Overview of comments received on “Questions and Answers document on Quality of Homeopathic Medicinal Product (Q 6-7)”*.

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Presentation at HMPWG Quality sub-working group</td>
<td>3 October 2016</td>
</tr>
<tr>
<td>Presentation for discussion at HMPWG</td>
<td>10-11 November 2016</td>
</tr>
<tr>
<td>Discussion at HMPWG Quality sub-working group</td>
<td>04 May 2017</td>
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<tr>
<td>Discussion at HMPWG</td>
<td>26-27 June 2017</td>
</tr>
<tr>
<td>Discussion at HMPWG Quality sub-working group</td>
<td>09 October 2017</td>
</tr>
<tr>
<td>Adoption for Public Consultation by HMPWG</td>
<td>05-06 December 2017</td>
</tr>
<tr>
<td>Transmission to HMA for release for consultation</td>
<td>26 February 2018</td>
</tr>
<tr>
<td>Deadline for comments</td>
<td>31 May 2018</td>
</tr>
<tr>
<td>Discussion of comments in HMPWG Quality sub-working group</td>
<td>24 September 2018</td>
</tr>
<tr>
<td>First discussion of comments in HMPWG</td>
<td>18-19 October 2018</td>
</tr>
<tr>
<td>Discussion of comments in HMPWG Quality sub-working group</td>
<td>20 March 2019</td>
</tr>
<tr>
<td>Adoption by HMPWG for publication on HMA-website</td>
<td>23-24 May 2019</td>
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</table>

*Explanatory note: At the 28th Meeting of HMPWG (18-19 October 2018, Vienna) it was decided to split the originally developed document “Questions and Answers document on Quality of Homeopathic Medicinal Product (Q 4-7)” as well as the overview of comments into two documents, one related to Q&A 4-5, and one related to Q&A 6-7. The present document includes general comments as well as specific comments on Q&A 6-7.
Overview of comments received

Table 1: Organisations and/or individuals that commented on the draft document “Questions and Answers document on Quality of Homeopathic Medicinal Products (Q 4-7)” as released for public consultation on 26 February 2018 until 31 May 2018.

<table>
<thead>
<tr>
<th>Organisations and/or individuals</th>
</tr>
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<tbody>
<tr>
<td>1 Association of the European Self-Medication Industry (AESGP)</td>
</tr>
<tr>
<td>2 European Coalition on Homeopathic &amp; Anthroposophic Medicinal Products (ECHAMP)</td>
</tr>
<tr>
<td>3 BPI e.V. - Bundesverband der Pharmazeutischen Industrie e.V.</td>
</tr>
<tr>
<td>4 Laboratoires Lehning</td>
</tr>
</tbody>
</table>
Table 2: Discussion of comments

<table>
<thead>
<tr>
<th>Interested party</th>
<th>Comment and Rationale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Coalition on Homeopathic &amp; Anthroposophic Medicinal Products (ECHAMP)</td>
<td>In its title the document refers to Questions 4 – 7 (Q 4-7) which is correct because in 2016 the HMPWG released Questions 1 – 3 (not on the HMPWG website anymore). The questions and answers themselves start with Question 3 instead of Question 4</td>
<td>☑ accepted</td>
</tr>
<tr>
<td>Association of the European Self-Medication Industry (AESGP)</td>
<td>Formal Comment:</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td><em>In its title the document refers to Questions 4 – 7 (Q 4-7) which is correct because in 2016 the HMPWG released Questions 1 – 3 (not on the HMPWG website anymore). The questions and answers themselves start with Question 3 instead of Question 4.</em></td>
<td></td>
</tr>
<tr>
<td>BPI e.V.</td>
<td>In its title the document refers to Questions 4 – 7 (Q 4-7) which is correct because in 2016 the HMPWG released Questions 1 – 3 (not on the HMPWG website anymore). However, the questions and answers themselves start in the newly released document with Question 3 instead of Question 4.</td>
<td>As above</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section number and heading</th>
<th>Interested party</th>
<th>Comment and Rationale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 6</td>
<td></td>
<td>In HMP CTD dossier (section 3.2.P.3.5), is the process validation always required?</td>
<td></td>
</tr>
</tbody>
</table>
**ECHAMP**

**Comment:**

If a manufacturing process is justified as a **standard process**, a common exemplary validation valid for identical galenic forms (dosage forms) **for a specific manufacturing site and process should be acceptable**.

