Harmonized approach to determine a worst-case (or a representative) test product to be taken into account for efficacy core assessment for a disinfectant BPF

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1. Background

In accordance with Article 19(6)(a) of the Biocidal Product Regulation (the BPR) and the new Biocidal Product Family (BPF) concept (CA-July19-Doc4.2-Final - Guidance note on BPF concept)[1], in the near future usually only one core efficacy assessment based on one "worst-case" or representative test product will be performed for a whole BPF. This test product (ideally an existing product of the family) must either be the worst-case for efficacy that can occur in the BPF, or it must be sufficiently close to the worst-case so that it can be considered representative for the entire BPF. In the following document, the phrase "worst-case test product" covers both.

This document intends to create a harmonised understanding on how to determine a worst-case test product for efficacy assessment for disinfectant BPFs (PT 1-5). For that purpose, it describes how a worst-case test product is defined and how bridging studies should be designed to substantiate the choice of the worst-case test product composition. After the worst-case test product composition has been identified, it can be used to demonstrate efficacy for each intended use of the whole BPF/the core assessment.

2. Proposal

The following proposals for defining a worst-case test product in a BPF as well as for designing appropriate bridging studies are intended to act as guidance for applicants and CAs when preparing and assessing efficacy dossiers for disinfectant BPFs.

2.1. Defining a worst-case test product

A worst-case test product is usually defined by:

- lowest (in use) concentration of active substance,
- lowest (in use) concentration of co-formulants positively affecting efficacy,
- highest (in use) concentration of co-formulants negatively affecting efficacy,
- physico-chemical property (e.g. pH value) which is most unfavourable for efficacy.

Identification and justification of the chosen worst-case product are within the responsibility of the applicant. However, the eCA must be able to retrace whether a suitable worst-case test product has been identified.

Often no literature data is available on the efficacy-related effects of different co-formulants and consequently it is not clear which co-formulants may have a positive, negative or no effect on the efficacy of the product. Thus, it is often not possible to define a worst-case test product *a priori* without experimental data.

[1] This BPC document concerns only the facilitation of choice of the worst-case test product for efficacy assessment and should be read in conjunction with the CA-July19-Doc4.2-Final - Guidance note on BPF concept: https://circabc.europa.eu/sd/a/71a22409-076c-4f2d-affe-dea810f128fd/CA-July19-Doc.4.2-Final%20-%20Guidance%20note%20on%20BPF%25

To substantiate the choice of the worst-case test product, bridging studies (Phase 2 Step 1 studies) should be performed with fresh products. With regard to the design of such studies, please refer to section 2.2 of this document.

The representative worst-case test product should be chosen based on the results from bridging studies and, possibly, sound waiving arguments (see section 2.2.3). This issue should be discussed with the eCA as soon as possible, ideally in the scope of a pre-submission meeting.

2.2. Designing appropriate bridging studies

There are multiple relevant factors when designing bridging studies to determine the worst-case test product, which are described in the following sections.

2.2.1. Test conditions

Phase 2 Step 1 bridging studies should be performed under the hardest conditions claimed in the application. This includes the following test conditions:

- highest soiling claimed in application,
- lowest temperature claimed in application,
- shortest contact time claimed in the application.

Bridging studies must be able to provide a sufficient resolution of the effects observed with the test formulations. Therefore, discrete log reduction values should be stated instead of "≥x" or "≤y" log reduction values, which may make adaptations with regard to dilutions necessary. Differences greater than 1 log units are usually considered relevant.

2.2.2. Test organisms

Testing should be performed for each claimed target organism group. However, it is acceptable to only test the most tolerant strain of each claimed target organisms group, as the whole BPF will be evaluated on basis of the worst-case test product. This covers the entire spectrum of target organisms and permits detection of possibly diverging effects between target organism groups. Exceptions may apply for unusual target organisms like amoebae, for which no standard test exists.

For example, a PT2 BPF with claims against bacteria and yeast will require bridging tests against the most tolerant of the bacterial standard strains and *C. albicans*. For further information on how to determine the most tolerant organism in a group, please refer to the respective Q&A in Annex 2.

2.2.3. Impact of different co-formulants

There are different groups of co-formulants in BPFs that may influence efficacy, e.g. surfactants, thickeners (viscosity modifiers), acids and others. Each co-formulant can potentially have a positive, a negative, or no influence on efficacy. To substantiate the choice of the worst-case test product the role of co-formulants on the efficacy has to be determined by providing bridging studies, but bridging studies may be waived, if a scientifically robust justification is available.

