Plasma Protein Therapeutics Association

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Reference: EMA 12007

By e-mail:
Silvia.Domingo@ema.europa.eu

Dr. Silvia DOMINGO

European Medicines Agency
7 Westferry Circus Canary Wharf
London E14 4HB,
United Kingdom

Subject: ePMF Database Issues

Dear Dr. Domingo,

In our recent correspondence (EMA12005, 17 July 2012) we have informed you that our member companies are unable to fulfil the requirements of the new ePMF application. We have respectfully requested to put the application procedure on hold until the significant issues are resolved. In preparation of the meeting scheduled for 11 October 2012 we would like to present you with more detailed information collected from PPTA's members. This list is also indicative of the hurdles, which prevent PMF holders from compliance with the new requirements.

It therefore appears that the ePMF data base is unworkable from the technical aspects and represents a bureaucratic burden of questionable value that eliminates the initial purpose of the PMF system to facilitate and streamline regulatory procedures.

More fundamentally, we question the legal basis of this new requirement. To our knowledge there are no legal provisions underpinning its introduction. We would appreciate clarification on this point before entering into a discussion on the significant shortcomings outlined below.

It seems that it is intended to make the data base public in the future including details of our plasma suppliers. Please note that we have no consent from our suppliers on publishing their data and consequently publication would violate legally binding agreements between suppliers and manufacturers.

GENERAL COMMENTS:

- As there is no test run, could wrong handling lead to non-validation of a submission? This would potentially impair patient access to plasma protein therapies with severe consequences for their health and well-being.

- Is the submission of a baseline required to import company-specific information into the database? How else will changes to already approved centres be reflected in subsequent submissions?

- Generally, more data is requested than required by the PMF Guideline in force today (e.g. contact persons for look back; number of mobile units per centre). What is the purpose and added value for collecting these additional data? What would be the consequence (if any) of not entering these additional data?

- According to information provided by EMA, *["this software does not allow parallel ongoing submissions, and prior to submit a new procedure the previous application needs to be closed. PMF holders should ensure that there are no overlap submissions and therefore plan well in advance their submissions."]* (http://fmapps.ema.europa.eu/pmf/)

- There should be an option to update the data base prior to issuance of an official closure letter.

