



Allergen Patch Test

T.R.U.E. TEST[®]*

*Thin-layer Rapid Use Epicutaneous Test

FOR TOPICAL USE ONLY

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DESCRIPTION: T.R.U.E. Test is a ready-to-use patch test system containing 28 of the most common allergens suspected of causing allergic contact dermatitis¹ and a negative control.

The source materials for the T.R.U.E. TEST allergens are obtained from outside suppliers who certify that the materials meet specific standards of purity. The manufacturer then determines the purity and identity of the source materials using validated in-house chemical analyses.

Each test consists of 3 pieces of surgical tape (5.2 x 13.0 cm), each with up to 12 polyester patches of approximately 0.81 cm². The allergen-containing patches are coated with a film containing a uniformly dispersed specific allergen or allergen mix. The negative control is an uncoated polyester patch. The test is covered by a protective sheet and sealed in a pouch of laminated foil. A desiccant paper is included in the Panel 2.1 for stability purposes.

The allergens are homogenized in 1 or more of the following materials to produce the allergen films that coat the patches: hydroxypropyl cellulose, methylcellulose, polyvidone, β-cyclodextrin. Butylhydroxyanisole (BHA) and butylhydroxytoluene (BHT) have been added to the colophony patch. No other excipients are used to produce the patches.

T.R.U.E. TEST is subjected to microbial load testing to assure that no more than 10² microorganisms per test are present. In addition, T.R.U.E. TEST is further analyzed to assure the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Each patch is analytically tested and contains ±20% of its labeled value at the time of batch release. These values are maintained through expiry under the recommended storage conditions, with the exception of fragrance mix, which may reach a lower limit of -30% of labeled value during shelf life.

The components of the patches containing mixtures, e.g., thiuram mix, have the potential to chemically interact, resulting in the formation of new substances.

Components: The individual components of T.R.U.E. TEST, Panels 1.1, 2.1 and 3.1 are listed below along with a quantitative description of each patch formulation. Panel 1.1 contains 11 allergens and a negative control; Panel 2.1 contains 12 allergens; Panel 3.1 contains 5 allergens.

Panel 1.1 Allergens

1. Nickel Sulfate: Nickel sulfate hexahydrate (purity $\geq 98.5\%$) is used to formulate this patch. The active allergenic component is nickel. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 0.20 mg of nickel sulfate hexahydrate per square centimeter, which corresponds to 0.036 mg of nickel per patch. Nickel is one of the most common metals in the environment and is found in most metal and metal-plated objects.

2. Wool Alcohols: Wool alcohols (lanolin), USP, is a natural product obtained from the fleece of sheep. This allergen is a highly complex mixture of alcohols containing cholesterol, lanosterol, agnosterol, and their dihydro derivatives plus straight- and branched-chain aliphatic alcohols. The active allergenic component has not been identified. The gel vehicle is polyvidone. The product is formulated to contain 1.00 mg of wool alcohols per square centimeter, which corresponds to 0.81 mg of wool alcohols per patch. Wool alcohols (lanolin) is a common constituent of many ointments, creams, lotions, and soaps.

3. Neomycin Sulfate: Neomycin sulfate, USP, an antibiotic drug substance, is used to formulate this patch. The gel vehicle is methylcellulose. The product is formulated to contain 0.23 mg of neomycin sulfate per square centimeter, which corresponds to 0.19 mg of neomycin sulfate per patch. Neomycin is a common antibiotic and is found in topical antibiotic creams, lotions, ointments, eyedrops, and eardrops.

4. Potassium Dichromate: Potassium dichromate (purity $\geq 98.5\%$) is used to formulate this patch. The active allergenic component is chromium. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 0.023 mg of potassium dichromate per square centimeter, which corresponds to 0.0067 mg of chromium per patch. Chromium is found in cement, as well as in many industrial chemicals.

5. Caine Mix: Caine mix is composed of 3 drug substances: benzocaine, USP (purity ≥ 99.0), tetracaine hydrochloride, USP (purity ≥ 99.0), and dibucaine hydrochloride, USP (purity ≥ 98.5). The gel vehicle is polyvidone. The product is formulated to contain 0.63 mg of caine mix per square centimeter, which corresponds to 0.364 mg of benzocaine, 0.063 mg of tetracaine, and 0.064 mg of dibucaine per patch. Benzocaine, tetracaine, and dibucaine are found in many topical anesthetic medications.

6. Fragrance Mix: Fragrance mix is composed of 8 substances: geraniol (purity $\geq 95\%$, identity of impurities unknown), cinnamaldehyde (purity $\geq 95\%$, contains trace amounts of cinnamyl alcohol), hydroxycitronellal (purity $\geq 95\%$, identity of impurities unknown), cinnamyl alcohol (purity $\geq 95\%$, identity of impurities unknown), eugenol, USP (purity $\geq 95\%$, identity of impurities unknown), isoeugenol (purity $\geq 88\%$, identity of impurities unknown), α -amylcinnamaldehyde (purity $\geq 90\%$, identity of impurities unknown), and oak moss. Oak moss, a dark green sticky paste, is a solvent extract of the lichen *Evernia prunastri*. The chemical composition is very complex. The acid fraction (95% of the extracted material) is made up of depsides including atranorin, evernic acid, usnic acid, chloratranorin,

and degradation products of these depsides. Atranorin is suspected as a prime allergenic component, and its peak (measured with gas chromatography) is used to determine the amount of oak moss in the fragrance mix patch.²

The gel vehicles used in this patch are hydroxypropyl cellulose and β -cyclodextrin. The product is formulated to contain 0.43 mg of fragrance mix per square centimeter, which corresponds to 0.070 mg of geraniol, 0.034 mg of cinnamaldehyde, 0.054 mg of hydroxycitronellal, 0.054 mg of cinnamyl alcohol, 0.034 mg of eugenol, 0.015 mg of isoeugenol, 0.015 mg of α -amylcinnamaldehyde, and 0.070 mg of oak moss per patch. The components of fragrance mix are commonly used in toiletries, fragrances, and flavorings.

