01 May 2025
EMA/188720/2025
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Azacitidine powder for suspension for injection 25 mg/ml product-specific bioequivalence guidance' (EMA/CHMP/172895/2023)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Cancer Patients Europe
2	AqVida GmbH, Germany
3	Z C Simic (VCLS), UK/France

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency i.e. accepted, partly accepted or not accepted (with a justification))*
1	It should be considered that powder is fully dissolved and there is no presence of microparticles that could cause pain, allergic reactions or disrupted biodispensability.	Accepted
2	We recently found that the European Medicines Agency has published a product-specific bioequivalence guidance on Azacitidine as draft version (4 December 2023, EMA/CHMP/172895/2023). AqVida GmbH, Marketing Authorisation Holder of Azacitidine in Germany and licence holder of the same product in several European countries as well as in UK and Canada, has gained deep knowledge and experience about this product in the course of numerous comparison studies and justifications. Regarding the conditions to justify a biowaiver for our Azacitidine product, we firstly introduced the so-called "time to clear solution" test, which was developed in-house, in April 2020. The time to clear solution test is an alternative method to the in vitro drug release method that was mentioned in the FDA`s draft guidance on Azacitidine (Nov. 2019), e.g. flow-through test, and even more, it is a direct determination of the decisive solubility properties of the product. We were delighted to realise that this time to clear solution test has now been included in the above-mentioned product-specific bioequivalence guidance as condition for waiver of the bioequivalence study. However, it is questionable why equivalent particle size distribution is also still stated,	Accepted PSD and morphological form are not relevant if time-to-clear-solution complies.

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	since the particle size of the Azacitidine powder is an insignificant surrogate parameter for this specific product, as discussed in the following. As it can be seen in the U.S., the originator product Vidaza is approved for both subcutaneous (25 mg/ml) and intravenous (10 mg/ml) use. This means that the pharmaceutical form of azacitidine lyophilizate is a solution with a concentration of 10 mg/ml at room temperature; a solution for which the particle size distribution (PSD) of the lyophilized powder of course does not play a role at all. The only reason why a "too little amount" of water for injection is added to the powder to obtain a suspension intentionally is that "Azacitidine rapidly degrades in aqueous solution via hydrolysis. Due to this instability, an aqueous solution formulation was not a viable option. Thus, a lyophilized dosage form was developed to minimize water activity in the medicinal product."[1] And as with almost every lyophilizate, the finished product is manufactured by filling an active substance fully dissolved in an aqueous solvent into vials, followed by freeze-drying of the filled vials and resulting in a freeze-dried powder. The lyophilisation is not intended to obtain a certain particle size of the powder. Even more, the PSD of a lyophilizate and the nature of the solid state of the freeze-dried powder (crystalline, amorphous, or even both) are irrelevant since it is only important that the powder dissolves quickly enough during reconstitution with water. Therefore, it is crucial to assess the reconstitution time, meaning the time until the powder is fully dissolved after addition of the recommended volume of water. As this is already covered by the time to clear solution test, there is no need to	

[1] EPAR Vidaza (January 2009)

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	assess the PSD or the solid state of the lyophilizate, as these are surrogate parameters only in case the solubility cannot be easily determined. We believe that there has been a misinterpretation in the FDA draft guidance about the character of the azacitidine lyophilized product being a suspension when prepared for s.c. application. Usual injectable suspensions are prepared from active substances having *low* aqueous solubility and provide an (intended) sustained release of the active substance, and the complete dissolution under physiological conditions is usually not directly accessible in an in-vitro laboratory setting. Therefore, surrogate parameters are measured to allow for comparison for bioequivalence / biowaiver justification. The dissolution of particles is, amongst others, a function of the surface of the particles, which is a consequence of the particle size and PSD. As such, the PSD is one of the main parameters for the comparison of generic and originator parenteral suspension products to justify their bioequivalence. In stark contrast, the Azacitidine lyophilizate is, as already explained, not a typical parenteral suspension product, because Azacitidine shows *good* aqueous solubility. This can be seen in numbers when looking at the solubilities of typical active substances of parenteral suspensions, e.g. corticosteroids: **Table 1. Solubility of active substances used for parenteral suspensions** | Active substance in suspension | Approx. solubility in water temperature | | --- | --- | | Betamethasone 21-acetate | 30 µg/ml |	

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Triamcinolone acetonide	21 µg/ml
Methylprednisolone acetate (as used in e.g. Methylprednisolone Acetate Injectable Suspension USP)	19 µg/ml
Budesonide (for inhalation application, but mentioned in the FDA draft guidance for azacitidine)	17 µg/ml

The solubility of the above active substances is about a 1000-fold lower than the solubility of azacitidine (17 mg/ml) at room temperature and even more at body temperature (solubility of Azacitidine at 37°C is greater than 25 mg/ml). For i.v. administration, the originator product Vidaza is reconstituted with 10 ml water for injection, which is a volume sufficient to fully dissolve the lyophilized powder. Once injected i.v., the active substance is immediately bioavailable. However, azacitidine shows a very rapid and temperature-dependent degradation in aqueous solutions. Depending on the temperature, a substantial degradation occurs within hours of even minutes. This is especially a problem during the time after reconstitution and before application to the patient. I.e., the Vidaza SmPC states that "*VIDAZA reconstituted for intravenous administration may be stored at 25 °C (77°F), but administration must be completed within 1 hour after reconstitution.*". For compounding pharmacies, such a short time interval is very challenging. To counter this problem, besides keeping the reconstituted azacitidine solution at controlled cooled conditions, a possible means to slow down the degradation would be to keep the active

