spring) controlled, as an example.

Table 2: Control strategy example for a DDC product

Where PFS/cartridge = prefilled syringe or sealed cartridge and PFP = prefilled pen

Potential Critical Quality Attributes (pCQAs)	Controlled attribute(s)	Target	Potential Controls (Actual controls are implemented based on risk assessment)
Drug product component quality	As per Drug Product Regulations	As per Drug Product component TPP	- Drug Product component control strategy (e.g. standalone specification if desired, long term stability assurance) - Development: confirm Drug Product quality/performance is not adversely affected by device component
Dose accuracy	Delivered volume Assay (label claim) Or Delivered dose (as combined test)	Delivered volume shall not be less than labelled volume Assay per Finished Product specification	- Design Verification Testing (DVT) - Control of input materials for Drug Product component - Device component supplier testing - DDC product manufacturing monitoring & In-Process Controls (IPC) (e.g. fill volume) - Finished Product release / stability
Dose uniformity	Fill volume Or Extractable volume or deliverable volume Or Content Uniformity of drug product component (e.g. if suspension)	Fill weight Or per pharmacopoeia	- Control of input materials for Drug Product component - DDC product manufacturing monitoring & IPC - PFS/cartridge testing - Finished Product release / stability
Microbiological quality	Container closure integrity (CCI) (primary container)	Per pharmacopoeia	- PFS/cartridge testing - DDC product assembly process risk assessment and/or controls - Finished Product stability CCI
	Sterility	Per pharmacopoeia	- DDC product manufacturing process controls (aseptic fill or terminal sterilization of drug-contact components) - PFS/cartridge testing - Finished Product release (sterility) - Risk assessment for PFP fluid path

Table 2 (continued): Control strategy example for a DDC product

Where PFS/cartridge = prefilled syringe or sealed cartridge and PFP = prefilled pen

Potential Critical Quality Attributes (pCQAs)	Controlled attribute(s)	Target	Potential Controls (Actual controls are implemented based on risk assessment)
Appearance	Particulate matter: visible and subvisible particles (prevents needle blockage)	Per pharmacopoeia	- DDC product manufacturing process monitoring and IPC - PFS/cartridge testing - Finished Product release and stability
	Visual Appearance	Description per PFP specification, no visible damage, no visible particles	- DDC manufacturing process monitoring and IPC - PFS/cartridge testing - Finished product release and stability
Device function	Cap removal force	Depending on PFP design	- DVT - by design, verified by component supplier testing, monitoring of DDC product, or IPC of DDC product manufacture.
	Activation force	Depending on PFP design e.g. per MIL-STD-1472F*	- DVT - by design, verified by component supplier testing, monitoring of DDC product, or IPC of DDC product manufacture.
	Injection time	Depending on PFP design and clinical context Typically, one sided distribution test Human Factors/clinical justification	- DVT - by design, verified by component supplier testing, monitoring of DDC product, or IPC of DDC product manufacture; includes flow rate, siliconisation. - Finished product release and stability (if insufficient data to justify non-routine control)
	Injection depth or needle extension	Depending on PFP design based on prior knowledge on sc tissue depth	- DVT - by design, verified by component supplier testing, monitoring of DDC product, or IPC of DDC product
	Needle cover functionality (Override force after injection)	Depending on PFP design	- DVT - by design, verified by component supplier testing, monitoring of DDC product, or IPC of DDC product - Finished product release / stability (manual test, if final assembly risk identified)

Table 2 (continued): Control strategy example for a DDC product

Where PFS/cartridge = prefilled syringe or sealed cartridge and PFP = prefilled pen

Potential Critical Quality Attributes (pCQAs)	Controlled attribute(s)	Target	Potential Controls (Actual controls are implemented based on risk assessment)
Bio-compatibility	Pyrogen, sensitization, Irritation test, Cytotoxicity (ISO 10993-1)	Per pharmacopoeia	- by design (materials selection) and by appropriate DDC product manufacturing process controls - Testing in development of input materials or supplier controls (device components)
Drug-device compatibility	Extractables and leachables	Per pharmacopoeia, Drug Product dose dependant	- Manufacturing process development and control - Input materials development and control - PFS/cartridge release and stability testing (if risk identified) - Finished product release and stability test (if risk identified) - Risk assessment for product contact components e.g. if plastic primary container
	Degradation products	Defined by drug product dose and non-clinical data	- PFS/cartridge release and stability testing (if risk identified) - Finished product release and stability test (if risk identified) - Finished product in-use stability demonstrated during development

As illustrated in the above discussion and in Table 2, it is important to note that a 'control' does not necessarily result in a registered finished product test. Device Design Verification ensures that some elements of quality control are designed into the device, provided that the prototype DDC product used for Design Verification remains representative of the commercial product. Control can also be implemented upstream of the finished product at different stages of the manufacturing process and may be achieved via a combination of in-process monitoring and in-process testing, thereby introducing a more robust level of product and process control. This ensures a high level of product quality and productivity in addition to a reduction in the number of specifications and tests needed for routine batch release, while maintaining robust overall control. This risk-based, reduced end-product testing approach can be described at a high level as exemplified in Figure 2 below. In this context, reduced end product testing applies only to batch release. Stability testing to confirm relevant CQAs at end of shelf life is required, although in some cases this could take place on the PFS/cartridge and not the finished DDC product.