7. Colophony: Colophony is produced from the resin of the pine trees *Pinus massoniana* and *Pinus tabulaeformis*. It is translucent, pale yellow or brownish yellow, brittle, and glassy in appearance. Colophony consists of 75% to 85% resin acids, 10% neutral fractions (i.e., terpenes), with the remaining part oxidation products. Oxidation products of abietic acid and other resin acids have been identified as the active allergenic components. The UV-absorbance measurement of 1 of the primary components, abietic acid, is used to quantify colophony. The gel vehicle is polyvidone. BHA and BHT are added in equal amounts of 0.05% as antioxidants. The product is formulated to contain 1.20 mg of colophony per square centimeter, which corresponds to 0.97 mg of colophony per patch. Colophony is found in adhesives, sealants, and pine oil cleaners.

8. Paraben Mix: Paraben mix contains the 5 ester derivatives of parahydroxybenzoic acid, methyl (USP), ethyl (USP), propyl (USP), butyl (USP), and benzyl parahydroxybenzoate, in equal parts (purity of each derivative $\geq 98.0\%$). The gel vehicle is polyvidone. The product is formulated to contain 1.00 mg of paraben mix per square centimeter, which corresponds to 0.81 mg of paraben mix per patch. The components of paraben mix can be found in cosmetics, dermatological creams, and paste bandages.

9. Negative Control: The negative control is an uncoated polyester patch.

10. Balsam of Peru: Balsam of Peru is a resin from a South American tree, *Myroxylon balsamum pereirae*. The resin consists of a mixture of fragrances and other substances that have not all been identified. Balsam of Peru patch content is quantitated by gas chromatography of its 2 major constituents, benzyl cinnamate and benzyl benzoate. Several components of Balsam of Peru have been identified as allergens, including cinnamic acid, benzyl alcohol, and vanillin. The gel vehicle is polyvidone. This patch is formulated to contain 0.80 mg of Balsam of Peru resin per square centimeter, which corresponds to 0.65 mg of Balsam of Peru resin per patch. This resin is found in many cosmetics and perfumes and is also used as a flavoring agent in cough syrups, lozenges, chewing gum, and candies.

11. Ethylenediamine Dihydrochloride: Ethylenediamine dihydrochloride (purity $\geq 98.5\%$) is used to formulate this patch. The active allergenic component is ethylenediamine. The gel vehicle is methylcellulose. The product is formulated to contain 0.050 mg of ethylenediamine dihydrochloride per square centimeter, which corresponds to 0.018 mg of ethylenediamine per patch. Ethylenediamine is used as a stabilizer, emulsifier, and preservative in topical fungicides, antibiotic creams, eye drops, and nose drops.

12. Cobalt Dichloride: Cobalt dichloride hexahydrate (purity $\geq 98.5\%$) is used to formulate this patch. The active allergenic component is cobalt. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 0.020 mg of cobalt dichloride hexahydrate per square centimeter, which corresponds to 0.0040 mg of cobalt per patch. Cobalt is found in metal-plated objects and costume jewelry.

Panel 2.1 Allergens

13. *p*-tert-Butylphenol Formaldehyde Resin: *p*-tert-Butylphenol formaldehyde resin (purity $\geq 95\%$) is used to formulate this patch. The active allergenic components have been identified as *p*-tert-butylphenol formaldehyde and numerous other compounds. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 0.045 mg of *p*-tert-butylphenol formaldehyde resin per square centimeter, which corresponds to 0.036 mg of *p*-tert-butylphenol formaldehyde resin per patch. This resin is found in many waterproof glues used in the leather goods, furniture, and shoe industries.

14. Epoxy Resin: Epoxy resin, a clear viscous liquid, is used to formulate this patch. It consists of 73% to 80% diglycidylether of bisphenol A (the active allergenic component), which is a monomer used for the preparation of polymer epoxy resins. The remaining part consists of the dimer and the trimer. The gel vehicle is hydroxypropyl cellulose. This patch is formulated to contain 0.050 mg of epoxy resin per square centimeter, which corresponds to 0.032 mg of diglycidylether of bisphenol A per patch. This resin is found in adhesives, surface coatings, and paints.

15. Carba Mix: Carba mix contains 3 chemicals used to stabilize rubber products: diphenylguanidine (purity $\geq 96\%$), zincdibutyldithiocarbamate (purity $\geq 96\%$), and zincdiethyldithiocarbamate (purity $\geq 96\%$) in equal parts. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 0.25 mg of carba mix per square centimeter, which corresponds to 0.20 mg of carba mix per patch. These chemical stabilizers are found in almost all rubber products, many pesticides, and some glues.

