NITROSAMINES RISK
ELECTRONIC SUBMISSION FORM

INSTRUCTIONS TO APPLICANTS

INFARMED, I.P - DAM

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

Infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

MAH RESPONSABILITIES

TAKING INTO ACCOUNT THEIR KNOWLEDGE OF THE MANUFACTURING PROCESSES AS WELL AS THE POTENTIAL SOURCES OF NITROSAMINE IMPURITIES, MAHs SHOULD WORK WITH MANUFACTURERS OF API AND FINISHED PRODUCTS IN ORDER TO REVIEW THE API AND FINISHED PRODUCT MANUFACTURING PROCESSES WITH RESPECT TO THE ARRANGEMENTS FOR PREVENTING NITROSAMINE FORMATION AS WELL AS CONTAMINATION OR CROSS-CONTAMINATION

STEP 1 RISK EVALUATION: MAHs should perform risk evaluation of their medicinal products containing chemically synthesised API.

STEP 2 CONFIRMATORY TESTING: in the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods in accordance with the prioritisation deriving from the risk evaluation conducted in step 1.

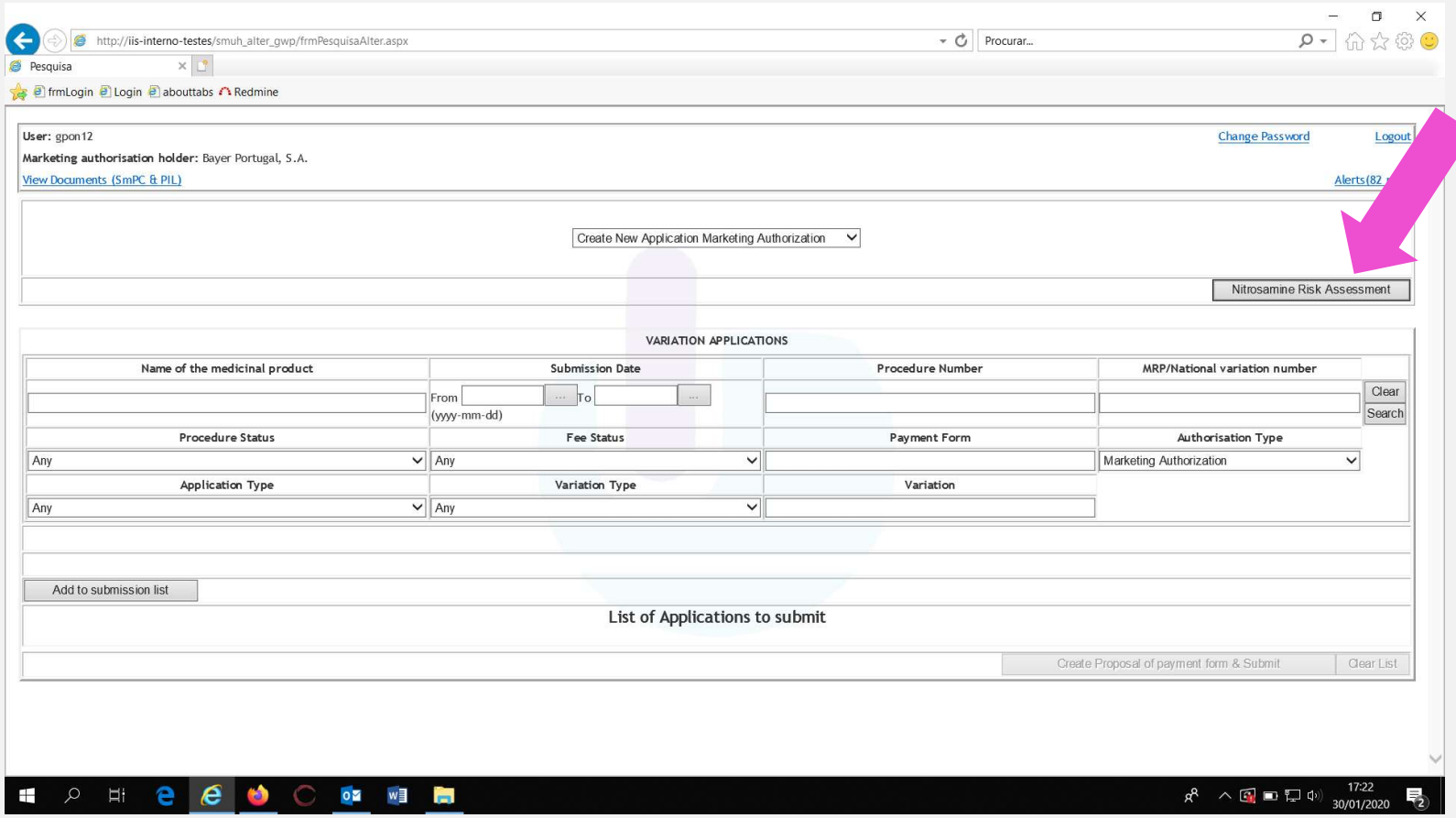
STEP 3 CHANGES TO THE MARKETING AUTHORISATION: MAHs should apply for a variation in a timely manner to introduce any required changes, such as amendment of the manufacturing process or changes to product specifications.