Moreover, a manufacturing process validation does not appear to be relevant in the context of a standard procedure described in the pharmacopoeia.

It is to be considered that the HAB/Ph.Eur. methods of preparation of final potencies are in use for decades with much experience gained on it. A pharmaceutical development as expected for new medicinal products according to actual guidelines has not taken place in most of the cases. Therefore, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches.

For standard manufacturing processes, it should also be acceptable that **no validation scheme is given in the dossier**, since this is a matter of GMP verified by the supervisory authority.

**Rationale:** In homeopathic products the concentration of chemically detectable drug substances is often very low. Therefore, the specification of the finished product contains only parameters of the dosage form, and no product-specific tests. In these cases, any influence of the drug substances on the quality of the finished product can be excluded.

**From the chemical view the products are identical when produced with the same qualitative and quantitative composition of excipients resulting in the same pharmaceutical form.**

**partially accepted**

For a standard manufacturing process, at least a process validation scheme for the drug product should be provided.

The validation of manufacturing process can be demonstrated by provision of data of a MAH/MRH own reference product of the same dosage form, under the following conditions:

- no identification or assay of the active substance(s) is possible due to the degree of dilution;
- the manufacture takes place at the same manufacturing site;
- the product is of the same qualitative and quantitative composition in relation to excipients;
- the products have the same specifications, all related to the pharmaceutical form only.

*Reference in Guideline on process validation for finished products - information and data to be provided in regulatory submissions EMA/CHMP/CVMP/QWP/749073/2016*

**Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.**

The process validation scheme should include a description of the manufacturing process, the tests to be performed and acceptance criteria, a description of the additional controls in place and the data to be collected. A justification for the chosen process validation scheme should be presented in
The subject of validation should be considered in the same way as the stability of finished products, where data are transferable in certain conditions.

For a harmonised view which manufacturing processes can be considered as standard or non-standard with regard to process validation, the Guideline on process validation for finished products – information on data to be provided in regulatory submissions (EMA/QWP/BWP/70278/2012-rev1) is of relevance. Annex II to this Guideline states several conditions, which can be considered to define a process as non-standard. For example, as non-standard are seen specialised pharmaceutical dose forms, new technologies, complex processes, non-standard methods of sterilisation.

Manufacturing validation in the first line is a matter of GMP and not of registration procedures.

Proposed change:

Yes, a process validation or alternatively an evaluation may be required.

A common exemplary validation valid for identical galenic forms (dosage forms) for a specific manufacturing site and process should be acceptable.

Complete data should be provided in the dossier for non-standard products or processes (e.g. aseptic processing). The process must be validated when an unconventional manufacturing method is used or when its implementation is decisive for the quality of the product. It is possible for the applicant to justify that the product process can be considered as a standard procedure for a manufacturer/site. In this case, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches. At least the process validation scheme (as described in Annex I of EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr. 1 guideline) should be provided, and the applicant commits on performing the

Line 27 has been deleted because already discussed in the specific guidance, to not have any misunderstanding.

Module 3.

The dossier is composed by documents supporting the registration/authorization of a specific homeopathic medicinal product therefore, the manufacturing process validation is related to a specific HMP; besides, GMP requirements are related to a specific manufacturing site involved in the production of different kind of dosage forms and their relative products.
**Validation on production scale batches prior to marketing of the product.**

“Validation of viral safety should be included in Part 3.2.A.2”

**Comment:** Generally, a risk assessment should be sufficient for proof of viral safety. A validation should be demanded only in exceptional cases.