16. Black Rubber Mix: Black rubber mix contains the antioxidant and antiozonate chemicals N-isopropyl-N'-phenyl paraphenylenediamine (purity $\geq 95\%$), N-cyclohexyl-N'-phenyl paraphenylenediamine (purity $\geq 90\%$), and N, N'-diphenyl paraphenylenediamine (purity $\geq 90\%$) in the ratio 2:5:5. The gel vehicle is polyvidone. The product is formulated to contain 0.075 mg of black rubber mix per square centimeter, which corresponds to 0.061 mg of black rubber mix per patch. The components of black rubber mix are found in almost all black rubber products, e.g., tires, handles, hoses.

17. Cl+ Me- Isothiazolinone: Cl+ Me- Isothiazolinone is an antibacterial preservative that consists of 2 active ingredients, 5-chloro-2-methyl-4-isothiazolin-3-one (1.05% to 1.25% w/w) and 2-methyl-4-isothiazolin-3-one (0.25% to 0.40% w/w) in a 3:1 ratio at a concentration of 1.5% in aqueous magnesium salts. The gel vehicle is polyvidone. The product is formulated to contain 0.0040 mg of Cl+ Me- isothiazolinone per square centimeter, which corresponds to 0.0032 mg of Cl+ Me- isothiazolinone per patch. This preservative is found in many shampoos, creams, lotions, and other skin care products.

18. Quaternium-15: Quaternium-15, 1-(3-chloroallyl)-3,5,7,-triaza-1-azonium-adamantane chloride (purity $\geq 94\%$), is a preservative. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 0.100 mg of Quaternium-15 per square centimeter, which corresponds to 0.081 mg of Quaternium-15 per patch. This preservative is found in creams, lotions, shampoos, soaps, and other cosmetics and skin care products.

19. Mercaptobenzothiazole: Mercaptobenzothiazole (purity $\geq 98.5\%$) is a vulcanization accelerator used in rubber products. The gel vehicle is polyvidone. The product is formulated to contain 0.075 mg of mercaptobenzothiazole per square centimeter, which corresponds to 0.061 mg of mercaptobenzothiazole per patch. This chemical is found in most rubber products, some adhesives, and is used as an industrial anticorrosive agent.

20. *p*-Phenylenediamine: *p*-Phenylenediamine (purity $\geq 97.5\%$), a blue-black aniline dye, is used to formulate this patch. The gel vehicle is polyvidone. The product is formulated to contain 0.090 mg

of *p*-phenylenediamine per square centimeter, which corresponds to 0.073 mg of *p*-phenylenediamine per patch. This dye is found most often in permanent and semipermanent hair dyes.

21. Formaldehyde: Formaldehyde is released from the proallergen N-hydroxymethyl succinimide, which is cleaved into succinimide and formaldehyde when it comes in contact with the transepidermal water on the surface of the skin. Formaldehyde is the active allergenic compound. The content of formaldehyde in the proallergen is 22.1% to 24.1%. The gel vehicle is polyvidone. The product is formulated to contain 0.18 mg of formaldehyde per square centimeter, which corresponds to 0.15 mg of formaldehyde per patch. Formaldehyde is found in many building materials and plastic industries.

22. Mercapto Mix: Mercapto mix is composed of 3 chemical accelerators that are benzothiazole sulfenamide derivatives. N-cyclohexylbenzothiazyl-sulfenamide (purity $\geq 85\%$), dibenzothiazyl disulfide (purity $\geq 97\%$), and morpholinylmercaptobenzothiazole (purity $\geq 85\%$) are present in equal parts. The gel vehicle is polyvidone. The product is formulated to contain 0.075 mg of mercapto mix per square centimeter, which corresponds to 0.061 mg of mercapto mix per patch. This group of chemicals is found in many rubber products, e.g., shoes, gloves, elastic.

23. Thimerosal: Thimerosal, USP (purity $\geq 97\%$) is a preservative that contains mercury. The gel vehicle is hydroxypropyl cellulose. The product is formulated to contain 0.0080 mg of thimerosal per square centimeter, which corresponds to 0.0065 mg of thimerosal per patch. Thimerosal is found in some cosmetics, nose drops, and eardrops.

24. Thiuram Mix: Thiuram mix is composed of 4 substances in equal parts; tetramethylthiuram monosulfide (purity $\geq 95\%$, contains small amounts of tetramethylthiuram disulfide), tetramethylthiuram disulfide (purity $\geq 95\%$, contains small amounts of tetramethylthiuram monosulfide); disulfiram, USP (tetraethylthiuram disulfide, purity $\geq 98.0\%$), and dipentamethylenethiuram disulfide (purity $\geq 95\%$, impurities unknown). The components of thiuram mix can chemically interact, resulting in the formation of mixed disulfides. Thiuram monosulfides and disulfides are the active allergens.

The gel vehicle is polyvidone. The product is formulated to contain 0.025 mg of thiuram mix per square centimeter, which corresponds to 0.0051 mg of tetramethylthiuram monosulfide, 0.0051 mg of tetramethylthiuram disulfide, 0.0051 mg of disulfiram, and 0.0051 mg of dipentamethylenethiuram disulfide per patch. These antimicrobial and antioxidant substances are found in almost all rubber products.

Panel 3.1 Allergens

25. Diazolidinyl urea (Germall® II): Diazolidinyl urea is a complex mixture. The gel vehicle is polyvidone. The product is formulated to contain 0.55 mg of diazolidinyl urea per square centimeter, which corresponds to 0.45 mg of diazolidinyl urea per patch. Diazolidinyl urea (Germall® II) is a preservative found in cosmetics.