INFARMED, I.P.

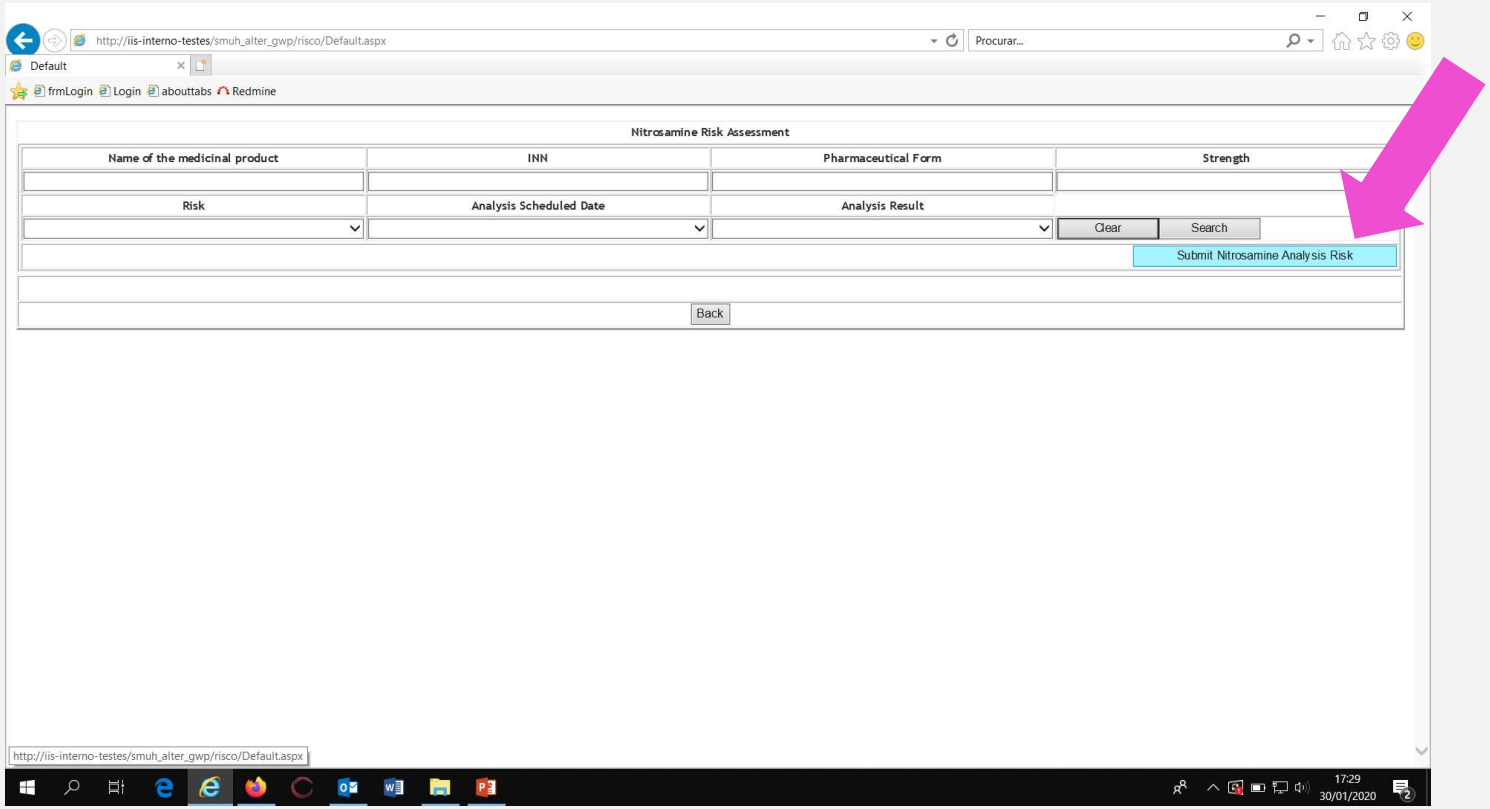
An electronic form was developed using SMUH-ALTER (national application for submission of Variation), where The MAH directly submits the results of its analysis and nitrosamine risk.

SMUH-ALTER – HOW TO USE THE SUBMISSION FORM?

