*Doc. Ref: CMDh/200/2007 Rev.10*

*May 2022*

**Note for RMS:**

The instructions (i.e. explanatory notes) regarding this template and also the instructions on the changes that should be made in the headings and/or statements when the D70 AR Overview is converted into the D120 AR Overview can be found in the document “Overview AR Template including instructions”.

**Decentralised Procedure**

**RMS Day 70 Preliminary Assessment report**

**OVERVIEW**

**AND**

**LIST OF QUESTIONS**

**<Invented Name>**

**<(Active Substance)>**

**AB/H/****nnnn****/{nnn}/DC**

**Applicant:**

|  |  |
| --- | --- |
| **Reference Member State** |       |
| **Start of the procedure:** |       |
| **Date of this report:** |       |
| **Deadline for comments:** |       |

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ADMINISTRATIVE INFORMATION

|  |  |
| --- | --- |
| **Proposed name of the medicinal product in the RMS**  |       |
| **Name of the drug substance (INN name):**  |       |
| **Pharmaco-therapeutic group(ATC Code):** |       |
| **Pharmaceutical form(s) and strength(s):** |       |
| **Reference Number(s) for the Decentralised Procedure** |  |
| **Reference Member State:** |  |
| **Concerned Member States:** |  |
| **Legal basis of application:** |  |
| **Applicant (name and address)** |  |
| **Names and addresses of all manufacturer(s) responsible for batch release in the EEA** |  |
| **Names and addresses of all manufacturer(s) of the medicinal products** |  |
| **Names and addresses of all manufacturers of the active substance** |  |
| **Names and addresses of all ASMF holders (if different from manufacturer of active substance)** |  |
| **Names and addresses of all CEP holders (if different from manufacturer of active substance)** |  |
| **Names and addresses of contract companies used for clinical trials (CRO(s))** |  |
| **RMS contact person** | **Name** Tel:      Email:       |
| **Names of the assessors:** | **Quality**: **Name(s)**Tel:      Email:      **Non-clinical**: **Name(s)** Tel:      Email:      **Clinical**: **Name(s)** Tel:      Email:      **Pharmacovigilance/Risk Management Plan:****Name(s)**Tel:Email: |

# RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for <product name>, in the treatment of <indication>,

<could be approvable provided that satisfactory responses are given to the preliminary list of questions (Section V)>

<is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section V)>

<The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies: >

# EXECUTIVE SUMMARY

## Problem statement

## About the product

## General comments on the submitted dossier

**<European Reference Product (ERP)**

A European Reference Product is used in <RMS> <and> <CMS XX>: [Name, strength, pharmaceutical form, MAH], registered in <YY>.

<The justification to use this product is based on information received from <YY>> <The justification to use this product is based on RMS’s own files>.

<The ERP information received from <YY> is attached as a separate document> <The ERP information received from <YY> was circulated during validation period>.>

**Assessment of similarity with authorised orphan medicinal product(s) under market exclusivity**

<**Potential similarity with orphan medicinal products>**

<According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.>

OR

<According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: [specify EU Orphan Designation Number(s)].

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should <submit a> <update the> report on similarity (Module 1.7.1) and, if applicable, <submit> the data to support derogation from orphan market exclusivity (Module 1.7.2).>

AND/OR

<The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product(s) under market exclusivity. The detailed RMS assessment of similarity is presented in the attached RMS Similarity AR.

Conclusion

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, <product name> is considered <similar><not similar> (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to <name of authorised orphan product>. <Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for <name of authorised orphan product> in the treatment of <orphan designation>, <prevents><does not prevent> the granting of the marketing authorisation of <name of product>. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.>

**<Derogation(s) from market exclusivity**

<The application contained a claim addressing the following derogation laid down in Article 8(3) of the Regulation (EC) No. 141/2000; <the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the applicant> or < the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product> or <the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.> Assessment of these claims is appended.>

## General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product <,except for…. Inspection of this site is needed, because……… >.

<For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.>

<For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.>

<GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.>

# SCIENTIFIC OVERVIEW AND DISCUSSION

## Quality aspects

**Drug substance**

<The chemical-pharmaceutical documentation and Quality Overall Summary in relation to <product name> are of sufficient quality in view of the present European regulatory requirements.>

<The control tests and specifications for drug substance product are adequately drawn up.>

<Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of <..> is justified.>

**Drug Product**

<The development of the product has been described, the choice of excipients is justified and their functions explained.>

<The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on <number> batches. The batch analysis results show that the finished products meet the specifications proposed.>

<The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.>

<The proposed shelf-life of <number> months with <storage conditions to be specified> for the drug product is considered acceptable.>

## Non clinical aspects

**Pharmacology**

**Pharmacokinetics**

**Toxicology**

**Environmental Risk Assessment (ERA)**

<Since <Product name> is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.>

OR

<Conclusion on assessment of the ERA to be included if ERA data have been submitted by the applicant.