**Rationale:** Risk assessments describe the manufacturing method, the nature and origin of raw materials, as well as the deducted risk of contaminations. In addition, specifications can further minimise the risk of contamination by specific viruses. Validations only should be required if questions stay open.

In any case, the rationale proposed is completely not in line with the provisions described in the “Points to Consider on Safety of Homeopathic Medicinal Products from Biological Origin”.

| AESGP | **Comment:** If a manufacturing process is justified as a standard process, a common validation for identical galenic forms (dosage forms) for a specific manufacturing site and process should be acceptable. Moreover, a manufacturing process validation does not appear to be relevant in the context of a standard procedure described in the pharmacopoeia. It is to be considered that the HAB/Ph.Eur. methods of preparation of final potencies are in use for decades with much experience gained on it. A pharmaceutical development as expected for new medicinal products according to actual guidelines has not taken place in most of the cases. Therefore, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches. For standard manufacturing processes, it should also be acceptable that no validation scheme is given in the dossier, since this is a matter of GMP verified by the supervisory authority.

**Rationale:** For a harmonised view which manufacturing processes can be considered as standard or non-standard with regard to process validation, the Guideline on process validation for finished products – information on data to be provided in regulatory submissions (EMA/QWP/BWP/70278/2012-rev1) is of relevance. Annex II to this... |

**See above**
Guideline states several conditions, which can be considered to define a process as non-standard. For example, as non-standard are seen specialised pharmaceutical dose forms, new technologies, complex processes, non-standard methods of sterilisation. Manufacturing validation in the first line is a matter of GMP and not of registration procedures.

**Proposed change:**
Yes, a process validation or alternatively an evaluation may be is required.

A common exemplary validation valid for identical galenic forms (dosage forms) for a specific manufacturing site and process should be acceptable. Complete data should be provided in the dossier for non-standard products or processes (e.g. aseptic processing). The process must be validated when an unconventional manufacturing method is used or when its implementation is decisive for the quality of the product. It is possible for the applicant to justify that the product process can be considered as a standard procedure for a manufacturer/site. In this case, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches at least the process validation scheme (as described in Annex I of EMA/CHMP/CVMP/QWP/BWP/70278/2012 Rev1, Corr. 1 guideline) should be provided, and the applicant commits on performing the validation on production scale batches prior to 19 marketing of the product.

“Validation of viral safety should be included in Part 3.2.A.2”

**Comment:** Generally, a risk assessment should be sufficient for proof of viral safety. A validation should be demanded only in exceptional cases.

**Rationale:** Risk assessments describe the manufacturing method, the nature and origin of raw materials, as well as the deducted risk of contaminations. In addition, specifications can further minimise the
| BPI e.V. | **General Comment:**
If a manufacturing process is justified as a standard process, a common exemplary validation valid for identical galenicals (dosage forms) for a specific manufacturing site and process should be acceptable. As homeopathic medicinal products often consist of very high diluted ingredients, no product-specific parameters can be tested. Therefore, influence of the active ingredients on the product can be excluded, whereas the excipients are the determining factor in that regard. Therefore, only dosage form-specific parameters can be tested deriving from the used excipients. As transfer of data is allowed in case of stability data under certain circumstances, this should also be possible for validations.

For standard processes described in the pharmacopoeia, process validation should not be relevant. For such processes evaluation of the results from in-process controls of three consecutive production batches should be sufficient.

It is to be considered that the HAB / Ph.Eur. methods of preparation of final potencies are in use for decades with much experience gained on... | See above |
it. A pharmaceutical development as expected for new medicinal products according to actual guidelines has not taken place in most of the cases. Therefore, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches. For standard manufacturing processes, it should also be acceptable that no validation scheme is given in the dossier, since this is a matter of GMP verified by the supervisory authority.

**Rationale:**
In homeopathic medicinal products the concentration of chemically detectable drug substances is often very low. Therefore, the specification of the finished product contains only parameters of the dosage form, and no product-specific tests. In these cases, any influence of the drug substances on the quality of the finished product can be excluded.

