Patch Testing Guidelines

CTPA guidelines for the supply of patch test materials for diagnostic patch testing

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Acknowledgements

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CTPA welcomes comments, questions, or suggestions for improvements to this guideline. These should be addressed to Caroline Rainsford, Director of Science, at the CTPA Secretariat or sent via email to: info@ctpa.org.uk.

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Section A: Overview

Patch testing is a procedure to determine whether a skin condition is caused or aggravated by an allergy to substances which have come into contact with the skin. The patch test is performed by applying allergens under occlusion on the skin under standardised conditions [1]. Dermatologists perform patch testing on patients to diagnose contact dermatitis or contact allergy to certain substances. Dermatologists have a baseline testing series with the most common contact allergens available for patch testing. However, patients may sometimes react to a specific cosmetic product, or a combination of substances within a cosmetic product, which may not be available from the baseline or other testing series that are available. In this instance, dermatologists are likely to contact the Responsible Person (RP) for that cosmetic product and request samples of the ingredients within the product to carry out the patch testing to aid the diagnosis of a possible allergy.

Below are useful definitions of the skin conditions that a dermatologist may be investigating by patch testing.

- Contact dermatitis is an inflammatory skin reaction caused by direct contact with noxious agents in the environment. The pathomechanism may involve immunological hypersensitivity (allergic contact dermatitis) or not (irritant contact dermatitis), or may be mixed [1].

- Contact allergy is an altered immune status of an individual induced by a particular sensitising substance, a contact allergen. This involves a clinically unapparent sensitisation phase (the induction phase), resulting in the expansion of a clone of allergen-specific immune T cells. At this point, an individual is immunologically sensitised. Upon re-exposure with the same, or a cross-reacting, allergen/antigen, the elicitation phase is triggered, leading to specific T cell activation with clinically visible disease. The substances inducing contact allergy are reactive chemicals, usually with a molecular weight of <500 Da, but exceptionally in the range of 500–1000 Da. These substances are generally antigenic after protein binding (also referred to as haptens). An individual in whom contact allergy has been induced will develop a secondary immune response if there is skin exposure to the same (or cross-reacting) allergen. This process is called elicitation, and will manifest as allergic contact dermatitis [1].

These 'CTPA Patch Testing guidelines' have been developed to inform cosmetics companies of the practical aspects of supplying patch test materials to dermatologists who request cosmetic ingredient samples for diagnostic patch testing; as well as to facilitate a dialogue between dermatologists and companies. It is important for companies to engage with dermatologists if they are contacted seeking patch testing samples. A discussion between the cosmetic company and the requesting dermatologist will help determine if patch test samples of ingredients are appropriate and attainable, or if other samples may be provided. If it is appropriate for patch test materials to be provided by the company to the dermatologist, this guidance provides information to help with this process. If samples for patch testing are provided, it is essential that the results from the testing are communicated back to the company from the dermatologist for inclusion in the company's cosmetovigilance programme.

This Guideline has been developed with reference to the European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice, and in collaboration with the CTPA Cosmetovigilance Advisory Group and the CTPA – British Society for Cutaneous Allergy (BSCA) Working Group.

The below table summarises the key steps and tasks for this process by both dermatologists and companies. The next section of this guideline analyses the preparation of the patch testing samples and the relevant steps in more detail.

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DERMATOLOGIST/ALLERGOLOGIST	COMPANIES
1. Examine the reproducibility of the reported skin reaction, where appropriate, by testing the finished product as it is or in a suitable dilution (recommended or mildly exaggerated use conditions). The dermatologist shall also exclude irritancy.	
2. Request the patch testing sample of the product's ingredients from the Responsible Person (RP) of the product, which is identifiable on the product's label. The samples can be requested 'neat and undiluted' or 'pre-diluted and ready for patch testing'. **a.** If the 'neat and undiluted' patch testing sample is requested: when diluting the raw material, care should be taken to ensure that the concentrations remain below the irritation threshold of the respective cosmetic ingredients; and that the pH is neutral.	
3. Provide the RP with the exact details and/or actual product implicated in the patient's dermatitis. For an unambiguous identification of a product the batch code is essential – the batch code is generally found at the bottom of the product packaging, or in the crimped part. If the actual product is not available, other reasonable means should be used to identify the product and its formula. These could include photographs, or other visual representations, of the product's packaging or artwork. Ideally, if visual images are requested, they should include both the front of packaging and the ingredients list if available.	
	4. Supply the samples of the raw materials used in the manufacture of the finished product as requested by the dermatologist. Remember that it is often extremely difficult for the dermatologist to obtain and prepare the chemicals in a ready-to-use format by other means. a. While chemicals are usually provided in a ready-to-use format, as testing with the neat material could put the patient at risk of a severe skin reaction, dermatologists may request neat samples in order to dilute them to their own preferred concentrations. Please see section B of this document for more information on this point. b. Should pH adjusters, such as sodium hydroxide and hydrochloric acid, be requested, it is preferable for the dermatologist to obtain them through the hospital pharmacy. However, this can be determined on a case-by-case basis.

