EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Work instructions

Title: Sampling and testing of centrally authorised products - update of spreadsheet for the identification of the products to be tested on the basis of a risk assessment		
Applies to: P-CI-MQC		
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1. Changes since last revision

New WIN.

2. Records

A spreadsheet that contains details of the scoring for <u>human products</u> for each year and all the reports generated from Siamed (human) are saved electronically in the appropriately labelled folder in DREAM (Scoring YYYY).
04. Inspections/5.Sampling and Testing/Programmes/YYYY/Risk ranking/Human.

A spreadsheet that contains details of the scoring for <u>veterinary products</u> for each year and all the reports generated from Siamed (human) are saved electronically in the appropriately labelled folder in DREAM (Scoring YYYY).
04. Inspections/5.Sampling and Testing/Programmes/YYYY/Risk ranking/Vet.

3. Instructions

3.1. Introduction

All the steps detailed in this WIN are carried out by the assistant in the Sampling and Testing Team in the MQC Section.

Inclusion of centrally authorised products (CAPs) for human and veterinary use in the annual sampling and testing programme is based on a risk assessment. A specific spreadsheet was prepared, which

allowed the risk ranking of all the authorised products and pharmaceutical forms. Human and veterinary products are scored and ranked separately.

n=year of the sampling and testing programme for which the risk assessment is being prepared.

The scoring of each risk factor is in a pilot phase and is subject to continuous review.

The structure of the spreadsheet is the following:

- the rows contain all the products/pharmaceutical forms authorised.

- the columns contain the various risk factor identified (either 'impact factors' or 'weighting factors').

The document is filled in by giving a value to each risk factor for each product/pharmaceutical form. Eventually, all the products/pharmaceutical forms will have a total score, determined by the formula:

Score = (sum of impact factors) x (sum of weighting factors) = $(i+r1)$ x $(w+r2)$

The total score will allow the risk ranking of the products/pharmaceutical forms. This information will be used to support the decision on the inclusion of a product in the annual sampling and testing programme.

This WIN provides guidance on how to update the above-mentioned spreadsheet. Guidance for human products contains guidance for human products and Guidance for vet products provides guidance for veterinary products.

The spreadsheet is updated on an annual basis by:

- adding new authorised products and pharmaceutical forms to the list and scoring these.

- scoring the existing products for the factors whose scores change over time.

In order to have the full list of previously scored products, the scoring list for the previous year has to be copied.

3.2. Documents needed for this WIN

The following documents are saved in DREAM:

Guidance for the population of the spreadsheet for risk-ranking of human products (hereinafter referred to as "Guidance for human products") (EMA/INS/S&T/165093/2012)
04. Inspections/5.Sampling and Testing/Planning and reporting/Procedures/Risk-based approach human

Guidance for the population of the spreadsheet for risk-ranking of veterinary products (hereinafter referred to as "Guidance for vet products") (EMA/INS/S&T/165094/2012)
04. Inspections/5.Sampling and Testing/Planning and reporting/Procedures/Risk-based approach vet

General database (EMA/INS/S&T/96791/2006)
04. Inspections/5.Sampling and Testing/Planning and reporting/Databases

Annual quality defect tracking sheet
04. Inspections/4. GMP/Planning and reporting/Q defect coordination/Quality Defects - YYYY

Proposal for development of risk-based approach for human products (EMA/INS/S&T/81176/2007)
04. Inspections/5.Sampling and Testing/Planning and reporting/Procedures/Risk-based approach human

Proposal for development of risk based approach for veterinary products (EMA/INS/S&T/75010/2009)

3.3. Attribution of values to the risk factors

Updating the spreadsheet includes the following steps:

3.3.1. Addition of products and pharmaceutical forms that have been authorised in year n-2.

3.3.2. Scoring all risk factors for the added products.

3.3.3. Updating previous scoring of existing products for risk factors for which scoring changes over time.

3.3.1. Addition of products and pharmaceutical forms that have been authorised in year n-2.

At the beginning of December of year n-2 prepare a report in Siamed for products and pharmaceutical forms that have been authorised in year n-2.

Due to the delay in receiving the Commission Decision (about 2 months) there are products and pharmaceutical forms that were not included in the above query. Therefore it is important to run the query again for November and December when preparing the scoring list for the **following** year.

1. Prepare a report of new products authorised, through the Reports/Summary of Procedures/New Applications (see screenshot below) with the following settings:

   - Status: valid, tick "Decision date", enter date range, and select all in "Fields".

   - Request an output in Excel and save report in DREAM.

2. Prepare a report with the list of new pharmaceutical forms authorised, through Reports/Summary of Procedures/Post-Authorisation (see screenshot below) with the following settings:

- Status: accepted, tick "Opinion", enter date range, in "Type of variation" choose "Annex II application", and select all in "Fields".

- Request an output in Excel and save report in DREAM.

3. The excel document will provide the changes introduced by Annex II applications. Check the column 'remarks' in the excel spreadsheet to identify those variation(s) that involved the addition of a new pharmaceutical form.

4. Add new products and new pharmaceutical forms to the end of the existing spreadsheet. When scoring is finished for all products, sort the data in alphabetical order.

3.3.2. Scoring all risk factors for the added products

All risk factors should be scored for new products and new pharmaceutical forms that have been added to the list.

Guidance for the scoring of these new products/pharmaceutical forms is contained in the Guidance for human products and Guidance for vet products documents.

3.3.3. Updating previous scores for risk factors for which scoring changes over time

The following risk factors have to be updated for all products included in the list for the previous year before making the final ranking for the selection of products.