26. Imidazolidinyl urea (Germall® 115): Imidazolidinyl urea, Imidurea USP, is a complex mixture. The gel vehicle is polyvidone. The product is formulated to contain 0.60 mg of imidazolidinyl urea per square centimetre, which corresponds to 0.49 mg of imidazolidinyl urea per patch. Imidazolidinyl urea (Germall® 115) is a preservative found in cosmetics.

27. Budesonide: Budesonide (purity $\geq 98.0\%$), is a corticosteroid. The gel vehicle is polyvidone. The product is formulated to contain 0.0010 mg of budesonide per square centimetre, which corresponds to 0.00081 mg of budesonide per patch. Budesonide is found in medical products. Patch testing with budesonide may be used to assist in the diagnosis of allergic contact dermatitis due to corticosteroids in Group B and to certain esters in Group D, based on the classification of topical corticosteroids by cross-reactivity.

28. Tixocortol-21-pivalate: Tixocortol-21-pivalate (purity $\geq 95\%$), is a corticosteroid. The gel vehicle is polyvidone. The product is formulated to contain 0.0030 mg of tixocortol-21-pivalate per square centimetre, which corresponds to 0.0024 mg of tixocortol-21-pivalate per patch. Tixocortol-21-pivalate is found in some medical products. Patch testing with tixocortol-21-pivalate may be used to assist in the diagnosis of allergic contact dermatitis due to corticosteroids in Group A, based on the classification of topical corticosteroids by cross-reactivity.

29. Quinoline mix: Quinoline mix is composed of 2 chemical germicides. Cloiquinol, USP (purity $\geq 93.0\%$) and clorquinaldol (purity $\geq 95\%$) are present in equal parts. The product is formulated to contain 0.19 mg of quinoline mix per square centimeter, which corresponds to 0.15 mg of quinoline mix per patch. The gel vehicle is polyvidone. Quinolines are found in paste bandages, medicated creams and ointments.

CLINICAL PHARMACOLOGY: A positive response to the patch test is a classical delayed cell-mediated hypersensitivity reaction (type IV), which normally appears within 9 to 96 hours after exposure.³ Following primary contact, an allergen penetrates the skin and binds covalently or noncovalently to epidermal Langerhans cells. The processed allergen is presented to helper T-lymphocytes, resulting in the release of lymphokines, including interleukin 2. Interleukin 2 stimulates the production of other lymphocytes, chemotactic factors that recruit macrophages, basophils, eosinophils, and migration inhibitory factor, all which induce macrophages to remain at the reaction site. The resulting inflammation produces a papular, vesicular, or bullous response with erythema and itching at the site of application.^{3,4}

Signs and symptoms of allergic contact dermatitis vary in intensity. Some patients may present with mild redness while others may present with severe swelling and bullae formation. Itching and vesiculation are common. The exposed areas of the skin, e.g., hands, forearm, face, neck, and dorsal surface of the feet, are primary initial sites of contact dermatitis. However, any area of the skin that comes into contact with a sensitizing allergen may also be affected.

The allergens in T.R.U.E. TEST were selected from those substances that have been widely reported to induce allergic contact dermatitis. They represent approximately 80% of the most common allergens. Nickel sulfate normally induces the greatest number of positive patch test responses when screening prospective patients. The frequency of positive responses to the various allergens can change depending upon the specific patient population as well as occupational and environmental influences. The epidemiology of allergic contact dermatitis and the frequency of positive patch test reactions to various causative allergens have been the subject of several extensive studies.^{1,3,5-7}

Clinical Studies: A basic description of the interpretation method used to evaluate the patch reactions obtained during the clinical studies is as follows. Please refer to the DOSAGE AND ADMINISTRATION: Interpretation section for a complete description of this evaluation method.

- ? Doubtful reaction
- + Weak (nonvesicular) positive reaction
- ++ Strong (vesicular) positive reaction
- +++ Extreme positive reaction
- Negative reaction
- IR Irritant reaction of different types

Six studies were done in North America to evaluate the clinical relevance of T.R.U.E. TEST. Patients with suspected allergic contact dermatitis, based on history or clinical signs, were tested in all studies. Results of each study are described below. Note that the doubtful (?) and irritant (IR) reaction scores were combined in most studies because of the difficulty in interpretation between these 2 types of reactions.

4 of the clinical studies were conducted using the T.R.U.E. TEST product that contained 24 allergen patches on Panel 1.1 and Panel 2.1. In the current product, Panel 1.1 and Panel 2.1, the configuration of the allergens has changed and a new panel 3.1 has been marketed. Quinoline mix, one of the original 12 allergens on Panel 1.1, was removed and replaced with a negative control patch. Quinoline mix now appears, reformulated in polyvidone, as one of the 5 allergens on Panel 3.1. Also, the positions of the epoxy resin and paraben mix patches have been changed on the panels. The change in allergen configuration should not affect the results of the reaction frequencies observed for T.R.U.E. TEST. Where there is allergen variation from the current patch, it is noted in the tables. Where there was a change in allergen vehicle, clinical studies were done to demonstrate equivalence. In the case of *p*-phenylenediamine, the patch was reformulated to utilize the base rather than the dihydrochloride form of the chemical. Dose response and irritation studies were used to support this reformulation. The results from the equivalency study done to compare the two formulations showed that *p*-phenylenediamine base give higher bioavailability than the dihydrochloride form. In the case of colophony, the patch was reformulated to stabilize the allergen. BHA and BHT were added as antioxidants. Results from the equivalence study to compare the stabilized formulation to the previous formulation showed no significant differences between the two formulations. BHA and BHT have been reported in the literature to be contact allergens. The allergen reaction frequency for BHA and BHT has been reported to be 0.2% and 0.1%, respectively.⁸ The concentration of BHA and BHT in the T.R.U.E. TEST colophony patch is 40 times less than that used in the referenced literature citation. Table 11 summarizes the data of reaction frequencies in the 4 studies and compares those frequencies to the results seen in the North American Contact Dermatitis Group (NACDG) studies.⁸⁻¹³ Data on adverse reactions and itching and burning at the patch test site from all 6 clinical studies are shown in Tables 17 and 18 in the ADVERSE REACTIONS section.

