Rapporteur's Progress Report on the 3rd IDEA Working Group meeting on the

Feasibility of a study to assess the effectiveness of QRA

December 7th, 2017 from 9:00 to 16:30

Martin's Grand Hotel Waterloo
Chaussée de Tervuren 198,
1410 Waterloo

1. Opening

This comprised the key conclusions of the two earlier WG meetings on the same topic, where it has been realized that it is not a simple task to demonstrate the effectiveness of QRA based risk management measures.
One isolated approach or study might not be sufficient to actually demonstrate the effectiveness and specifically not the surveillance work alone. It was therefore agreed that complimentary work is necessary. That formed the basis of the discussions during the one day workshop.

A tour de table of the participants (listed in Annex I of this report) was organized.

2. Surveillance Study – status update and plans

The workshop participants were updated on what activities took place since the last WG meeting of February 2017 (see also presentation on IDEA Surveillance system – Status update, att. 01). Progress had already been made around ethical concerns, on data management, quality control and patch test preparation, a remaining critical part being what materials to test in addition to FMI and FMII and/or the SCCS 26 fragrance materials and oxidized limonene and linalool.
Based on this information and after intensive discussion of 5 major points the group finally agreed on the following key conclusions:

The working group reaffirmed its support for a surveillance system and discussed details as follows:

- Specific materials will be selected such that they allow for correlation with contact allergy trends, which may direct additional work.
- Product concentration for patch testing of the new ingredients needs to be first determined in a **range finding study**. For this, a protocol will be developed by a sub- team.
- **Data management** will be arranged either through the EECDRG and/or the ESSCA system. Both systems and their compatibility with each other and with the study design will be assessed in a pilot study.
- The WG agreed additional criteria (e.g. Standard driven by dermal sensitization, non- natural ingredient, consider the EU Commission list for consumer information and the number of the table of the 2012 SCCS Opinion on fragrance allergens) for the **selection of 5 fragrance materials**. Against these, 3 fragrance materials ingredients have been provisionally selected and another 3 are under consideration. Those and others remain subject to further review.

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- It was agreed to carefully assess critical logistic questions for the large scale study first in a **pilot study**. For this, a protocol will be developed by a sub-team.

In detail, the working group supported to continue the evaluation of a surveillance study and discussed the following five major points:

I. Determination of patch test concentrations

The relevance of adequate patch test concentration was broadly supported and it was agreed that not choosing the right patch test concentration can become a decisive factor. It was further regarded crucial to study active sensitization. An approach used in France by Martine Vigan was named as reference, which in principle makes it mandatory for the patients to return after a certain time to check for late occurring reactions, which may be indicative for active sensitization.

An overview of critical elements for determination of patch test concentrations for new materials was presented (att. 02). The aim is to find an as high as possible concentration which is not irritating and does not lead to active sensitization. While the composition and concentrations of FM1 where not systematically derived, this changed with the development of specific patch test concentrations for the 26 allergens. A kind of decision tree was presented. Starting point is often based on reported cases. It was mentioned that a factor 10 to 20 between normal uses and patch test concentration seems to be typical. It was recommended that for materials having a successful history of clinical use, to rely on already established patch test concentrations.

The approach presented to determine the patch test concentration was largely supported, but some suggestions for improvement were made.
The study will have to be performed in one clinic. It is assumed that industry will be able to provide helpful information for the new materials such as information on use level, potency. As a further source of information the book “Patch Testing” from Anton de Groot was mentioned (now in its 3rd edition).
It was agreed to reach out for a written proposal in form of a protocol, prepared by a small team – and then get it endorsed by the whole WG.
The dose range finding study can cover all 5 materials at once. It typically involves about 100 patients, meaning it can take several months if performed in one clinic. There is ethical approval required.
The WG suggested to have the process and results published.

ACTION: IDEA Management Team to follow up with Magnus Bruze for a draft protocol on determining patch test concentrations of new materials for the IDEA surveillance project

II. Data Management

The group was then presented several options on how data management in existing systems could be performed and what level of detail with regard to individual patient information could be expected (att. 03).