History of quality defects with the product

Include scores for the two preceding years (e.g. for the 2013 programme include scores for 2010 and 2011). Delete scores for the irrelevant year (e.g. year 2009 for the 2013 programme). Use the

relevant quality defects tracking sheet to score year n-2 (e.g. year 2011 for the 2013 programme) according to instructions in Guidance for human products and Guidance for vet products.

History of adverse sampling and testing outcomes in previous programmes

Delete all previous scores. Use the General database to score results from the last 3 years according to instructions in Guidance for human products and Guidance for vet products.

History of GMP non-compliance at manufacturing sites

Delete all previous scores. Use the EudraGMP database to prepare a list of manufacturing sites where critical deficiencies have been reported within the last 5 years. Score according to instructions in Guidance for human products and Guidance for vet products.

Major variations related to the quality part of the dossier

Include scores for the two preceding years (e.g. for the 2013 programme include scores for 2010 and 2011). Delete scores for the irrelevant year (e.g. year 2009 for the 2013 programme).

Score type II and type I variations within the last 12 months according to instructions in Guidance for human products and Guidance for vet products.

Duration of marketing experience

Where to find the relevant information: the duration of marketing experience will be measured on the basis of the authorisation date, which is indicated in the spreadsheet in the "Commission Decision Date" column. Score according to instructions in Guidance for human products and Guidance for vet products.

Period of time since last testing

Use the General database to score according to instructions in Guidance for human products and Guidance for vet products.

3.4. Additional updates for the preparation of the list of products to be tested

The following updates are also required:

- Make sure that the default value of either factor **(i+r1) or (w+r2)** is 1.

- A filtering step should be included to remove all products tested in the previous 3 years (for the 2013 programme products tested in 2010, 2011 and 2012 were deleted) unless deliberately added again to current year's programme (e.g. Rapporteur's recommendation due to previous testing result). These products should be listed under a separate worksheet to allow easy copying to next year's scoring list.

- Add products tested 4 years before but deleted for previous programme. For example, products tested in 2010 are deleted for the 2013 programme but should be added again for the 2014 programme.

- Identify and delete biological products subject to Official Control Authority Batch Release (OCABR). There is no need to score these products as they were already tested as part of the marketing authorisation procedure.

- Human biological products can be identified by checking who the Quality PTM is. The laboratory responsible for carrying out the OCABR testing is listed in Siamed in:

  – Quick product overview/product/presentation data/other manufacturers/Medicines Control Laboratory.

  OR

  – In part 2.5.1.b of the Application for Marketing Authorisation.

- Veterinary biological products (IVMPs) can be identified by a document called "Procedure for application for art 82 for official control authority batch release of immunological veterinary medicinal products" published by EDQM on their website.

  http://www.edqm.eu/medias/fichiers/Procedure_Article_82.doc

  A shortlist of diseases for which OCABR is compulsory is listed in annex I of the above document. Whether a CAP veterinary product falls under any of these can be identified according to the SPC in 2. Qualitative and quantitative composition and 4.2 Indications for use, specifying the target species.

- The General database spreadsheet also needs to be updated with products subject to OCABR.

- Delete products and pharmaceutical forms with withdrawn/rejected/suspended status. Make sure that suspended products are included again in a following programme if authorised in the meantime.

Where to find the relevant information:

- In Siamed prepare a report through Query builder/Current status and add: cancelled, rejected, surrendered, suspended, withdrawn by right-clicking in the field on the right-hand side.

- Request an output in Excel and save report in DREAM.

3.5. Additional steps for the preparation of the ranking of the products

- Copy the complete list to the "Ranking" worksheet including the name, pharmaceutical form and scoring of the product. Sort them in descending order of scoring mark and rank them accordingly (i.e. product with the highest score will be number 1).

- The ratio between human and veterinary products is calculated on the basis of the total number of products for each. Enter the figure in the "Statistics" worksheet, which will then give the percentage for each. For example the ratio for the 2013 programme is 83% human and 17% vet.

- Get the number of human products to be included in the initial list by calculating how much is 83% of 45 products. The figures for the 2013 programme are 37 human and 8 veterinary products.

- Select 25% of products on a random basis by using a random integer generator on the internet. For example www.random.org and use the "True Random Number Generator". Save results in DREAM. 25% of the 37 human products is 9 and 25% of vet products is 2. For example for the 2013 programme 28 human products will be selected based on the risk ranking and 9 products on a random basis.

- Add other pharmaceutical forms of a product that is selected in both the risk ranking and by randomly so they are all tested together in the same year. As a result, it is possible that there will be more than 45 products initially.

- From the 2011 programme, generic products are also included in the sampling and testing programme.

  – If a generic product comes up in the list, it is tested as an individual product. In addition:

  1. Check what is the originator product.

  2. Check if there are other generic products related to this originator. If there are at least 4 other generic products (to make it financially worthwile) the EMA will decide if these should be included in the programme as a separate generic program.

  – If an originator product comes up in the list:

  1. Check how many generics is related to this product.

  2. If less than 4 generics are related to the originator, it is not worth financially to test them as individual products. EMA will make the decision if products are included as a specific generic program or are not included at all.

Number of generics	Cost if included in normal programme	Cost if included in specific generic programme
2	EUR 20,400	EUR 19,600
3	EUR 30,600	EUR 31,250
4	EUR 40,800	EUR 34,200
5	EUR 51,000	EUR 45,850
6	EUR 61,200	EUR 48,800

- Calculation of number of products:

  – Identical and informed consent products are treated as 1 product.

  – Other pharmaceutical forms of a product are added to the list and they are treated as separate products.

  – If a generic comes up on the list, it is tested individually and the originator is not tested.

  – If a generic group is tested, a separate generic programme comes into effect and calculation of products will be further assessed.