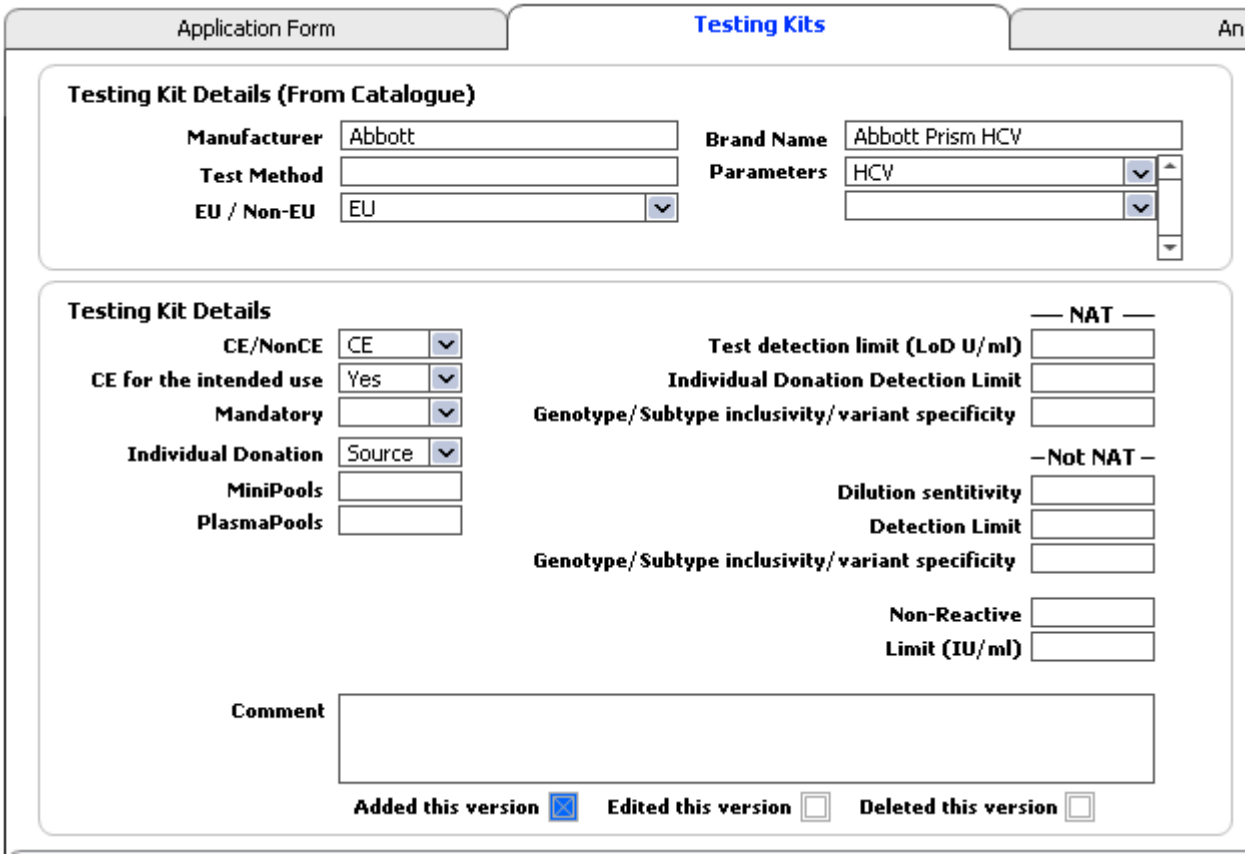
- We have already pointed out previously that the mode of data entry is far from user-friendly. For example a PMF section is only accessible by one person at a given time. The database must be amended to allow access by more than one person at a time, e.g. to work on Annex II and Annex A simultaneously.

- If the database is corrected by EMA and has to be re-installed by PMF-Holders on their local drives, will the data already entered on this local drive be replaced? Data migration must be possible, to avoid re-entry of the full data set.

APPLICATION FORM

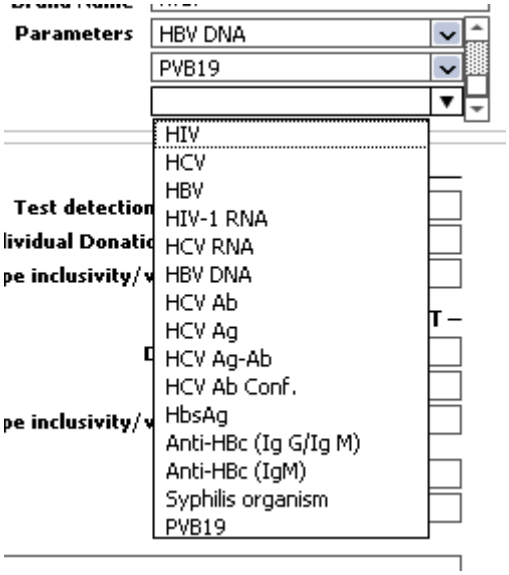
- The requirement to prepare the application forms as PDFs leaves no option to enter additional data.
- PMF holder information sometimes seems to be locked, thus it isn't possible to change the name and function of contact person in case of changes of responsibility at the PMF holder.
- When the applicant fills out the annexes first the application form becomes unreadable. The order for completion of the information should be left to the applicant. We would respectfully request to amend the system accordingly.