Study No. 1: This study was conducted by 6 independent investigators to demonstrate the performance of T.R.U.E. TEST Panel 1.1. A total of 128 patients with suspected contact dermatitis were recruited. Patients ranged in age from 17 to 79 years (mean age, 40.6 years). Females accounted for 86 (67%) of the 128 patients; 110 were Caucasian, 12 were African-American, and 6 were of other racial origin. The study period was approximately 8 months.

T.R.U.E. TEST Panel 1.1, containing 12 allergens, was applied to the patients back and remained there for 48 hours. The results were evaluated after 48, 72, or 96 hours.

Forty-five patients showed a total of 64 reactions to 11 of the 12 allergens in Panel 1.1. There were 18 weak (+), 37 strong (++) and 9 extreme (+++) positive reactions. There were positive test reactions to all allergens except chromium (see Table 1 below). In a follow-up of positive test reactors, 35% reported mild transient hyperpigmentation. No scarring was reported. Three patients required treatment for their reactions.

In all 128 patients there was good adhesion of the test tape to the skin. Some itching and burning sensations were reported (see Table 18). Such reactions are not unexpected and are considered a normal part of patch testing. Four patients (3%) experienced tape irritation.

Table 1: Allergen Reaction Frequencies Observed in Study No. 1

Allergen	+ (% Frequency)	++ (% Frequency)	+++ (% Frequency)	+,++,+++ Reaction Frequency(%)	IR/?	Missing
Nickel sulfate	8 (6.3)	9 (7.0)	4 (3.1)	16.4	1	
Neomycin sulfate	3 (2.3)	0	0	2.3	1	
Potassium dichromate	0	0	0	0	1	1
Caine mix	2 (1.6)	0	0	1.6	0	
Fragrance mix	1 (0.8)	7 (5.5)	1 (0.8)	7.1	1	
Colophony*	0	3 (2.3)	1 (0.8)	3.1	0	
Epoxy resin†	1 (0.8)	1 (0.8)	1 (0.8)	2.4	0	
Balsam of Peru‡	1 (0.8)	4 (3.1)	0	3.9	1	
Ethylenediamine dihydrochloride	0	2 (1.6)	0	1.6	0	
Cobalt dichloride	2 (1.6)	6 (4.7)	1 (0.8)	7.1	1	
p-Phenylenediamine§	§	§	§	§	§	§
Thiuram mix	0	5 (3.9)	1 (0.8)	4.7	0	

*Colophony vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone, and BHA and BHT have been added as antioxidants.

†Epoxy resin has been replaced by paraben mix on Panel 1.1 on the current format of allergens. Epoxy resin is on Panel 2.1 where paraben mix was previously.

‡Balsam of Peru vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

§*p*-Phenylenediamine patch is dihydrochloride salt, 0.050 mg/cm²; vehicle is hydroxypropyl cellulose. One patient experienced a 2+ reaction for a reaction frequency of 0.8%. Current patch is on Panel 2.1 and contains 0.090 mg of *p*-phenylenediamine base per square centimeter; vehicle is polyvidone.

|| Thiuram mix vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone. Current patch is on Panel 2.1.

Study No. 2: This study was done to evaluate the performance of T.R.U.E. TEST Panel 2.1. A total of 122 patients with suspected contact dermatitis were recruited. Patients ranged in age from 10 to 77 years (mean age, 41.2 years). Females accounted for 83 (68%) of the 122 patients; 107 were Caucasian, 14 were African-American, and 1 was of other racial origin. Five investigators participated in this study that was completed in approximately 8 months.

T.R.U.E. TEST Panel 2.1, containing 11 allergens and a negative control, was applied to the patient's back and remained there for 48 hours. The results were evaluated after 72 or 96 hours. Thirty-three patients showed a total of 47 positive test reactions: 19 weak (+), 25 strong (++), and 3 extreme (+++). There were positive responses to all of the allergens except quinoline mix and paraben mix (see Table 2 below). Healing times for positive reactions ranged from 2 to 21 days; 5 patients required treatment.

In 108 patients (89%) there was satisfactory adhesion of the test tape to the skin. In 14 patients (11%), however, tape adhesion was not satisfactory. This was subsequently attributed to the particular lot of adhesive used to manufacture the clinical test tape. One patient (0.8%) experienced a tape irritation.