With regard to a scientifically robust justification for waiving bridging studies, literature data or sound physico-chemical considerations, which describe the (likely) effect of the respective co-formulant on efficacy of the products of the BPF, may qualify. If an applicant presents waiving arguments, CAs will judge whether these are of sufficient quality or whether new data (including bridging studies) will be requested. Annex 1 of this document lists relevant groups of co-formulants for disinfectants and some considerations on the necessity of testing or the possibility of waiving for these groups. Annex 1 is supposed to be a living document, that should be adjusted and updated regularly.

When bridging studies are necessary, they can be conducted on:

- existing biocidal products included in the family that contain the active substance at the lowest concentration and the co-formulant in question at its lowest and highest concentration. This approach is only acceptable if any observed difference can be clearly

ascribed to the co-formulant in question, i.e. when the test products do not differ in any other co-formulant that may have an influence on efficacy.

- "dummy products" containing the minimum amount of active substance. Concentrations of all relevant co-formulants should be set at 0% or their respective minimum to produce a reference product. Any co-formulant in question should be compared to that reference product by creating another product, which is equal to the reference product except that the co-formulant in question is at its maximum concentration. Table 1 in Annex 3 presents an example of a hypothetical BPF and the necessary bridging studies that would be required for this BPF when this approach is used.

Independent of the chosen approach (existing or dummy products) bridging studies have to be comparative. This means that in all bridging studies performed for a BPF, the products used for elucidating the effects of co-formulants should be tested in parallel to a reference product that is identical across all bridging studies. In case of dummy product testing, this should be the reference product; for testing of existing products, the reference product or the presumed existing worst-case product should be used. It is usually not acceptable to use studies performed at different times or in different laboratories to determine the effect of the same co-formulant.

Co-formulants that are present across the entire BPF with a fixed nominal concentration require no bridging/justification. The worst-case test product should contain such co-formulants at their fixed concentration.

Usually combinatory effects of co-formulants do not need to be investigated. However, if the eCA has a clear indication of combinatory effects between co-formulants, it retains the freedom to request additional data. In general, co-formulants should be grouped according to the new BPF concept. However, if viscosity modifiers are not (or cannot be) grouped and the range of the BPF allows the use of different viscosity modifiers together, they also have to be tested in combination at the highest concentration (e.g. see Annex 3, footnote 3).

2.3. Efficacy assessment of the BPF (core assessment)

The identified worst-case test product is then used for the efficacy assessment of the whole BPF/the core assessment. To do this, every use is assessed individually using this worst-case test product.

Annex 1: Co-formulants which might affect efficacy

Formulations of disinfectants may include different co-formulant groups as described below. This Annex intends to address some of the most relevant groups of co-formulants in disinfectants with regard to their respective expected effects on efficacy and the necessity of bridging studies for the determination of a worst-case test product. As such, it is considered a living document, that may be updated based on experiences gained in the authorisation process.

The nomenclature of co-formulant groups has been harmonised with an APCP WG document on definitions of co-formulants.

When a substance falls into several groups at the same time, the consequences should be drawn based on expert judgement of the innate properties of the substance and its context in the BPF. Typically, there are the following priorities (1>2>3):

1. substances that should usually be minimised/maximised in worst-case test products,
2. substances that usually require bridging studies,
3. substances that usually can be disregarded.

This means, e.g. that a substance with functions that fall into categories 1 and 2 should usually be minimised/maximised in the worst-case test product and does not need to be tested in bridging studies[2].

Substances that are active substances[3] in Main Group 1

If the substance is an active substance in Main Group 1, its concentration in the worst-case test product should be minimised unless there are clear scientific reasons to believe that the substance will actually be detrimental to efficacy in the specific case. Bridging studies usually are not necessary.

Acids

Acids are usually expected to have a positive effect on efficacy for most microorganisms unless the active substance requires a basic pH. Therefore, usually the amount of acids in representative worst-case test products should be minimised and bridging studies will not be required.

Bases

Bases are often just used for pH regulation in otherwise acidic or neutral products. In such cases, they should be treated like pH regulators (see below). In cases where the products are alkaline, bases should be treated equivalently to acids (see above).

Surfactants

Some anionic and non-ionic surfactants often have a positive impact on efficacy. However, this is dependent on the individual surfactant and the active substance used in the formulation. Surfactants might, in rare cases, also have a negative impact on efficacy. Thus, bridging studies will usually be necessary.

Emollients (and other compounds for skin compatibility)

Emollients used in biocidal products appear to encompass diverse chemical compounds. Some have been reported in the scientific literature to have negative effects on efficacy of skin disinfectants. Others may have no or a positive influence. Thus, bridging studies will usually be necessary.