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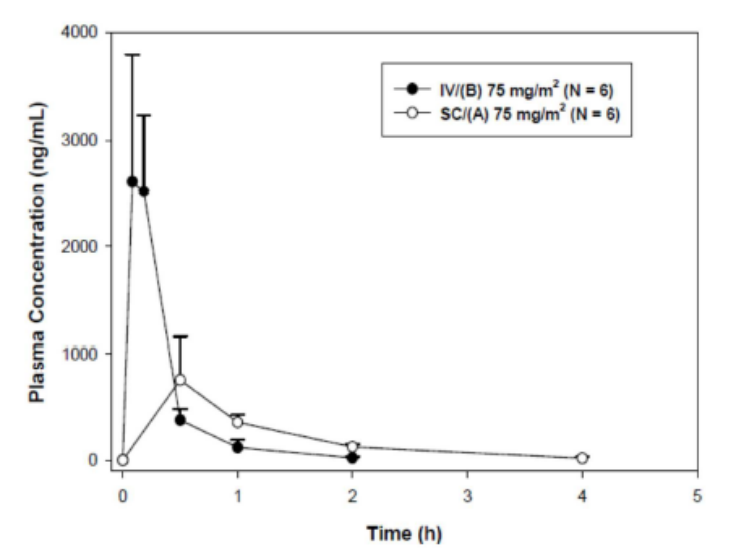
	substance not yet fully dissolved until administration. Therefore, the originator decided that the Vidaza lyophilizate could be reconstituted with an amount of water which is intentionally too low to fully dissolve the azacitidine powder, i.e. 4 ml of *cold* water for the 100 mg Vidaza product. In order to prove the bioequivalence between the i.v. and the s.c. administration route, the originator conducted a bioequivalence study. This study and the mean plasma azacitidine concentration curve is published in the EPAR for Vidaza (procedure no. EMEA/H/C/000978) and it is shown in copy here as Figure 1.  **Figure 1: Mean plasma azacitidine concentration graph copied from Vidaza® EPAR (study AZA-2002-BA-002)**	

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	The results were, as cited from the Vidaza SmPC: "*The pharmacokinetics of azacitidine were studied in 6 MDS patients following a single 75 mg/m^2 subcutaneous (SC) dose and a single 75 mg/m^2 intravenous (IV) dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes.*" The study shows not only the bioequivalence, but that after s.c. administration, azacitidine is very quickly bioavailable, with the c_{max} already at the first point of sampling at 30 minutes. This can be expected, since at body temperature of 37 °C the 100 mg dose of azacitidine is fully dissolved in the 4 ml of water used for the reconstitution. In consequence, although at first sight appearing as a suspension, azacitidine lyophilisate using s.c. administration is not at all a sustained release product, which makes the product a unique case, which cannot be assessed by the same parameters as for typical suspensions. Not only is azacitidine lyophilisate an immediate release product with a proven bioequivalence of the s.c. administration pathway compared to the i.v. injection; there is further literature which examines the way of administration and the biological response.	

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	In short, the science group which conducted the study (partially sponsored by Celgene, the originator of Vidaza®) "*A phase I biological study of azacitidine (Vidaza™) to determine the optimal dose to inhibit DNA methylation*" (*Epigenetics 5:8, 750-757; November 16, 2010*) states, that "*We did not observe significant differences in DNA methylation inhibition between intravenous and subcutaneous administration*. *Previous studies have shown intravenous versus subcutaneous administration do not produce significantly different biologic responses*" and further, "*The comparable bioavailability may account for the similar mean decline in methylation in patients treated with IV and SC azacitidine in this study*". In result, s.c. and i.v. administration are bioequivalent with regard to plasma levels and even more also with regard to their biological response profiles. This underlines once more the situation that the generic azacitidine lyophilisate is an immediate release dosage form, and that the i.v. injection is the comparator. Having said all this, the directly observable final solution covers all potential ranges of PSD or changes thereof, which makes the specific testing of the powder PSD irrelevant. In addition, in-vitro dissolution testing as a surrogate parameter is irrelevant as well, since the actual dissolution can be easily and reliably determined in real time using the test for time to clear solution, which is already stated in the EMA draft guidance. Therefore, we strongly recommend reconsidering the condition of equivalent particle size distribution as condition to waive the bioequivalence study, as it is in our opinion not based on scientific grounds.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table (Bioequivalence study design)	1	**Comments:** Considering the conversion from suspension to solution at body temperature, could be interesting to test if that can be affected by the location of the injection at different subcutaneous tissues (if influenced by environment, pH or vascularisation) **Proposed change:** Test in all locations proposed for the injection.	Not accepted. Local differences at injection sites are not expected to influence dissolution.
Table (Waiver of bioequivalence study)	3	Change "microphotographs" to "photo- or electron-micrographs". Oxford English Dictionary: microphotograph - a photograph reduced to microscopic or very small size (e.g. for archiving) photomicrograph - a photograph of an image produced by a microscope. **Proposed change:** *"Similar crystal morphology of the drug substance immediately prior to use as documented by ~~microphotographs (e.g. optical and scanning electron microscopy)~~* ***photo- or electron-micrographs****.*	Not accepted. A specific test on the crystal morphology is no longer considered necessary.