Table 2: Allergen Reaction Frequencies Observed in Study No. 2

Allergen	+ (% Frequency)	++(% Frequency)	+++(% Frequency)	+, ++, +++ Reaction Frequency (%)	IR/?
Wool alcohols*	1 (0.8)	1(0.8)	0	1.6	0
Quinoline mix†	0	0	0	0	3
<i>p</i> -tert-Butylphenol formaldehyde resin	1 (0.8)	3 (2.5)	1 (0.8)	4.1	0

(continued on next page)

Table 2: Allergen Reaction Frequencies Observed in Study No. 2 (cont'd)

Allergen	+ (% Frequency)	++(% Frequency)	+++(% Frequency)	+, ++, +++ Reaction Frequency (%)	IR/?
Paraben mix [†]	0	0	0	0	2
Carba mix	2 (1.6)	0	0	1.6	2
Black rubber mix [§]	1 (0.8)	2 (1.6)	0	2.4	5
Cl+ Me- Isothiazolinone	3 (2.5)	1 (0.8)	0	3.3	1
Quaternium-15	2 (1.6)	5 (4.1)	0	5.7	1
Mercaptobenzothiazole	2 (1.6)	4 (3.3)	0	4.9	0
Mercapto mix	0	5 (4.1)	0	4.1	0
Thimerosal	7 (5.7)	4 (3.3)	2 (1.6)	10.6	3

*Wool alcohols is on current Panel 1.1.

[†]Quinoline mix has been replaced with a negative control patch on Panel 1.1 and transferred to current panel 3.1. The vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

[‡]Paraben mix has been replaced by epoxy resin on Panel 2.1 on the current format of allergens. Paraben mix is on Panel 1.1 where epoxy resin was previously.

[§]Black rubber mix vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

^{||}Mercaptobenzothiazole vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

Study No. 3: This study was conducted to demonstrate the performance of T.R.U.E. TEST Panels 1.1 and 2.1 in a North American patient population referred for patch testing. One hundred twenty-two patients were enrolled. Patients ranged in age from 13 to 76 years (mean age, 42.6 years). Females accounted for 89 (73%) of the 122 patients; 100 were Caucasian, 13 were African-American, and 9 were of other racial origin. Five investigators participated in this study that was completed in approximately 8 months.

T.R.U.E. TEST Panels 1.1 and 2.1, containing 24 allergens, were applied to the patient's back and remained there for 48 hours. The results were evaluated at either 72 or 96 hours after application.

Results show that 71 patients had a total of 122 positive test reactions: 50 weak (+), 58 strong (++), and 14 extreme (+++). Eleven patients demonstrated a total of 14 doubtful (?) reactions. Three patients experienced an irritant (IR) reaction. There were positive test responses to all of the allergens. See Table 3 below for distribution of allergen reactivities.

No unexpected adverse effects were reported. Healing times reported ranged from 1 to 34 days. Nineteen patients (16%) were prescribed medication to either promote healing or to relieve itching and/or burning sensations.

Two patients in this study reported reactions that are interpreted as possible sensitizations. One patient displayed a 1+ reaction to *p-tert*-butylphenol formaldehyde resin at a follow-up visit on day 25. A potential positive reaction to wool alcohols on day 23 was observed for the second patient, although no description of the reaction was recorded. Neither patient was retested to verify whether these delayed reactions were indeed sensitizations.

In 120 patients (98%) there was good adhesion of the test tape to the skin. Seven patients (6%) reported an irritation related to the tape adhesive. Few itching and burning events were reported.

Table 3: Allergen Reaction Frequencies Observed in Study No. 3

Allergen	+ (% Frequency)	++ (% Frequency)	+++ (% Frequency)	+, ++, +++ Reaction Frequency (%)	?	IR
1. Nickel sulfate	11 (9.2)	10 (8.3)	8 (6.7)	24.2	1	0
2. Wool alcohols	0	1 (0.8)	0	0.8	0	0
3. Neomycin sulfate	3 (2.5)	5 (4.2)	0	6.7	0	0
4. Potassium dichromate	1 (0.8)	1 (0.8)	1 (0.8)	2.4	1	0
5. Gaine mix	1 (0.8)	3 (2.5)	0	3.3	0	0
6. Fragrance mix	6 (5.0)	3 (2.5)	1 (0.8)	8.3	1	0
7. Colophony*	1 (0.8)	0	1 (0.8)	1.6	0	0
8. Epoxy resin†	1 (0.8)	0	0	0.8	0	0
9. Quinoline mix‡	0	2 (1.7)	0	1.7	2	0
10. Balsam of Peru	3 (2.5)	0	1 (0.8)	3.3	1	0
11. Ethylenediamine dihydrochloride	2 (1.7)	0	1 (0.8)	2.5	0	0

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Table 3: Allergen Reaction Frequencies Observed in Study No. 3 (cont'd)

Allergen	+ (% Frequency)	++ (% Frequency)	+++ (% Frequency)	+, ++, +++ Reaction Frequency (%)	?	IR
12. Cobalt dichloride	4 (3.3)	3 (2.5)	1 (0.8)	6.6	0	2
13. <i>p</i> - <i>tert</i> -Butylphenol formaldehyde resin	1 (0.8)	1 (0.8)	0	1.6	3	0
14. Paraben mix†	3 (2.5)	1 (0.8)	0	3.3	0	0
15. Carba mix	1 (0.8)	2 (1.7)	0	2.5	3	0
16. Black rubber mix	2 (1.7)	0	0	1.7	0	0
17. Cl+ Me- Isothiazolinone	1 (0.8)	2 (1.7)	0	2.5	0	0
18. Quaternium-15	0	6 (5.0)	0	5.0	0	0
19. Mercapto-benzothiazole§	1 (0.8)	0	0	0.8	0	0
20. <i>p</i> -Phenylenediamine¶	¶	¶	¶	¶	¶	¶
21. Formaldehyde	2 (1.7)	3 (2.5)	0	4.2	0	1
22. Mercapto mix	1 (0.8)	1 (0.8)	0	1.6	0	0
23. Thimerosal	3 (2.5)	10 (8.3)	0	10.8	1	0
24. Thiuram mix¶	2 (1.7)	4 (3.3)	0	5.0	1	0

*Colophony vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone, and BHA and BHT have been added as antioxidants.