- The ESSCA system (currently locally on computers, online version expected in 2018) seems to provide the broadest flexibility and options to expand.
- The EECDRG approach is more targeted but less flexible. Data are only recorded for patients that show a reaction, not for the negative cases. Negative cases are nevertheless counted to determine the denominators.
- Third option presented was a vigilance approach to deep dive into individual cases.

The choice of system depends on the target of the exercise, which mainly is to get reliable data on the frequency of contact allergy over various clinics.
It was suggested to consider starting with the EECDRG approach, but offering participants to use ESSCA, where it is already established and new ones joining should have the choice.

The vigilance approach as presented was not regarded suitable for the project planned, but as a very useful approach that should be kept in sight.

It was pointed out that some payment to the clinics needs to be considered to support the above work, but there was neither unanimous position on the actual need nor the amount. This requires further investigation, as it seems that in some systems, e.g. the UK there might not be an expectation of remuneration.

It was mentioned that there is a new EU Directive that makes it more difficult to link results on individual patients back and in any case requires the consent of the patient.

III. Test Material

It was recognized that ideally candidates to be tested in addition to the routine materials should include one or more "new" allergens, i.e. new to the market fragrance ingredients, which are not already used or cross reactive with other existing allergens. Nevertheless, it is proposed for various reasons to include 5 fragrance ingredients, which not currently being patch tested, being in line with agreements made at the WG meeting of February. It was agreed that this would position the surveillance project more in the sense of a product stewardship program, with limited capacity to directly conclude on the effectiveness of the QRA.

Whether new to the market, or as a new patch test material, the WG participants confirmed that a surveillance system will provide valuable information, even if it has limited value concerning drawing conclusions on the effectiveness of the QRA.

With regard to key criteria it was agreed to have scientific publications on the outcome.

With regard to testing patients, the WG did not propose selection criteria.

An industry led subgroup had developed a list of suggested candidates, considering the following criteria:

- Be part of the 2012 SCCS lists 13-1, 13-2 or 13-3 and or the 2013 Commission proposal and or receiving a new IFRA Standard as part of the upcoming 49th Amendment
- Cover a variety of potencies
- Preferably be a synthetic material (reduce likelihood of cross reactions)
- Be used in high volume and in product types leading to relevant consumer exposure
- Consider 'other uses'

The WG in principle confirmed the criteria. It was asked to ensure that there is indeed for some materials that are considered by the Commission for consumer information. It was further agreed not to include natural extracts, due to issues of ensuring consistent quality and doubts about the quality and composition that the consumer was exposed to when he/she got sensitized. The group reemphasized the importance of having information on exposure (volume, breadth of use, etc.). However, as IFRA Standards will likely also consider systemic toxicity for newly restricted materials it should be ensured that the limits are driven by the sensitization endpoint. When it comes to the SCCS list, it was suggested to ensure that the materials are mainly taken from table 13-1, meaning that they are considered sensitizers based on human data.

The group reviewed the list of proposed materials against the original criteria and the newly agreed / emphasized ones. Against these, 3 fragrance ingredients have been provisionally selected and another 3 are under consideration. Those and other remain subject to further review. The subgroup that had worked out the first proposal was asked to revisit the list of materials considering all of the above and come back to the group by mail with a revised list.

The selection of the materials to be included is a critical rate limiting step, as most of the other activities (like determination of patch test concentration, see below) depend on it.

IV. Hypothesis

The group agreed that the overarching hypothesis would be to follow the trends in CA of individual ingredients and hopefully see a reduction of the CA rate in the (clinical) population consequent upon the implementation of QRA2. However, the challenge will be how to interpret the results.