From the chemical view the products are identical when produced with the same qualitative and quantitative composition of excipients resulting in the same pharmaceutical form. The subject of validation should be considered in the same way as the stability of finished products, where data are transferable in certain conditions.

For a harmonised view which manufacturing processes can be considered as standard or non-standard with regard to process validation, the *Guideline on process validation for finished products – information on data to be provided in regulatory submissions* (EMA/QWP/BWP/70278/2012-rev1) is of relevance. Annex II to this Guideline states several conditions, which can be considered to define a process as non-standard. For example, as non-standard are seen specialised pharmaceutical dose forms, new technologies, complex processes, non-standard methods of sterilisation. Manufacturing validation in the first line is a matter of GMP and not of
registration procedures.

Proposed change:
Yes, a process validation or alternatively an evaluation may be required.
A common exemplary validation valid for identical galenicals (dosage forms) for a specific manufacturing site and process should be acceptable.
Complete data should be provided in the dossier for non-standard products or processes (e.g. aseptic processing). The process must be validated when an unconventional manufacturing method is used or when its implementation is decisive for the quality of the product.
It is possible for the applicant to justify that the product process can be considered as a standard procedure for a manufacturer/site. In this case, for these standard processes it should be sufficient to prove the validity of the process by submitting the in-process control results of three consecutive production batches.

a. Validation of viral safety should be included in Part 3.2.A.2

Comment:
Regarding viral safety, a risk assessment, evaluating potential risks as well as defining specification of minimizing contaminations with human-pathogenic organisms, should be sufficient for proof of safety. Such risk assessments are already commonly in use. Only in special cases involving high risk material, validation of e.g. inactivating processes should be required.

Rationale:
Risk assessments describe the manufacturing method, the nature and origin of raw materials, as well as the deducted risk of contaminations. In addition, specifications can further minimise the risk of
contamination by specific viruses. Validations only should be required if questions stay open.

<table>
<thead>
<tr>
<th>Specification and testing Question 7</th>
<th>ECHAMP</th>
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</table>
| How many batches are required in 3.2.5.4.4 (Batch analysis) section? | **General comment:**
The term CoA – Certificate of Analysis is not applicable in the context of a CTD dossier.
In order to maintain correct and consistent wording with EMA and HMPWG regulatory guidance on CTD the term batch analyses and results of batch analyses is to be used here.
**Proposed change:**
Replace Certificate of analysis (CoA) with Results of batch analysis

a. Raw material
- The following answer should be read in the context with Questions 2 and 3 of the HMPWG Q&A document of 2016 and the corresponding comments from the industry.

**Comment:**
We propose to submit 2 batch results of the most frequent supplier, if available.

**Proposed change:**

a. Raw material
Certificates of analysis (CoA) Results of analyses of at least two batches of the raw material(s) should be provided. In case of more than one supplier, at least one CoA for each supplier should be provided, unless

- accepted

Batch Analyses instead of Certificate of Analysis.

Description of batches and results of batch analyses should be provided.

- rejected

The genuine sentence foresees justification acceptance for such specific cases.
otherwise justified.

Rationale:
In many cases, especially in the case of fresh herbal plants, it is not realistic to supply 2 batch results per supplier.

For the manufacture of medicinal products with active substances of herbal origin it is of vital importance to have the possibility to quickly switch between different qualified raw material suppliers. This is especially relevant for homeopathic medicinal products where several hundreds of different (often fresh) herbal raw materials are used in often very small amounts. The quality and availability of medicinal plants depend on natural variables such as climatic conditions, pests, harvests, seasonal differences etc. Crop failure or very slow plant growth may occur. These conditions can lead to sudden and frequent changes in the suppliers. If the manufacturer does not have the possibility to quickly fall back on another plant supplier, he will not be able to produce the product or to maintain the given quality in compliance with the respective requirements of the pharmacopoeia and/or other relevant specifications. Therefore, the possibility of a short-termed change of plant suppliers is needed on the one side due to the above-mentioned unforeseeable events and on the other side this is even a measure of quality management.