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	c. The samples should all be taken from factory dispensary stock or equivalent grades used in the manufacture of finished products. Laboratory analytical grade materials should not be supplied. d. A copy of the pack 'INCI' list **and** a 'composite ingredient list'* should also be supplied with the ingredient samples. e. The samples provided should be labelled in such a way as to allow the dermatologist to identify the individual substances or blends in each container, along with the concentration and vehicle if relevant.** While companies are urged to make every effort to provide samples from factory dispensary stock or equivalent grades used in the manufacture of finished products, it must be acknowledged that this may not always be possible especially for a global company with manufacturing sites around the world. If it is not possible for such samples to be obtained, companies should contact the dermatologist to explain the situation and to discuss and agree what samples can be provided and in what form.
	5. Inform the dermatologist of the timescale for supplying the samples, so that an appointment may be made for the patient at the clinic for patch testing. It is important to keep the dermatologist informed about the progress in preparing the samples.
	6. When providing the patch testing samples to the dermatologist, the company shall also return the original product if provided.
7. Perform the patch testing on the patient.	
8. Communicate the outcome of the patch testing to the cosmetics company within an agreed timescale, to allow for its inclusion in the company's cosmetovigilance programme.	
	9. Include the outcome of the patch testing and any other relevant information in relation to the product and the ingredients tested within the cosmetovigilance information for that product.

* A 'composite ingredient list' is a list which exemplifies the specific composition of each Ingredient added into the formula at the time of manufacture. This composite list should include any subsidiary substances such as antimicrobial preservatives or antioxidants which may be present in the ingredients (see Annex 1 – Example of a composite ingredient list).

** If the labelling system used only displays a Dispensary Code (DC), a decode list should be provided to allow the identification of the container's contents.

Despite completion of the patch testing, an ongoing dialogue between dermatologists and the cosmetics industry is an essential part of an effective cosmetovigilance process.

In order for dermatologists to contact the correct personnel responsible for cosmetovigilance within companies and so help improve the dialogue between companies and the dermatologists, CTPA has collated and holds, in confidence, these company contact details to be shared with dermatologists on request.

This important initiative has been approved by the CTPA Scientific Committee and Cosmetovigilance Advisory Group. Please contact patchtesting@ctpa.org.uk for details.

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Section B: Detailed Guidance on the Preparation of the Patch Testing Samples

1. Ingredients Requested in the 'Neat and Undiluted State'

If a dermatologist wishes to prepare patch test allergens using their own preferred concentration(s) and vehicles, they will request that companies supply the product's ingredients in the 'neat and undiluted state'. If companies receive such a request, it is important to understand how the dermatologist or practitioner intends to process the allergens into a format ready for patch testing, because the materials should not be used directly on patients in their neat and undiluted state.

- ✓ The sample size should be in the range of 5g to 10g, contained in virgin glass bottles of an appropriate size, sealed with polypropylene screw caps.
    - For ingredients of high commercial value, peptides for example, the sample size can be reduced to 500mg.
- ✓ Ideally, the samples should be labelled with the relevant INCI name(s) of the component substances, in the composite format described earlier, where relevant. If another method is used to identify the samples, the advice given earlier should be followed. The samples should also be marked with the:
  - date of packing;
  - lot or batch number;
  - expiry date.

- ✓ A copy of the contemporary Safety Data Sheet (SDS) in the EU or GB Format (in English) should always be supplied for each ingredient sample. Ideally, a copy of technical data sheet for each ingredient should also be supplied to allow the presence or absence of subsidiary materials (antimicrobial preservatives for example) to be corroborated.

- ✓ Once prepared, the samples should be stored and transported under appropriate, documented conditions. It is recommended for the manufacturer of the samples to provide this information to the dermatologists. Transport and storage conditions will be determined depending on the type of formulation.

- ✓ The stability of the materials when transported should be taken into consideration.

2. Ingredients Requested in the Prediluted Format, Ready for Patch Testing

In some cases, individual dermatologists may not have a hospital pharmacy available to prepare the patch test materials for them from the 'neat or undiluted' raw material. In this instance, the dermatologist is therefore likely to ask companies for the ingredient(s) in the prediluted format, ready for patch testing. If such a request is received, cosmetic companies should arrange for the patch testing samples to be manufactured, either in their own laboratories or using the services of a contract manufacturing pharmacy company. If manufacturing in their own laboratories for a non-UK country, companies must ensure they are in compliance with the national law regarding the regulatory status of the patch test material.