Assuming that QRA2 works one might see a change, in case sufficiently large numbers of CA cases of selected substances out of the 26 allergens have been investigated. But it would be hard to understand the drivers of change, especially as for most of the individual fragrance allergens the reaction rates are in the range of 0.3 to 1%. This led to a wider discussion of these issues. The maximum QRA2 can achieve (always keeping the issue of confounding factorrs in mind) is an overall reduction in contact allergy over time – 5 to 10 years, depending on the VoU, the potency, speed of the intervention, etc. Even a ban on a substance does not lead to the elimination of contact allergy entirely – it can take many years to "wash out" the effects in a sensitised population.
In case of new substances, there may be no cases at all, which could be due to the consequence of using QRA2 guided concentrations, low to moderate potencies or low market penetration.

The surveillance system should serve as an early alert system, by collecting information on development of CA rates in the clinics and allow learning on the exposure conditions of the patients to get a better insight in whether the risk assessment and management measure in place are adequate and broad enough in their scope, to allow to take corrective measure if needed. There was agreement that interpretation should be on a material-by-material basis, taking as much information (use trends, etc.) as possible into consideration.

It has also been emphasized that patch test diagnoses contact allergy, but not allergic contact dermatitis. CA as such is not a disease but a delayed immunological reaction during patch testing. It does not answer directly what caused the induced state nor triggered the patient to come to a clinic.

In this context the importance of the work to determine the adequate patch test concentration was pointed out again, as only then negative patch test results are meaningful.

V. Pilot study

In the subsequent pilot study the focus will be on checking whether the operational aspects and elements (e.g. the data reporting) as well as logistics are working well. 2 – 3 centres involved (with about 50 patients) was regareded sufficient. Centers should preferrably be from different regions. It was highlighted that the pilot could also provide some insight with regard to the 'additional effort' and the resulting 'need' for payments to the clinics.
There was agreement that there needs to be a formal proposal for the pilot study for testing the system and the data management.
By the time of the pilot study, there needs to be a finalized study protocol and CRF.

3. Complementary work - status update and plans

The group was updated on the status of potential complimentary work (att. 04) to allow more insight in the effectiveness of the QRA.
The major development compared to what was worked out and reported at the February 2017 WS was some additional insight into ethical concerns.

Due to limited time, the proposal could not be discussed in full detail. Nevertheless, even so not unanimous, there was expression of support for the current proposal. It was stated that in case it finds ethical support, it could indeed provide relevant insight into the effectiveness of the QRA, as it directly addresses the research question.
With regard to the approach it was suggested to consider working with only two groups – the QRA and control group, which reduces the number of subjects needed for the study. It was asked to reconsider the need for doing a patch test at the beginning of the study.
From a practical point of view it was asked to check whether the material can be formulated in the type of products considered for the study.

It was concluded that there is a continued need to further evaluate the study and dedicate more time at the next meeting.

4. Attachments

Att. 01: Presentation IDEA Surveillance system – Status Update
Att. 02: Presentation on procedure for determination of patch test concentrations
Att. 03: Presentation on data management systems
Att. 04: Presentation on the complimentary work (prospective study)

Annex 1: List of participants

Academia	
Donald Belsito	Columbia University, NY
Magnus Bruze	Lunds University Malmö
Thomas Diepgen	Ruprecht-Karls University Heidelberg
David Gawkrodger	University of Sheffield
Axel Schnuch	IVDK/University of Göttingen
Wolfgang Uter	ESSCA, University of Erlangen
SCCS Observer:	
Pieter-Jan Coenraads	University Medical Centre Groningen
Industry:	
Anne Marie Api	RIFM
David Basketter	DABMEB Consultancy
Graham Ellis	Givaudan
Nicola Gilmour	Unilever
Joe Huggard	Consultant
Petra Kern	P&G
Maya Krasteva	L'Oréal
Boris Müller	Symrise
Shawn Blythe	IFF
Scott Schneider	Firmenich
Other Observers:	
Pilar Velencoso Cuenca	European Commission, DG Grow
Federica De Gaetano	European Commission, DG Grow
Florian Schellauf	Cosmetics Europe
IDEA Management Team:	
Hans Bender - moderator	
Cécile Gonzalez	
Matthias Vey	
IDEA Supervisory Group:	
Helmut Greim	Technical University of Munich, Rapporteur on behalf of the IDEA Supervisory Group