TO START THE REGISTRATION CLICK ON THE BUTTON“NITROSAMINE RISK ASSESSMENT”

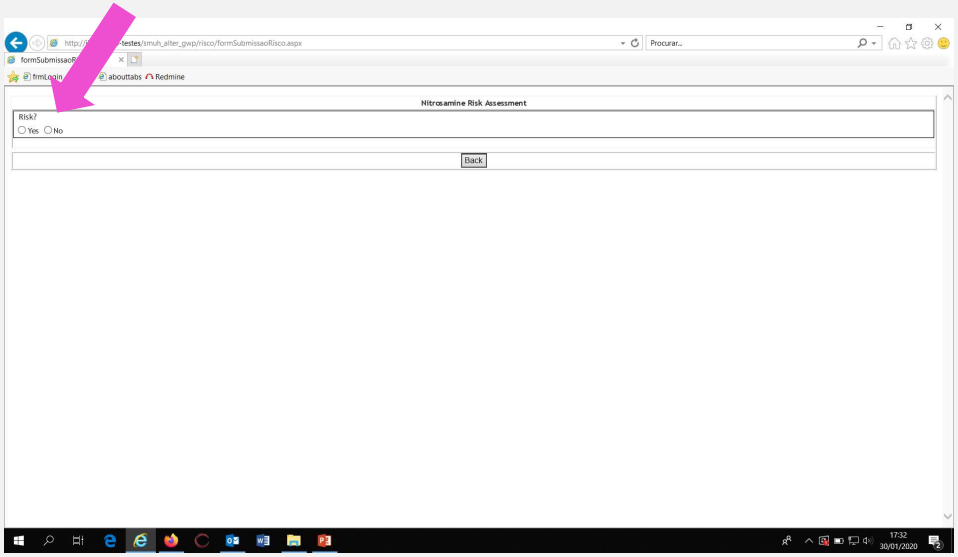


TO SUBMIT THE RISK ANALYSIS, CLICK ON THE BUTTON“SUBMIT NITROSAMINE ANALYSIS RISK”



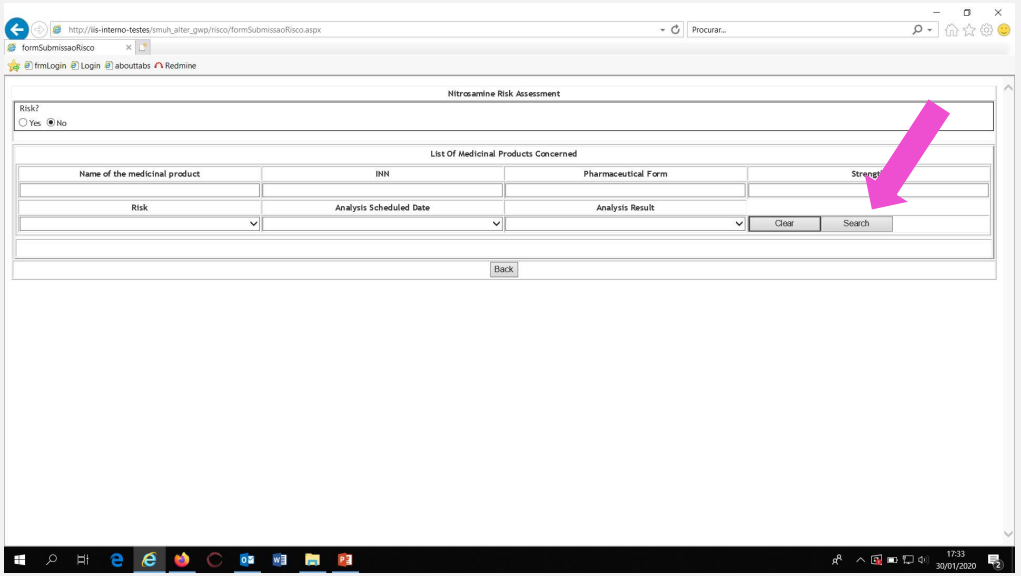
IF YOU WANT TO SUBMIT RISK ANALYSIS TO “NO”