Substances to be supplied in the prediluted format should be manufactured using the concentration(s) and vehicles described in the book 'Patch Testing' by de Groot [2] (including updates since publication in 2008). It is important to note that the patch testing samples must NOT be supplied at the concentration used in the product.

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The de Groot contains information on patch test concentrations and vehicles for defined chemicals, mixtures of defined chemicals, plant-derived substances, products, and groups of either chemically or functionally related substances and chemicals, as published in literature and other official resources. CTPA has a copy of de Groot should companies need to ask for dilution advice. Alternatively, reference can be made to the catalogues published by third party companies which supply patch test materials. Please contact CTPA at patchtesting@ctpa.org.uk for further information if required. In the event that the concentrations differ between the commercial catalogues and de Groot, the de Groot dilution should be used [2].

There may be instances where the dermatologist may request a particular concentration. If this differs from de Groot [2], then the manufacturer should query this with the dermatologist. In rare instances, a dermatologist may request a "novel" material at different test concentrations.

- ✓ **What to do when there is more than one concentration and/or vehicle in the de Groot**

In order to choose the most suitable concentration and/or vehicle, companies may wish to review the literature available on patch testing for those ingredients (de Groot states the reference paper that led to the suggested concentrations and vehicles [2]). The choice may also be based on the usage of the ingredient in the product. Physico-chemical properties should be taken into account when determining an appropriate vehicle; for example the solubility of the ingredient. If companies are unsure, they may want to check with the dermatologist how the samples should be prepared, as the dermatologist may wish to advise the appropriate choice of concentration and vehicle.

- ✓ **What to do if the ingredient to be patch tested is not in de Groot**

Companies may decide upon a suitable concentration and vehicle based on their own expert judgement, online literature research (e.g. the journal 'Contact Dermatitis', or the US journal 'Dermatitis'), and other available information on the ingredient available from its SDS (consider also contacting the raw material supplier, as they may have more information), the US Cosmetic Ingredient Review (CIR) reports (which may help identify the highest non-irritant concentration of the chemical and provide further details on the skin tolerance levels). The vehicle should be chosen mainly by solubility of the ingredient, but also with reference to the standard conditions specified for similar materials in de Groot. If insoluble, the material should be suspended homogenously in white soft paraffin (petrolatum). Ultimately, companies may need to check with the dermatologist how the samples need to be prepared, which concentration and vehicle shall be used. A conversation between the company and the dermatologist will be vital in this instance. The dermatologist may also advise preparing samples with three or more concentrations (a dilution series), to allow a more thorough investigation of which concentration may trigger the reaction. When the irritant threshold is unclear, lower concentrations may be applied first to avoid the risk of an adverse reaction.

- ✓ Substances supplied in the prediluted state should be labelled in such a way as to allow the dermatologist to identify the constituent substance(s), together with the:
  - concentration of the substance of interest;
  - vehicle;
  - batch or lot number;
  - date of manufacture;
  - nominal expiry date***.

- ✓ Composite ingredients should be diluted so that the concentration of the principal constituent complies with the concentration conditions described by de Groot [2] or other selected data source.

- ✓ A sample of the vehicle used to prepare the allergens should accompany the manufactured samples on dispatch to the requesting dermatologist.

- ✓ Occasionally, de Groot [2] may stipulate the testing of substances in their neat and undiluted state. In these cases, the principles described earlier for this format should be followed.

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- ✓ Occasionally a dermatologist may stipulate the conditions which should be used for the manufacture of the patch testing samples.

- ✓ The sample size should be in the range of 5g to 10g, contained in appropriate packaging.

- ✓ Once prepared, the samples should be stored and transported under appropriate, documented conditions, as well as the material's relevant Safety Data Sheets. It is recommended for the manufacturer of the samples to provide this information to the dermatologists. Transport and storage conditions will be determined depending on the type of formulation.

- ✓ The stability of the materials when transported should be taken into consideration.

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References

[1] European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice'
[2] Anton C. De Groot. Patch Testing. Test Concentrations and Vehicles for 5200 Chemicals, 5th Edition; Wapserveen, the Netherlands: acdegroot publishing, 2022.

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Annex I – Example of a Composite Ingredients List

Dispensary Code (DC)	Aqua
DC	Aqua + Sodium laureth sulfate + Phenoxyethanol + Methyparaben
DC	Aqua + Cocamidopropylbetane
DC	Aqua + Methylisothiazolinone
DC	Parfum + dipropylene glycol + benzyl alcohol + benzyl benzoate + linalool

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