TEST KIT LISTING

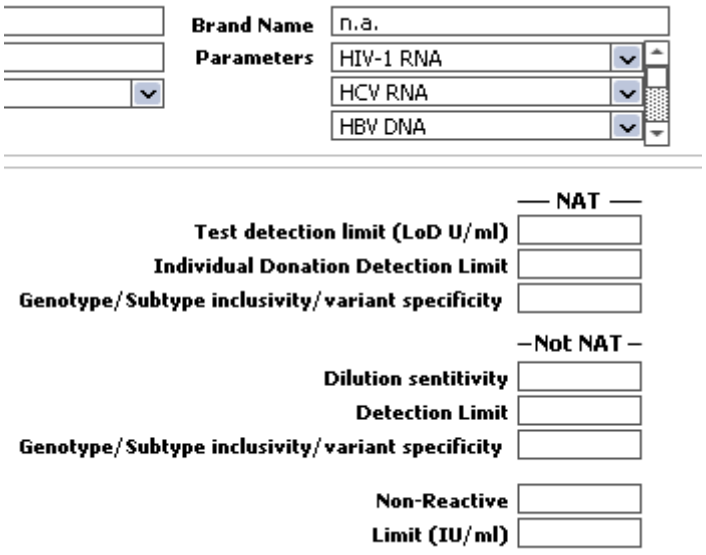


- What is meant by “test method” (viral marker?)
- What does “EU/Non-EU” refer to? (the place of the test kit manufacturer, origin of the plasma, the location of the test lab…?)
- What is meant by “Mandatory” yes/no?
- Does the PMF holder need to enter a test kit twice if it is used for testing of both source and recovered plasma donations, or is it admissible to leave the field “individual donation” empty?

- What should we enter in the fields “MiniPools” and “PlasmaPools”? The requested information should be specified.
- The information on the right-hand side (LoD etc.) is currently not described for each test kit and would need to be collected even for CE-marked test kits. What happens if this information is not provided?
- In case of CE-marked test kits, data should already be available at the EMA and the list also suggests that there is a catalogue available. In fact it isn't and all data have to be entered by each applicant manually.
- HAV is not included in the drop-down list for parameters. Does this mean that the relevant test kits are not regarded as part of the PMF license anymore?



- One test kit can be used for several parameters, but LoD etc. can only be entered once:



ANNEX A:

- The drop-down list of common names is incomplete and cannot be edited manually.
- What exactly is meant by “type” (Active substance/recipient/reagent/…)?
- Some information (e.g. pharmaceutical form, clinical trial number) is currently not included in Annex A and would need to be compiled for the data base.
- In the section "Marketing authorisation" several countries and marketing authorisation numbers can be given for one product. For products authorised via MR-/DC-Procedure the invented name of the product and/or the marketing authorisation holder may vary between countries. This information can in fact only be given once per dataset in the section "Plasma-derived Product Information. Does this mean that one dataset per country and product has to be created even for MR-/DCP products?
- The drop-down list "Auth by/Country" does not include all relevant countries (e. g. Romania, Iceland, Liechtenstein are missing) and cannot be edited manually.
- There is no option to choose the authorising agency e.g. TÜV. Should combination medical devices not be included in the list?

ANNEX II:

- Switzerland is not in drop-down list for non-EEA competent authority inspection and can only be entered manually.
- The overview of centres does not show the location, only a centre’s name and the first letters of the address. A centre’s location could only be determined if each centre had an individual name.
- The exact date of the last audit and date when a centre became non-operational have to be entered (DD/MM/YYYY), but not the exact date of the last inspection MM/YYYY. In the old system, it was sufficient to indicate the month when a centre became non-operational. Also, when printing the pdfs only MM/YYYY is shown for audit and non-operational dates. We therefore do not see the value of adding the data in the DD/MM/YYYY format.

1. We also noted that he format of audit dates is DD/MM/YYYY whereas the format of inspection dates is MM/YYYY. In case of inspections (EU and non-EU) the system change automatically the format from MM/YYYY to DD/MM/YYYY and therefore it assigns automatically (by default) the last day of the month or the first day of the next month. This discrepancy leads to a different date in the list of centres from the date that is given when opening the respective tab for said center.