1. Click on “NO”



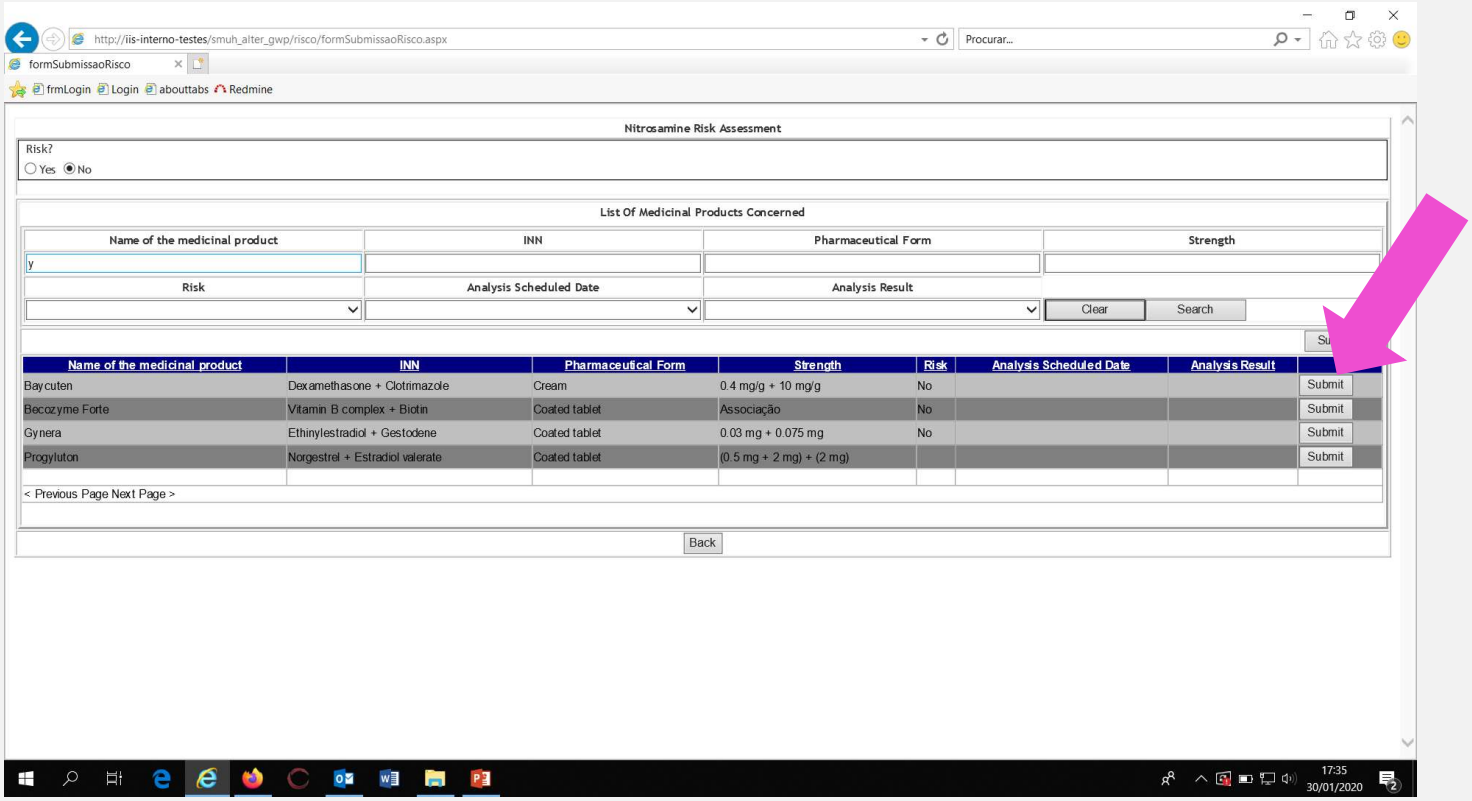
2. It is always necessary to include a search criteria

Then click on“Search”



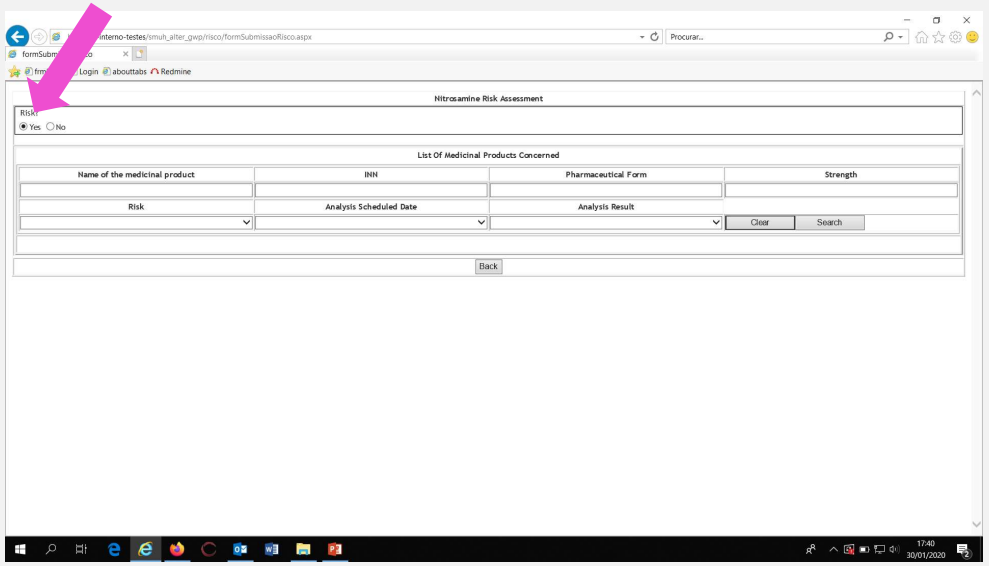
IF YOU WANT TO SUBMIT RISK ANALYSIS TO “NO”