Viscosity modifiers (thickeners)

Viscosity modifiers again show diverse chemical structures and properties with regard to polarity. Furthermore, increasing the viscosity of a formulation may have no, a positive or a negative

[2] CAs retain the liberty to require bridging studies of co-formulants for which usually no testing is deemed necessary, if there are indications that the co-formulants in question may have an effect on efficacy in the specific family or if the co-formulants are present in unusually high concentrations.
[3] This includes approved active substances and active substances still under evaluation.

impact on efficacy (also related to the use, e.g. disinfectants for toilet bowls). Thus, bridging studies will usually be necessary.

pH regulators

pH regulator systems do have an impact on efficacy by ensuring a specific pH value/range in the formulation. However, the effect is in our experience usually dependent on the pH value/range maintained and not related to different pH regulator systems. Therefore, pH values of representative worst-case test products should be adjusted to the pH value(s) most unfavourable to the active substance, but bridging studies will usually not be necessary.

Complexing agents

Some active substances may react with metal ions in solution, e.g. by forming complexes that are no longer biocidally active. Complexing agents can be used to bind such ions before they react with the active substance, thereby improving the efficacy of the product. For this reason, complexing agents should usually be minimised, unless it can be convincingly argued that their function is unrelated to efficacy.

Stabilisers

Some active substances require the addition of stabilisers to ensure storage stability of the biocidal product. These stabilisers may belong to very different chemical groups, but they are often added in minute amounts that can be expected to not directly influence efficacy (exceptions exist). As long term stability is not relevant for the choice of a worst-case for efficacy testing, stabilisers, when present in minute amounts, usually can be disregarded and do not need to be included in bridging studies to determine the representative worst-case test product.

Solvents (other than water)

Many organic solvents are known to be membrane-toxic, i.e. to destabilise biological membranes. This action can be expected to increase the efficacy of biocides by facilitating uptake into cells and by generally subjecting test organisms to stress. Thus, usually the amount of solvents should be minimised in representative worst-case test products and bridging studies will not be required.

Colouring agents and odorants (PPD)

Colouring agents and odorants (perfumes and dyes) are normally present in low concentrations and not expected to influence efficacy in BPFs. Thus, usually they are disregarded, and testing is not required.

Other co-formulants

For co-formulants that cannot be included in one of the groups mentioned above, case-by-case decisions will be necessary. In case of uncertainty, bridging studies should be performed.

Annex 2 – Question and Answers

Annex 2 is a collection of interpretations and decisions related to the determination of representative worst-case test products for BPFs. For that reason, it should be regarded as a living document that will be updated based on experience gained in the authorisation process.

1. ***A product is intended to be used against bacteria and mycobacteria. Is it acceptable to conduct the bridging study only with the most robust mycobacteria strain?***

   As bacteria and mycobacteria both belong to the same organism group (bacteria), it is acceptable to only test the most tolerant strain, which often would be a mycobacterial strain.

2. ***A test/bridging study was only conducted with a product not containing the highest concentration of a co-formulant having a negative effect on efficacy. Would this be acceptable if there is only a small difference between the tested product and the product with the highest concentration of the respective co-formulant?***

   As long as the relative difference of the co-formulant nominal concentration in both products is <10% in use (meaning that if highest possible concentration of co-formulant in the BPF is 10%, the tested product may not contain less than 9% of this co-formulant), this would be acceptable.

3. ***A test/bridging study was only conducted with a product not containing the lowest active substance concentration. Would this be acceptable if there is only a small difference between the test product and the product with the lowest possible active substance concentration in the BPF?***

   No. The active substance content in use must be the lowest one possible in the family.

4. ***After taking bridging studies and waiving arguments into account, two (or more) real products appear suitable as representative worst-case test products, as they do not differ in in-use active substance content and co-formulants that have an effect on efficacy. How to deal with this situation?***

   If two (or more) real products are functionally identical as worst-case test products, i.e. differing only in co-formulants that have no effect on efficacy, one or the other can be used interchangeably for efficacy testing.

5. ***A co-formulant has one effect on some target organisms (e.g. a positive effect for bactericidal efficacy), but the opposite effect on another target organism (e.g. a negative effect on virucidal efficacy). How can this be reflected with regard to the worst-case test product?***

   In such a case, two worst-case test products will be required. The test product for bacteria should contain the lowest amount of this co-formulant, while the test product for viruses should contain the highest amount. In this case, studies on bacteria should only be conducted with the worst-case test product for bacteria and vice versa for viruses. No refinement is required in such cases, but the situation should be described clearly.