This situation leads to the practical fact that in the moment of dossier submission results of 2 batches of the same supplier, or even of one batch of a future replacement supplier do not exist.

b. Stock/Mother tincture

In case of more than one manufacturer / supplier the analysis of...
batch results of one manufacturer / supplier is sufficient.

Rationale:
The results of batch analysis are exemplary. All manufacturers / suppliers of mother tinctures are listed in the dossier and deliver according to the same specification, in the majority of cases according HAB.

Often, the purchased batches are really small, because the mother tinctures produced thereof are highly diluted, so that only a small amount of the mother tincture is required. Moreover, often rare plant species used in homeopathy. Unfavourable weather conditions can cause crop failures. All these conditions lead to frequent changes in the suppliers of the mother tinctures. In order to maintain the broad spectrum of homeopathic products, and therewith meet the demands of the homeopathic therapy, flexibility in the purchase of mother tinctures is absolutely necessary. At the time of submission, it is infeasible to have certificates of all possible manufacturer / supplier of mother tinctures.

c. Dilutions

Comment: We propose to delete this new requirement.

Rationale:
There is no legal basis for this requirement. Neither EU Directive 2001/83/EC Art. 15 nor EU Directive 2003/63/EC, which is the basis of the requirements for a CTD dossier, especially taking account of the specific manufacture and indicating the requirements for homeopathic medicinal products, foresee that analyses of batch results for intermediate potencies are submitted in a registration dossier. Also, according to the HMPWG guidance on module 3 of the homeopathic medicinal products dossier no analyses of batch results of intermediate dilutions are required in the dossier. Therefore, this demand should be rejected.

For stored dilutions appropriated specifications should be set and the evidence of compliance to those should be included.
This requirement is a new requirement which after more than a decade of submitting CTD dossiers to European agencies has arisen now without an evident reason in terms of safety of the public. The production of intermediate dilutions is regulated by the homeopathic manufacturing methods and GMP. As a principle, dossiers should contain only relevant information as foreseen by relevant guidances to limit the workload for both, authorities and companies (e.g. by variations). Unnecessary expanding of information should be avoided in the frame of good regulatory praxis.

**Requirement results of batch analyses not older than 3 years**

**Comment:**
This request should be erased.
This request is regarded as not appropriate and not realistic due to the large order cycle of a particular stock. Also, batch analyses of raw materials and homeopathic stocks may be older than three years due to proven shelf life and rare production. Moreover, the legal basis of this request is unknown, even in other kind of medicinal products.

**AESGP**

The term CoA – Certificate of Analysis is not applicable in the context of a CTD dossier.
In order to maintain correct and consistent wording with EMA and HMPWG regulatory guidance on CTD the term batch analyses and results of batch analyses is to be used here.

**Proposed change:**
Replace Certificate of analysis (CoA) with Results of batch analysis

**a. Raw material**

- The following answer should be read in the context with Questions 2 and 3 of the HMPWG Q&A document of 2016 and the corresponding comments from the industry.

**Comment:**
See above
We propose to submit 2 batch results of the most frequent supplier.

**Proposed change:**

- a. Raw material

  **Certificates of analysis (CoA)** Results of analyses of at least two batches of the raw material(s) should be provided. In case of more than one supplier, at least one CoA for each supplier should be provided, unless otherwise justified.

**Rationale:**

In many cases, especially in the case of fresh herbal plants, it is not realistic to supply 2 batch results per supplier.

For the manufacture of medicinal products with active substances of herbal origin it is of vital importance to have the possibility to quickly switch between different qualified raw material suppliers. This is especially relevant for homeopathic medicinal products where several hundreds of different (often fresh) herbal raw materials are used in often very small amounts.