Summary of main study results

|  |
| --- |
| **Substance (INN/Invented Name):** |
| **CAS-number (if available):** |
| ***PBT screening*** |  | Result | **Conclusion** |
| *Bioaccumulation potential-* log *K*ow | OECD107 or … |  | Potential PBT (Y/N) |
| ***PBT-assessment*** |
| **Parameter** | **Result relevant for conclusion** |  | **Conclusion** |
| Bioaccumulation | log *K*ow  |  | B/not B |
| BCF |  | B/not B |
| Persistence | DT50 or ready biodegradability |  | P/not P |
| Toxicity | NOEC or CMR |  | T/not T |
| **PBT-statement :** | The compound is not considered as PBT nor vPvBThe compound is considered as vPvBThe compound is considered as PBT |
| ***Phase I***  |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC surface water, default or refined (e.g. prevalence, literature) |  | μg/L | > 0.01 threshold (Y/N) |
| Other concerns (e.g. chemical class) |  |  | (Y/N) |
| ***Phase II Physical-chemical properties and fate*** |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Adsorption-Desorption | OECD 106 or … | *K*oc = | List all values |
| Ready Biodegradability Test | OECD 301 |  |  |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | DT50, water =DT50, sediment =DT50, whole system =% shifting to sediment = | Not required if readily biodegradable |
| ***Phase IIa Effect studies***  |
| **Study type**  | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species*  | OECD 201 | NOEC |  | µg/L | species |
| *Daphnia* sp*.* Reproduction Test  | OECD 211 | NOEC |  | µg/L |  |
| Fish, Early Life Stage Toxicity Test/*Species*  | OECD 210 | NOEC |  | µg/L | species |
| Activated Sludge, Respiration Inhibition Test  | OECD 209 | EC |  | µg/L |  |
| ***Phase IIb Studies*** |
| Bioaccumulation | OECD 305 | BCF |  | L/kg | %lipids: |
| Aerobic and anaerobic transformation in soil | OECD 307 | DT50%CO2 |  |  | for all 4 soils |
| Soil Microorganisms: Nitrogen Transformation Test | OECD 216 | %effect |  | mg/kg |  |
| Terrestrial Plants, Growth Test/*Species* | OECD 208 | NOEC |  | mg/kg |  |
| Earthworm, Acute Toxicity Tests | OECD 207 | NOEC |  | mg/kg |  |
| Collembola, Reproduction Test | ISO 11267 | NOEC |  | mg/kg |  |
| Sediment dwelling organism  |  | NOEC |  | mg/kg | species |

*NB: In case Phase I or Phase II studies or results of specific parameters have not been submitted these tables/parameters should be deleted.*

Conclusions on studies:

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, <active substance> is not expected to pose a risk to the environment.

OR

<Active substance> PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

OR

<Active substance> is not a PBT substance or if PBT add a specific conclusion according to the PBT assessment.

- Considering the above data, <active substance> is not expected to pose a risk to the environment.

- Considering the above data, <active substance> should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.>

<The applicant committed to perform the following studies as follow-up measures:

*[list of tests to be performed]* >

## Clinical aspects

**Pharmacokinetics**

**Pharmacodynamics**

**Clinical efficacy**

**Clinical safety**

**Summary Pharmacovigilance system**

<The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's\* Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.>

OR

<The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's\* Pharmacovigilance System.

The provided summary/summaries is/are not in accordance with the legislation and needs to be updated; *e.g. the statement included in the summary of the pharmacovigilance system is only signed by the QPPV.>*

\* applicable in case the future MAH in RMS/CMSs will be different from the applicant

**Risk Management Plan**

The following introductory statement can be included

<The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to (*insert name of medicinal product*).”>

Safety specification

[Insert summary table of proposed safety concerns (Summary of safety concerns from RMP Part II: Module SVIII)].

Pharmacovigilance Plan
<[Insert summary of the pharmacovigilance plan (On-going and planned additional pharmacovigilance activities from RMP Part III.3)]>

*OR*

<Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.>

Risk minimisation measures

<[Insert summary table of proposed risk minimisation measures (Summary table of pharmacovigilance activities and risk minimisation measures per safety concern from RMP Part V.3].>

 *OR*

<Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.>

Summary of the RMP

<The submitted Risk Management Plan, version <XX> signed <date> is considered acceptable.> <The submitted Risk Management Plan, version <XX> signed <date> is not considered acceptable. See <the separate RMP AR/or Non Clinical / Clinical AR for Generics and> List of Questions for further details.>

<The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

* At the request of the RMS;
* Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.>

**Periodic Safety Update Report (PSUR)**

<Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

* PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
* For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
* In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.>

<Active substance is currently not listed in the published EURD list

<The MAH shall submit the first periodic safety update report for this product with a period of{xx} months/{xx} years (i. e. DLP of {xx} months after authorization) following authorisation. Further, MAHs shall continuously check the European medicines web-portal if the active substance has been included in the list of Union reference dates (EURD list). If yes, after publication in the EURD list the PSURs shall be submitted in accordance with the requirements set out in the EURD list.>

<The medicinal product is authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC. No routine PSURs need to be submitted unless it is stated as a condition in the marketing authorisation. Marketing authorisation holders shall continuously check the European medicines web-portal to see if the active substance has been included in the list of Union reference dates (EURD list). If yes, the PSURs shall be submitted in accordance with the requirements set out in the EURD list.>