†Epoxy resin has been replaced by paraben mix on Panel 1.1 on the current format of allergens. Epoxy resin is on Panel 2.1 where paraben mix was previously.

‡Quinoline mix has been replaced with a negative control patch on Panel 1.1 and transferred to current panel 3.1. The vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

[§]Mercaptobenzothiazole vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

^{||}*p*-Phenylenediamine patch tested in this study is dihydrochloride salt, 0.05 mg/cm²; vehicle is hydroxypropyl cellulose. Two patients experienced a 1+ reaction and three patients experienced a 2+ reaction for an overall reaction frequency of 4.2%. The current patch contains 0.090 mg of *p*-phenylenediamine base per square centimeter; vehicle is polyvidone.

[†]Thiuram mix vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

Study No. 4: An open, multicenter, within-patient study was done to evaluate the clinical relevance of T.R.U.E. TEST and to obtain information on late reactions and persistent local responses at a day 21 safety visit. A total number of 50 prospective patients with suspected contact dermatitis were recruited. The most common dermatitis site was hand, and the most common dermatitis type was allergic. Patients ranged in age from 19 to 82 years (mean age, 44.3 years). Females accounted for 36 (72%) of the 50 patients; 46 were Caucasian, 2 were African-American, and 2 were of other racial origin.

T.R.U.E. TEST Panels 1.1 and 2.1 were applied to the patient's back and remained there for 48 hours. The results were evaluated after 72, 96, 120, or 168 hours. The patch sites were re-examined after 21 days for persistent local responses and late reactions. No additional safety data were collected after 21 days.

The tape adhered perfectly in 45 patients. The incidence of itching and burning sensation was absent for 34 patients, mild for 14, and moderate for 2. One of 50 patients had a weak irritation from the test tape.

Thirty-two patients showed a total of 66 reactions to 21 of the 24 allergens included in T.R.U.E. TEST (see Table 4 below). The following allergens gave no reactions: caine mix, epoxy resin, and quinoline mix. The allergen that gave most reactions was nickel sulfate, 9/66 (13.6%) reactions. Quaternium-15 showed 7/66 (10.6%) reactions, and fragrance mix, Balsam of Peru, cobalt dichloride, formaldehyde, and thimerosal showed 5/66 (7.6%) reactions each.

Eight patients had a total of 10 persistent local responses at the day 21 examination. One of these patients had a late reaction, a 2+ reaction to Cl+ Me- isothiazolinone, moderate erythema, and a persistent local response. There were no other adverse events reported in this study.

Table 4: Allergen Reaction Frequencies Observed in Study No. 4

Allergen	+ (% Frequency)	++ (% Frequency)	+++ (% Frequency)	+, ++, +++ Reaction Frequency (%)	?	ME*
1. Nickel sulfate	4 (8.0)	5 (10.0)	0	18.0	0	0
2. Wool alcohols	1 (2.0)	0	0	2.0	0	0
3. Neomycin sulfate	2 (4.0)	0	0	4.0	0	0

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Table 4: Allergen Reaction Frequencies Observed in Study No. 4 (cont'd)

Allergen	+ (% Frequency)	++ (% Frequency)	+++ (% Frequency)	+, ++, +++ Reaction Frequency (%)	?	ME*
4. Potassium dichromate	1 (2.0)	1 (2.0)	0	4.0	0	0
5. Caine mix	0	0	0	0	0	0
6. Fragrance mix	1 (2.0)	1 (2.0)	0	4.0	0	3
7. Colophony [†]	1 (2.0)	0	1 (2.0)	4.0	0	0
8. Epoxy resin [‡]	0	0	0	0	0	0
9. Quinoline mix [§]	0	0	0	0	0	0
10. Balsam of Peru	3 (6.0)	2 (4.0)	0	10.0	0	0
11. Ethylenediamine dihydrochloride	1 (2.0)	1 (2.0)	0	4.0	0	0
12. Cobalt dichloride	5 (10.0)	0	0	10.0	0	0
13. <i>p-tert</i> -Butylphenol formaldehyde resin	1 (2.0)	1 (2.0)	0	4.0	0	0
14. Paraben mix [‡]	1 (2.0)	0	0	2.0	0	0
15. Carba mix	0	1 (2.0)	0	2.0	0	0
16. Black rubber mix	0	0	0	0	0	1
17. Cl+ Me- Isothiazolinone	0	1 (2.0)	0	2.0	0	0
18. Quaternium-15	5 (10.0)	2 (4.0)	0	14.0	0	0

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Table 4: Allergen Reaction Frequencies Observed in Study No. 4 (cont'd)

Allergen	+ (% Frequency)	++ (% Frequency)	+++ (% Frequency)	+, ++, +++ Reaction Frequency (%)	?	ME*
19. Mercapto-benzothiazole	1 (2.0)	0	0	2.0	0	0
20. <i>p</i> -Phenylenediamine	2 (4.0)	0	0	4.0	0	0
21. Formaldehyde	3 (6.0)	2 (4.0)	0	10.0	0	0
22. Mercapto mix	2 (4.0)	0	0	4.0	0	1
23. Thimerosal	2 (4.0)	2 (4.0)	1 (2.0)	10.0	0	0
24. Thiuram mix	4 (8.0)	0	0	8.0	0	0

*Macular erythema only.