Figure 2: Reduced testing approach – 'Blobs' show where each CQA is confirmed to enable batch release

DDC Manufacturing inputs and process steps →

Potential CQA's

	Input: Product design and development	Input: Drug Product component	Input: Primary pack component	Fill process control	Post-fill testing	Device sub-component process & release	DDC Assembly process control	Finished DDC testing
Drug Product component quality	●	●			●			
Dose accuracy	●	●		●		●		●
Dose uniformity		●		●				
Microbiological quality		●			●			
Appearance (particulate, visual damage)					●		●	
Device function	●		●			●	●	
Bio compatibility	●					●		
Drug/Device Compatibility	●	●	●			●		

Note that the DDC product specification itself can be presented in the dossier in different ways, depending on how a company's Quality System is designed. For example, the drug product component and device component CQAs could be presented as separate stand-alone specification(s). Alternatively, the CQA acceptance criteria for multiple contributing components could be listed as one, combined, DDC product specification. Regardless of how the specification(s) are presented in Module 3 of the MAA dossier, as long as the control strategy is adequately described, the in-process controls and/or tests to assure the CQA acceptance criteria are met may be performed at an appropriate point in the manufacturing process where the attribute is controlled, or as dictated by the analytical method capability. The data reported on the finished product certificate of analysis could theoretically come from earlier points in the process, assuming the approach has been agreed with the Regulatory Agency. Although the example illustrates minimal testing on the final product, the finished product release process would evaluate all the available information, not simply the results of finished DDC product testing.

4. Conclusions and path forward

The control strategy process for DDC product development as presented in this paper is based on concepts outlined in globally harmonised guidelines such as ISO and ICH. The fundamental principles underpinning drug product component and device component guidance are broadly aligned. Manufacturers designing and developing DDC products within a well-established Quality System are already using these principles to define the control strategy through the knowledge gained during the development of the DDC product and associated unit manufacturing processes.

Existing guidance could therefore be adapted to incorporate considerations for single integral products with respect to the overall approach to control of such products and, ultimately, what information is presented within the MAA Module 3 (Quality). Industry interpretation of current guidance is that a robust product development and a strong pharmaceutical quality system can be leveraged to optimise the regulatory content, including reduced end-product testing. Since the building blocks for product development are already in place, adapting and clarifying Module 3 content for DDC products should be possible with minimal disruption to existing 'best practice'.

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6. Conflict of interest declaration

The authors declare that they have no competing interests.

7. Glossary of terms and definitions

Single Integral Product: MDR Article 1(9), second paragraph, gives the following definition: "if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable"

ADR: Adverse Drug Reactions

API: Active Pharmaceutical Ingredient

AQL: Acceptance Quality Limits

CQA: Critical Quality Attribute, as defined in ICH guidance

DDC: Drug-Device Combination

Drug Product: bulk Drug Product (pre-filled syringe or sealed cartridge)

DVT: Design Verification Testing

E&L: extractables and leachables

ICH: International Conference on Harmonisation, www.ich.org/

IPC: In-process control

ISO: International Organisation for Standardisation, https://www.iso.org/

MAA: Marketing Authorisation Application

MDR: Medical Device Regulation 2017/745

MDD: Medical Device Directive 93/42/EEC

NB: Notified Body

PFS: Pre-filled Syringe

PFP: Pre-filled Pen

PQS: Pharmaceutical Quality System, as defined in ICH guidance

PQAA: Product Quality Attribute Assessment (internal definition)

PQRA: Product Quality Risk Assessment (internal definition)

QTPP: Quality Target Product Profile, as defined in ICH guidance

8. References

(1) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance)

In Annex I to Directive 2001/83/EC, point 12 of Section 3.2.

Where applicable and if needed, a CE marking which is required by Community legislation on medical devices shall be provided is replaced by the following:

- Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (*), a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

- If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.

(2) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

(3) Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, Official Journal of the European Communities, No L 169/1, 1993

(4) Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product, EMA/CHMP/QWP/BWP/661488/2016, November 2016

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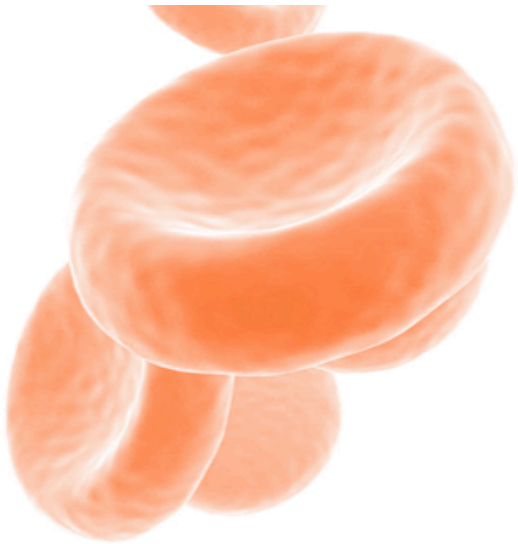
(6) 'An Industry Perspective on Article 117 of the EU Medical Devices Regulation and the Impact on how Medicines are Assessed', EBE-EFPIA reflection paper, July 2018, https://www.ebe-biopharma.eu/wp-content/uploads/2018/07/EBE-EFPIA_-Reflection-paper_-Industry-Perspective-on-Art-117-of-MDR_Final_2018.07.12-copy.docx

(7) A Biopharmaceutical Industry Perspective on the Control of Visible Particles in Biotechnology-Derived Injectable Drug Products. Mathonet, S.; Mahler H-C.; Esswein, S. T.; Mazaheri, M.; Cash, P. W.; Wuchner, K.; Kallmeyer, G.; Das, T. K.; Finkler, C. and Lennard, A. *PDA J. Pharm. Sci. Technol.* **2016**, *70* (4), 392–408, http://journal.pda.org/content/70/4/392.abstract?etoc



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