The quality and availability of medicinal plants depend on natural variables such as climatic conditions, pests, harvests, seasonal differences etc. Crop failure or very slow plant growth may occur. These conditions can lead to sudden and frequent changes in the suppliers. If the manufacturer does not have the possibility to quickly fall back on another plant supplier, he will not be able to produce the product or to maintain the given quality in compliance with the respective requirements of the pharmacopoeia and/or other relevant specifications. Therefore, the possibility of a short-term change of plant suppliers is needed on the one side due to the above mentioned unforeseeable events and on the other side this is even a measure of quality management.

This situation leads to the practical fact that in the moment of dossier submission results of 2 batches of the same supplier, or even of one batch of a future replacement supplier do not exist.
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</table>
| **b. Stock/Mother tincture** | *In case of more than one manufacturer / supplier the analysis of batch results of one manufacturer / supplier is sufficient.*  
Rationale:  
The results of batch analysis are exemplary. All manufacturers / suppliers of mother tinctures are listed in the dossier and batches of the same specification, in the majority of cases according HAB.  
Often, the purchased batches are really small, because the mother tinctures produced thereof are highly diluted, so that only a small amount of the mother tincture is required. Moreover, often rare plant species used in homeopathy. Unfavourable weather conditions can cause crop failures. All these conditions lead to frequent changes in the suppliers of the mother tinctures. In order to maintain the broad spectrum of homeopathic products, and therewith meet the demands of the homeopathic therapy, flexibility in the purchase of mother tinctures is absolutely necessary. At the time of submission it is into always possible to have certificates of all possible manufacturer / supplier of mother tinctures. |   |

| **c. Dilutions** | **Comment:** We propose to delete the sentence: *Certificates of analysis (CoA) of at least two batches of intermediate dilutions (if stored or purchased), should be provided. In case of more than one manufacturer, at least one CoA for each manufacturer should be provided, unless otherwise justified.*  
**Rationale:** There is no legal basis for this requirement. Neither EU Directive 2001/83/EC Art. 15 nor EU Directive 2003/63/EC, which is the basis of the requirements for a CTD dossier, especially taking account of the specific manufacture and indicating the requirements for homeopathic medicinal products, foresee that analyses of batch results for intermediate potencies are submitted in a registration dossier. Also, |   |
according to the HMPWG guidance on module 3 of the homeopathic medicinal products dossier no analyses of batch results of intermediate dilutions are required in the dossier. Therefore, this demand should be deleted from the Q&A document.

This requirement is a new requirement which after more than a decade of submitting CTD dossiers to European agencies has arisen now without an evident reason in terms of safety of the public. The production of intermediate dilutions is regulated by the homeopathic manufacturing methods and GMP. As a principle, dossiers should contain only relevant information as foreseen by relevant guidance documents to limit the workload for both, authorities and companies (e.g. by variations). Unnecessary expanding of information should be avoided in the frame of good regulatory praxis.

**Requirement results of batch analyses not older than 3 years**

**Comment:**
This request is regarded as not appropriate and not realistic due to the large order cycle of a particular stock. Also, batch analyses of raw materials and homeopathic stocks may be older than three years due to proven shelf life and rare production. Moreover, the legal basis of this request is unknown, even in other kind of medicinal products.

Given that the retest period of MT or stocks may by 4 or 5 years, certificates of analysis dating from less than 3 years may be not available.

We propose thus to modify the sentence as follows:
“Certificates should be as recent as possible and not be older than five years, unless appropriately justified.”

<table>
<thead>
<tr>
<th>Question 7</th>
<th>BPI e.V.</th>
<th><strong>General comment:</strong></th>
</tr>
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<tbody>
<tr>
<td>How many batches are required in 3.2.5.4.4 (Batch analysis) section?</td>
<td></td>
<td>The term CoA – Certificate of Analysis is not applicable in the context of a CTD dossier. In order to maintain correct and consistent wording with EMA and HMPWG regulatory guidance on CTD the term batch analyses and results of batch analyses is to be used here.</td>
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See above
<table>
<thead>
<tr>
<th><strong>Proposed change:</strong></th>
<th>Replace Certificate of analysis (CoA) with Results of batch analysis</th>
</tr>
</thead>
</table>

**a. Raw material**
Certificates of analysis (CoA) of at least two batches of the raw material(s), should be provided. In case of more than one supplier, at least one CoA for each supplier should be provided, unless otherwise justified.