3. After the search, click on the button “Submit” in the line corresponding to the medicinal product for which the risk analysis is to be submitted

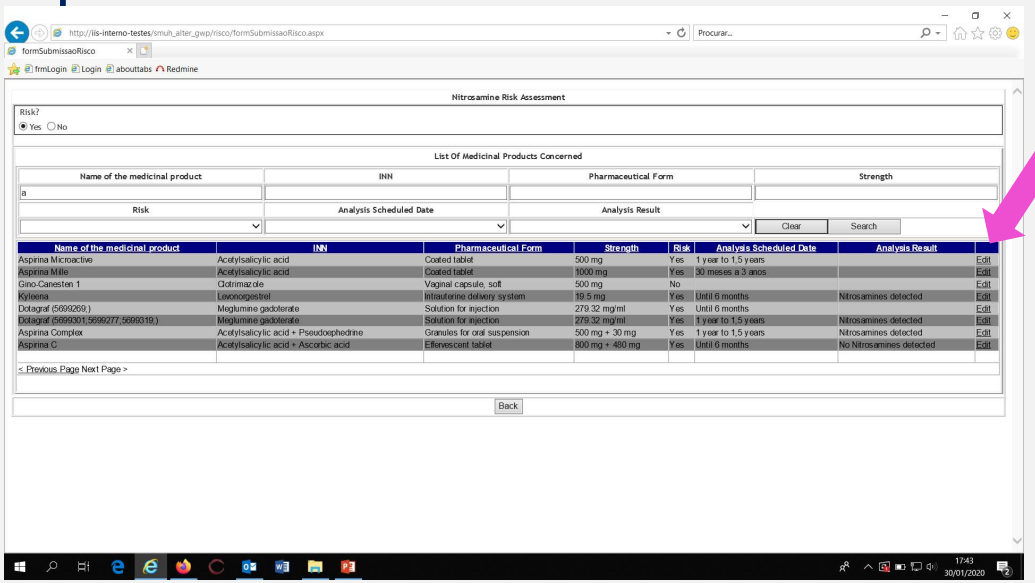


IF YOU WANT TO SUBMIT RISK ANALYSIS TO “YES”