6. ***When several use areas are part of the application, for which different Phase 2, Step 1 standards exist (e.g. for bacteria EN 1276, EN 13727 and EN 1656), which standard should be used for bridging studies?***

   When there are several standards that can be used, the one that most closely reflects worst-case use conditions should be used for bridging studies.

7. ***If an applicant decides to conduct bridging studies only on the most tolerant target organism of a group, should the most tolerant target organism be determined among all intended target organisms of this group in the entire BPF?***

   Yes. For example, in a BPF with uses in PT2 and PT3 that is intended to be used against bacteria, this would mean that the most tolerant target organism would have to be determined among *E. coli*, *P. aeruginosa*, *P. vulgaris*, *E. hirae* and *S. aureus*.

8. ***If an applicant decides to conduct bridging studies only on the most tolerant target organism of a group, which test products can be used to determine the most tolerant target organism?***

   There are no strict rules for choosing the product used to determine the most tolerant target organism used for bridging studies. In general, the product for these tests should be representative for the BPF, so its composition should be in the intended ranges. Pre-existing efficacy tests for a product of the BPF can be used for this purpose.

9. ***If the application contains different combinations of use temperature, soiling and contact time, how should the "hardest conditions claimed in the application" be applied in bridging studies?***

   For each parameter, the hardest claimed condition in the entire application for authorisation should be used in bridging studies, even if this combination of conditions does not exist in any intended use. Bridging studies do not need to pass the log reduction criteria used for normal efficacy tests, as their aim is only to substantiate the choice of the worst-case test product.

10. ***Two or more co-formulants are chemically incompatible with each other. How can this be addressed when defining the composition of the worst-case test product?***

    This is usually only relevant for co-formulants with a negative influence on efficacy.

    If two or more co-formulants are chemically not compatible, it is assumed that these are not present in the same product. When these co-formulants are grouped according to the CA document: CA-July19-Doc4.2-Final (grouping of co-formulants) in one group, it is therefore assumed that these co-formulant will only be used either or. In this case it is acceptable to only include the co-formulant with the strongest effect in the worst-case test product.

Annex 3 – Bridging study requirements and study results: Example

In this Annex, we provide an example of a hypothetical BPF to demonstrate the requirements of bridging tests with regard to different co-formulants (see section 2.2.3).

The BPF contains one active substance, five co-formulants in two groups and the solvent water (which has been left out of the table for simplicity). In this example, no waiving arguments have been made for any co-formulant, so that bridging tests are necessary for all of them. Consequently, one reference product containing the minimum of all co-formulants is compared to five bridging test products. Each bridging test product contains one co-formulant at its highest possible concentration, while all others remain at their minimum concentration.

Table 1: Testing requirements with regard to co-formulants in a hypothetical BPF.

Function	Level 1 - Family		Reference product w/o co-formulant	Viscosity modifier bridging test products		Surfactant bridging test products		
	min (%)	max (%)		Visc. Mod. 1	Visc. Mod. 2	Surf. 1	Surf. 2	Surf. 3
Active substance	**10**	**20**	**10**	**10**	**10**	**10**	**10**	**10**
Viscosity modifiers	**0**	**3**						
Visc. Mod. 1	0	3	0	3	0	0	0	0
Visc. Mod. 2	0	3	0	0	3	0	0	0
Viscosity modifiers are used alternatively[4]								
Surfactants	**1**	**3**						
Surfactant 1	0	1	0	0	0	1	0	0
Surfactant 2	1	2	1*	1*	1*	1*	2	1*
Surfactant 3	0	2	0	0	0	0	0	2
Surfactants can be used in combination								
Exemplary study results								
Study	**Product concentration//log Reduction (logR)**							
EN 1276 (most tolerant bacterial strain)	80% >5 logR		80% >5 logR	80% >5 logR	80% >5 logR	80% >5 logR	80% >5 logR	
	60% <2 logR		60% 3.1 logR	60% 3.2 logR	60% 3.3 logR	60% 3.8 logR	60% 3.9 logR	
EN 1650 - yeast	60% 2.8 logR		60% 2.9 logR	60% 3.0 logR	60% 3.1 logR	60% 3.2 logR	60% 3.3 logR	

* Alternatively, a concentration of 0% is permitted as well. However, the chosen concentration has to be consistent across all test products.

In this example, the "reference product w/o co-formulant" or a similar real product would be considered as worst-case test product.

[4] If viscosity modifiers cannot be grouped and no restriction is set, a product containing 3% viscosity modifier 1 and 3% viscosity modifier 2 also has to be tested (6 % viscosity modifier in total).