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- Information on mobile units has to be provided per centre whereas in current practice, it is provided per organization, since all its centres or mobile/satellite units operate under the same SOPs. The required data would often fail to provide correct information, e.g. if a mobile unit is not linked to a centre but to the organization's headquarters.

ANNEX III:

- Switzerland is not in the drop-down list for non-EEA competent authority inspection and can only be entered manually. (see Annex II above).

- When linking the test laboratory to the relevant collection centres, the information cannot be separated for viral marker/NAT or single donation/plasma pool testing. If e.g. a laboratory performs single donation testing for 5 centres and pool testing for 500 centres, then a separate entry needs to be created (see below). Would it be possible to create one entry per test laboratory and link centres for each "type of testing (viral marker/NAT)"?

- When linking laboratories to test kits, the information on test kits is not completely visible (e.g. which one applies to source/recovered plasma; see test kit listings below), and testing kits are not in any recognizable (e.g. alphabetical) order.

- Why are the collection centres' sequence numbers listed next to the test kits (even before linking kits to a laboratory and thus centre)?

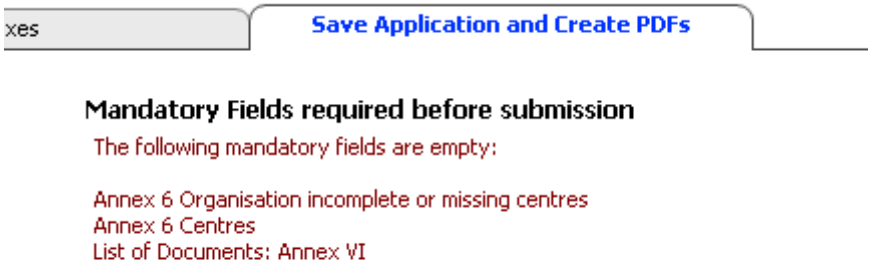
ANNEX IV:

- Switzerland is not in drop-down list for non-EEA competent authority inspection and can only be entered manually. (see Annex II above).

ANNEX V:

- Information on the country(ies) for which the transport organisation is responsible is currently given in Annex V, but no longer included in the ePMF-Application. This is considered important information. Where should it be given?

SAVING THE APPLICATION AND CREATING PDFS



- According to EMA's homepage, "PMF-Holders are invited to include the fractionation plants" into Annex VI, but it is not mandatory (http://fmapps.ema.europa.eu/pmf/). The above warning message should therefore not appear.
- Printed pdf files are partly not legible, e.g. headlines are printed on top of collection centres' address fields; sequence numbers in Annex II are partially covered by subsequent headings.
- Sequence numbers are not shown in Annex II; during review of the pdf documents, it would therefore be impossible to connect Annex II to Annex III.
- Only one of a number of testing kits entered into the data base could be found on the pdf file "Testing kits".
- Information in Annex A is divided into separate documents, which could have an impact on handling Annex A in the eCTD structure. Annex A should be rendered only as one pdf document. Additionally, not all information on countries, MA numbers etc. is rendered on the pdf file.
- It would be nice to have an alert notice if e.g. a centre is not linked to any testing laboratory.
- After saving the application and creating pdf files, the data still appear as new entries and additional changes/later changes are not marked/ highlighted (impact e.g. on responses to LoQ? Please refer also to our general comment on the possible necessity of a baseline).
- Changes are not marked/highlighted in pdf documents (impact e.g. on handling of internal review)
- Only MM/YYYY is shown for audit and non-operational dates (see Annex II above). How should internal reviews be handled?

- Modifications to the AF are apparently not possible after creating pdfs (see above), and typos etc. can no longer be corrected. This situation is against general industry practices which require internal review and approval of all regulatory submissions.

Dr. Ilka von Hoegen
Senior Director, Quality and Safety