1. Click on “YES”

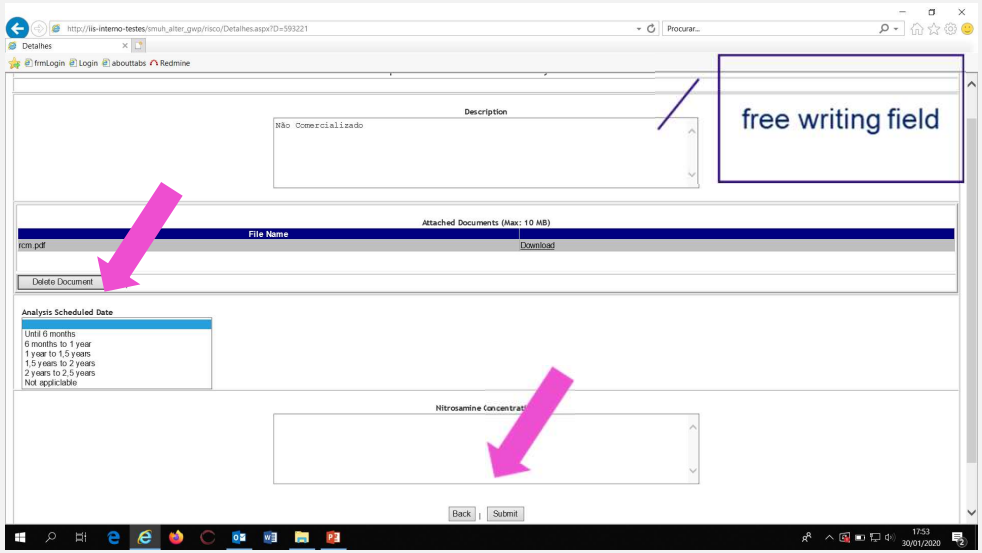


2. Then click the button “Edit” to have access to the medicinal product sheet



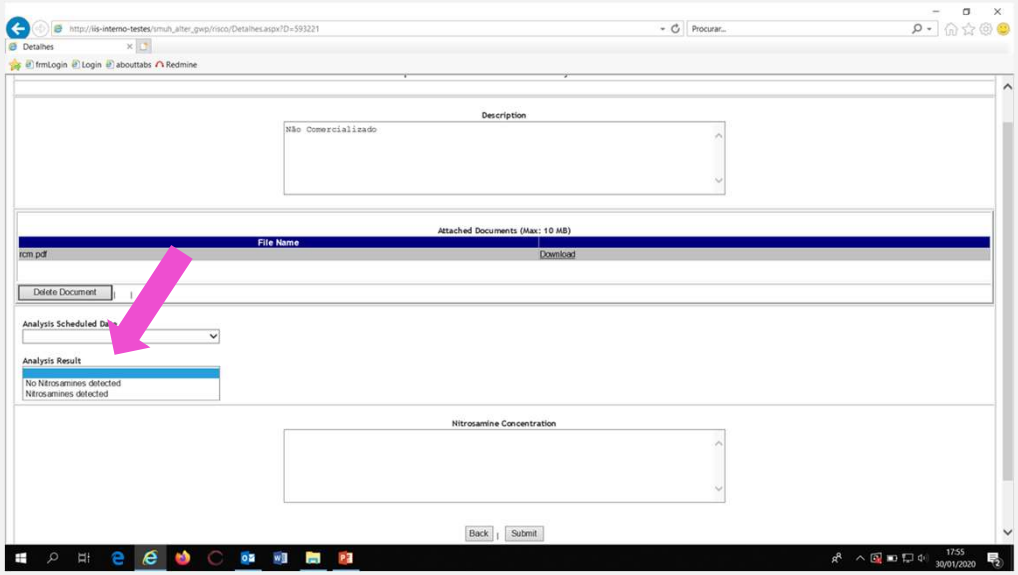
MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO “YES”

In the field “Analysis Scheduled Date” the proposed time for carrying out the confirmatory test must be selected. Click on “Submit”.



In the field “Analysis Result” select the final result after the confirmatory test.

Select No Nitrosamines detected or Nitrosamines detected



MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO "YES"

when in the field "Analysis Result" has beeen selected as the final result of the confirmatory test - Nitrosamines detected

Must be included in the field "Nitrosamine concentration", information regarding the level of nitrosamines detected, copying in full the sentence corresponds to the applicable scenario:

- Scenario A - exceeding the AI or exceeding the lifetime excess cancer risk of 1:100,000

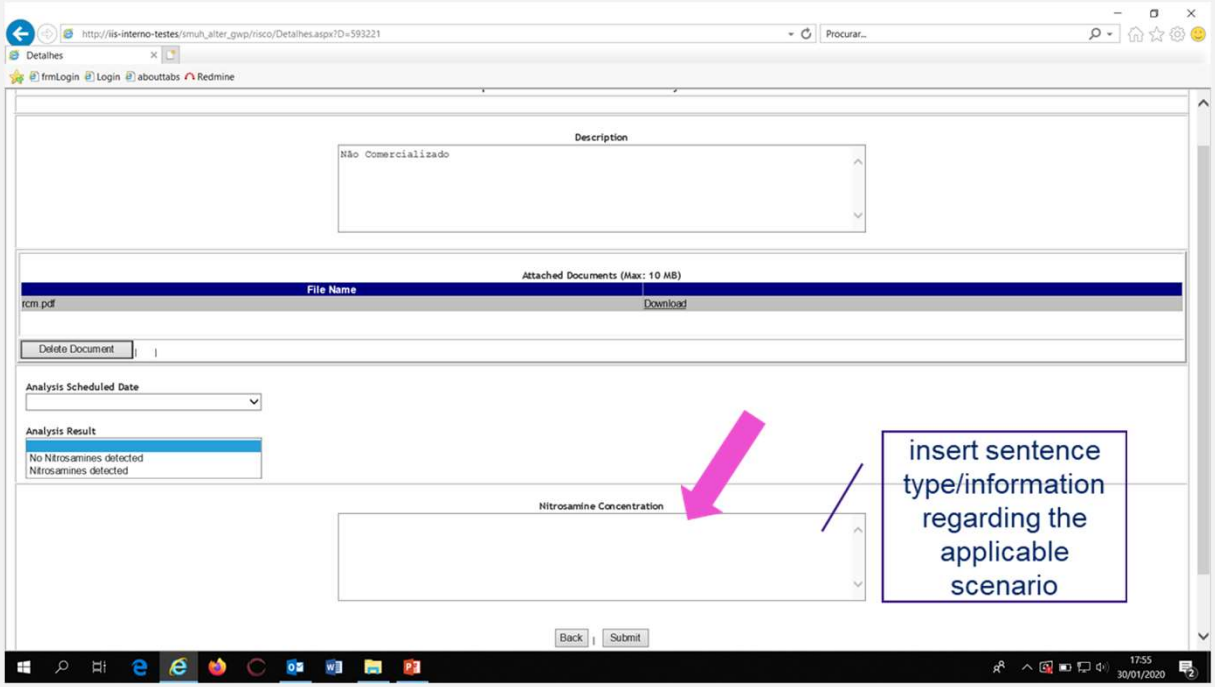
- Scenario B - not exceeding the AI or the lifetime excess cancer risk of 1:100,000 but its content is above 10% the AI