**Proposal change:**
a. Raw material

- The following answer should be read in the context with Questions 2 and 3 of the HMPWG Q&A document of 2016 and the corresponding comments from the industry.

**Comment:**
Submission of results from two batches of the most frequent supplier should be sufficient.

**Proposed change:**
a. Raw material
Certificates of analysis (CoA) Results of analyses of at least two batches of the raw material(s) should be provided. In case of more than one supplier, at least one CoA for each supplier should be provided, unless otherwise justified.

**Rationale:**
In most cases, especially for fresh plant material, results from two batches per supplier are not realistic.

Plants as naturally grown material are prone to crop failures due to e.g. climatic changes or pest infestation. Additionally, the fact that in homeopathy several hundred different plants are used and only low amounts are required for production, make it difficult to find a proper supplier at all, also offering the required quality. Therefore, the possibility to quickly switch the supplier is vital for manufacturers of homeopathic medicinal products using such material, as otherwise the product portfolio typical for homeopathy and required by the homeopathic practitioners could not be maintained anymore. Therefore, flexibility is required in the choice of the suppliers for homeopathic raw material.
b. Stock/Mother tincture
Certificates of analysis (CoA) of at least two batches should be provided. In case of more than one supplier/manufacturer, at least one CoA for each supplier/manufacturer should be provided, unless otherwise justified.

c. Dilutions
Certificates of analysis (CoA) of at least two batches of intermediate dilutions (if stored or purchased), should be provided. [...]

Practically, this results in the fact, that results from two batches of the same supplier are often not available at the time of the dossier submission.

b. Stock/Mother tincture
The requested number of batch analyses results seems realistic.

c. Dilutions
Comment:
This requirement should be deleted.

Rationale:
There is no legal basis for this requirement, as neither EU Directive 2001/83/EC Art. 15 nor EU Directive 2003/63/EC requires batch analysis of intermediates to be put in the dossier. Same is true for the HMPWG Guideline on Module 3 of homeopathic medicinal products, which also does not require CoAs for intermediate products.

The production of intermediate products is defined by the homeopathic manufacturing procedures used and regulated by GMP.
<table>
<thead>
<tr>
<th>Comment</th>
<th>Response</th>
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<tbody>
<tr>
<td><strong>d. In any case, the certificates should not be older than three years, unless appropriately justified.</strong></td>
<td>This new requirement has now entered this Q&amp;A draft after more than 10 years of submitting CTD dossiers to agencies without any obvious reasons. Dossiers should only contain information required by the relevant guidelines to avoid extra workload for the applicant as well as the agency, also considering future life-cycle-management.</td>
</tr>
<tr>
<td><strong>d. Requirement results of batch analyses not older than 3 years</strong></td>
<td>This requirement should be deleted. Due to the low order frequency in homeopathic manufacturing, results from batches not older than three years are not realistic. Additionally, raw materials and homeopathic stocks can be older than three years but still be used for further processing due to their proven shelf life and rare production. Additionally, it is not clear on which legal basis this request is based on, as there are no comparable requirements known to us for any kind of medicinal products.</td>
</tr>
<tr>
<td><strong>Laboratoires Lehning</strong></td>
<td>In any case, the certificates should not be older than three five years, unless appropriately justified”. Indeed, it is quite common for active substances and for medicines to have 5 years of retest or shelf life. Furthermore, we are dealing with homeopathy and for some stocks, a low inventory turnover. Then for some raw materials, stocks or dilutions, it may be difficult to present 2 certificates of analysis dated less than 3 years. That is why we would suggest not older than 5 years.</td>
</tr>
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</table>