**Common renewal date**

# BENEFIT RISK ASSESSMENT

# LIST OF QUESTIONS as proposed by RMS

## Quality aspects

**Major objections**

**Drug substance**

**Drug product**

**Other concerns**

**Drug substance**

**Drug product**

## Non clinical aspects

**Major objections**

Pharmacology

Pharmacokinetics

Toxicology

**Other concerns**

Pharmacology

Pharmacokinetics

Toxicology

## Clinical aspects

**Major objections**

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

Risk Management Plan

**Other concerns**

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

Risk Management Plan

# RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

## Legal Status

## List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

|  |  |
| --- | --- |
| **Description** | **Due date** |
|  |  |
|  |  |
|  |  |

## List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

* **<Additional risk minimisation measures (including educational material)>**

The educational material should contain the following key elements:

* **<Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83>**

The MAH shall complete, within the stated timeframe, the below measures:

|  |  |
| --- | --- |
| **Description** | **Due date** |
|  |  |
|  |  |
|  |  |

* **<Specific obligation to complete post-authorisation measures for <the marketing authorisation under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC>**

<This being a marketing authorisation under exceptional circumstances and pursuant to Article 22 of Directive 2001/83/EC, the MAH shall complete, within the stated timeframe, the following measures:>

| **Description** | **Due date** |
| --- | --- |
|  |  |
|  |  |
|  |  |

## Module I – Application related comments (including product name)

**Product name**

## Summary of Product Characteristics (SmPC)

## Package Leaflet (PL)

### **Package Leaflet**

### **Assessment of User Testing**

<Assessment of the User Testing is attached in the ‘QRD Guidance and Checklist for the Review of User Testing Results’.> or <The applicant has stated that the readability test will be performed during clock stop: The RMS agrees with this.>

## Labelling

# APPENDIX

# QRD GUIDANCE AND CHECKLISTFOR THE REVIEW OF USER TESTING RESULTS

**PRODUCT INFORMATION**

|  |  |
| --- | --- |
| **Name of the medicinal product:** |  |
| **Name and address of the applicant:** |  |
| **Name of company which has performed the user testing:** |  |
| **Type of Marketing Authorisation Application:** |  |
| **Active substance:** |  |
| **Pharmaco-therapeutic group****(ATC Code):** |  |
| **Therapeutic indication(s):** |  |

- Full user testing report provided [ ]  yes [ ]  no

- Bridging report provided [ ]  yes [ ]  no

- Grounds for bridging based on a sound justification:

[ ]  extensions for the same route of administration

[ ]  reference to test on same class of medicinal product

[ ]  reference to test with same safety issues

[ ]  other \_\_\_­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Is the justification for bridging acceptable? [ ]  yes [ ]  no

Is the justification for not submitting a report acceptable? [ ]  yes [ ]  no

Reasons

*\_\_\_\_\_\_\_\_\_*\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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**1 TECHNICAL ASSESSMENT**

**1.1 Recruitment**

* Is the interviewed population acceptable? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**1.2 Questionnaire**

* Is the number of questions \_\_\_\_\_\_\_ sufficient? [ ]  yes [ ]  no
* Questions cover significant (safety) issues for the PL concerned? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**1.3 Time aspects**

* Is the time given to answer acceptable? [ ]  yes [ ]  no
* Is the length of interview acceptable? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**1.4 Procedural aspects**

* Rounds of testing including pilot \_\_\_\_\_\_\_

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**1.5 Interview aspects**

* Was the interview conducted in well-structured/organised manner? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**2 EVALUATION OF RESPONSES**

**2.1 Evaluation system**

* Is the qualitative evaluation of responses acceptable? [ ]  yes [ ]  no
* Does the evaluation methodology satisfy the minimum prerequisites? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**2.2 Question rating system**

* Is the quantitative evaluation of responses acceptable? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**3 DATA PROCESSING**

* Are data well recorded and documented? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**4. QUALITY ASPECTS**

**4.1 Evaluation of diagnostic questions**

* Does the methodology follow Readability guideline Annex 1? [ ]  yes [ ]  no
* Overall, each and every question meets criterion of 81% correct answers [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**4.2 Evaluation of layout and design**

* Follows general design principles of Readability guideline [ ]  yes [ ] no
* Language includes patient friendly descriptions [ ]  yes [ ]  no
* Layout navigable [ ]  yes [ ]  no
* Use of diagrams acceptable [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**5. DIAGNOSTIC QUALITY/EVALUATION**

* Have any weaknesses of the PL been identified? [ ]  yes [ ]  no
* Have these weaknesses been addressed in the appropriate way? [ ]  yes [ ]  no

Comments/further details\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**6. CONCLUSIONS**

* Have the main objectives of the user testing been achieved? [ ]  yes [ ]  no
* Is the conclusion of applicant accurate? [ ]  yes [ ]  no
* Overall impression of methodology [ ]  positive [ ]  negative
* Overall impressions of leaflet structure [ ]  positive [ ]  negative

**CONCLUSION/OVERVIEW**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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