In this case, must also be indicated, the purpose of the variation and expected date of submission.

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO "YES"

- Scenario C - is consistently below 10% of the AI or the risk level of 1:100,000

CLICK ON "SUBMIT"



MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO "YES"

when in the field "Analysis Result" has beeen selected as the final result of the confirmatory test - Nitrosamines detected, the templates available on the CMDh website, must be attached to the SMUH-ALTER.

It is possible to upload many documents on the SMUH-ALTER platform. Although MAH does not view all documents, Infarmed is able to view them.

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO "YES"

If new nitrosamines are detected (Scenario D) must also be include the information in the SMUH-ALTER plataform, in the field "Nitrosamine concentration", including the following sentence:

"New nitrosamina detected – Name of nitrosamine – Scenario proposed: A, B ou C", and attaching all expected supporting documentation:

1 - Template(s) available on the CMDh website

MEDICINAL PRODUCT SHEET- RISK ANALYSIS TO "YES"

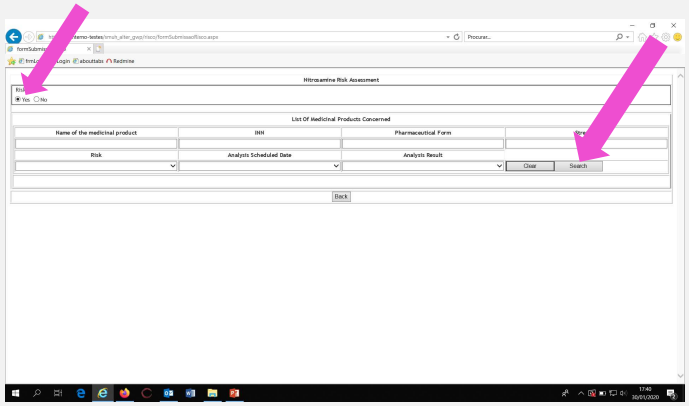
2 - All quality and toxicological documentation regarding step 2 of the procedure, namely (if applicable):

- Type of method used
- Detection and quantification limits (LoD, LoQ)
- Results of the analyzed batches
- Methods Validation
- SAR Evaluation assessment

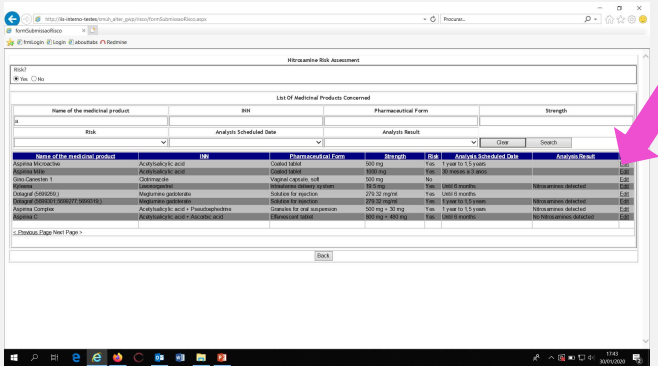
In parallel, this situation must be communicated to the email pt_chmp_referrals@infarmed.pt.

CHANGE THE RISK ANALYSIS FROM “NO” TO “YES”

1. Click on “**YES**” and insert a search criteria for the medicinal product that is necessary to change the risk. Then click on “Search”

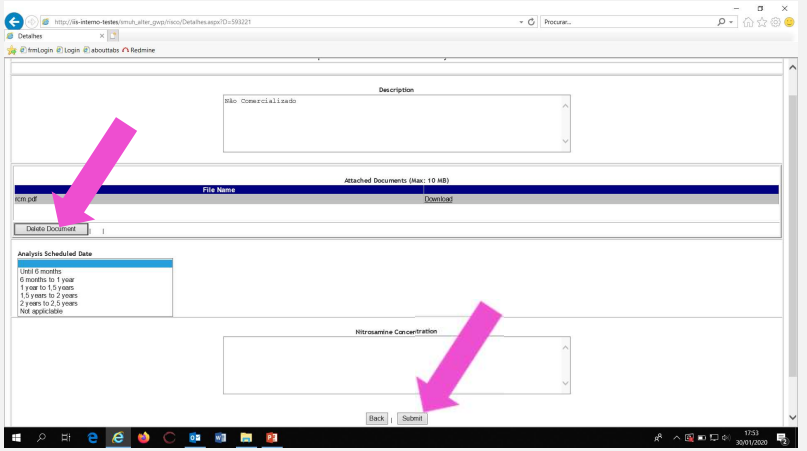


2. Click on “Edit” in the line of the medicinal product to be changed and you will have access to the medicinal product sheet



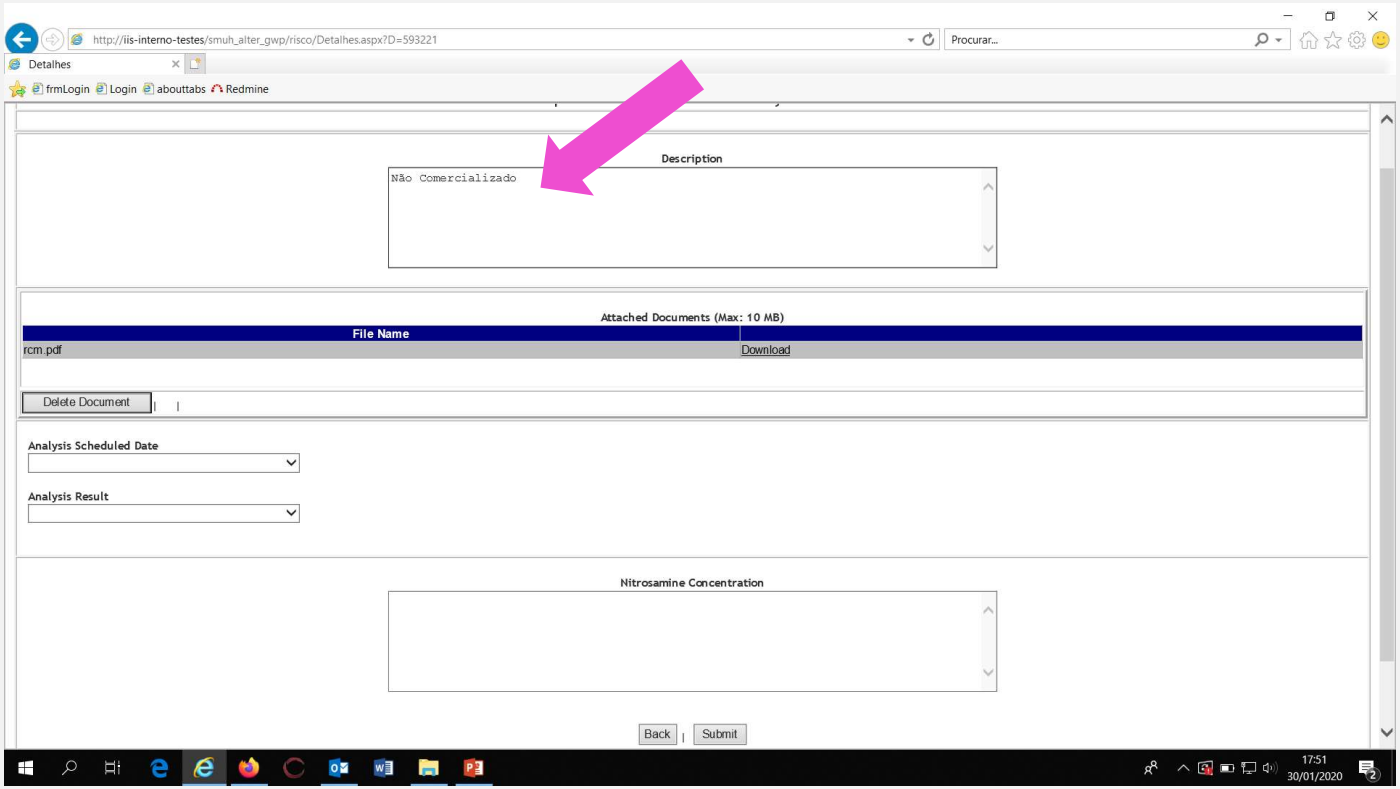
3. In the field “Analysis Scheduled Date” the proposed time for carrying out the confirmatory test must be selected. Click on “Submit”.

The risk will become YES



RISK ANALYSIS “NO” BECAUSE THE MEDICINAL PRODUCT IS NOT MARKETED

Submit the risk “NO”. Then access the medicinal product sheet as if it were a submission “YES” and in the field “DESCRIPTION” write “NOT MARKETED”.



THANKS

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