†Colophony vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone, and BHA and BHT have been added as antioxidants.

‡Epoxy resin has been replaced by paraben mix on Panel 1.1 on the current format of allergens. Epoxy resin is on Panel 2.1 where paraben mix was previously.

§Quinoline mix has been replaced with a negative control patch on Panel 1.1 and transferred to current panel 3.1. The vehicle is hydroxypropyl cellulose; vehicle in current patch is polyvidone.

Study No. 5: This study was conducted to demonstrate the performance of T.R.U.E. TEST panel 3.1 allergens diazolidinyl urea (DU) and imidazolidinyl urea (IMID) for diagnosing allergic contact dermatitis in a North American patient population. Comparison of allergen reactivity between allergens in T.R.U.E. TEST and allergens in petrolatum were made.

One hundred thirty patients were enrolled and included consecutive patients (n=100) with a clinical history consistent with allergic contact dermatitis together with patients with a positive patch test reaction to petrolatum-based DU (n=15) and IMID (n=15) allergens in the past 5 years and clinical history of allergic contact dermatitis. Patients ranged in age from 19 to 86 years (mean age, 52.5 years). Females accounted for 88 (68%) of the 130 patients; 110 were Caucasian, 17 were African-American, 1 was Asian and 2 were Hispanics. One investigator participated in this study that was completed in approximately 5 months.

T.R.U.E. TEST Panel 3.1 DU and IMID allergens were applied to the patient's back and remained there for 48 hours. Patch test reactions were evaluated 3-4 days and again 7 days after application using the study endpoints including measurements of positive reaction frequencies, specificity, sensitivity, concordance and discordance as shown in Tables 5 to 7. 21 days after application the

patients were examined for late reactions and persistent local responses. No late reactions were observed to any of the patches. A persistent reaction (mild pruritus) to both the DU- and IMID-patch was observed in one subject. A total of 50 patients experienced from mild (n=34), moderate (n=15) to severe (n=1) itching or burning sensations at Day 2; however this observation includes also the reference petrolatum product. A total of 22 patients experienced from weak (n=12) to moderate (n=10) tape irritation at Day 2; again this observation also includes the reference petrolatum product. A total of 18 adverse events in 17 patients were reported where only 4 of them were related to the test tape (dermatitis flare, rash and mild pruritus) and the remaining 14 adverse events were not related to the study product. All events related to the test tape were resolved after 1 to 20 days. There were no serious adverse events reported. No patients experienced irritation to any of the patches. On one of the consecutive patients the test tape fell off after 24 hours; this patient was included in the final calculation of results as one of the patients reacting negative to both patches.

Table 5: Positive Reactions Observed to T.R.U.E. TEST DU and IMID Allergens in Study No. 5

		T.R.U.E. TEST diazolidinyl urea (DU)	T.R.U.E. TEST imidazolidinyl urea (IMID)
Previously positive patients	Positive to DU (n=15)	6	4
	Positive to IMID (n=15)	6	4
Consecutive patients (n=100)		7	4
Total Positives (% Frequency, n=130)		19 (15%)	12 (9%)
Frequency 95% Confidence Interval		9%-21%	4%-14%

Reactions were compared between T.R.U.E. TEST DU and IMID allergens and their corresponding petrolatum-based allergens in all tested patients. As shown in Table 6 below the overall concordance of positive and negative reactions was 87% for DU and 93% for IMID. The overall discordance of positive and negative reactions was 14% for DU and 7% for IMID. For DU, 10 of 18 (55%) positive reactions were concordant between T.R.U.E. TEST and the petrolatum-based allergen. For IMID, 11 of 19 (58%) positive reactions were concordant between T.R.U.E. test and the petrolatum-based allergen.

Table 6: Comparison of Reactions between T.R.U.E. TEST and Petrolatum-Based Allergens in Study No. 5

A. Diazolidinyl urea (DU)

Number of subjects		Petrolatum-based DU		
		Neg	Pos	Sum
T.R.U.E	Neg	103	8	111
Test	Pos	9	10	19
DU	Sum	112	18	130

Concordance (95% Confidence Interval) = 87% (81%-93%)

Discordance (95% Confidence Interval) = 14% (8%-20%)

B. Imidazolidinyl urea (IMID)

Number of subjects		Petrolatum-based IMID		
		Neg	Pos	Sum
T.R.U.E	Neg	110	8	118
Test	Pos	1	11	12
IMID	Sum	111	19	130

Concordance (95% Confidence Interval) = 93% (89%-97%)

Discordance (95% Confidence Interval) = 7% (3%-11%)

As shown in Table 7, the T.R.U.E. TEST DU and IMID diagnostic sensitivity is 56% and 58%, and specificity is 92% and 99%, respectively. Although the sensitivity of T.R.U.E. TEST DU and IMID positive reactions was lower than expected, these data are consistent with other studies comparing T.R.U.E. TEST and petrolatum-based allergens where concordance has ranged from 57-78%, depending on the allergen and study design^{14,15}. In addition, in a recently published study, only 71% (5 of 7) of DU-sensitive patients gave concordant reactions at retest when using commercially available petrolatum test materials.¹⁶

Table 7: Sensitivity and Specificity Estimates for T.R.U.E. TEST DU and IMID Allergens in Study No. 5

	Diazolidinyl urea (DU)	Imidiazolidinyl urea (IMID)
Sensitivity (95% Confidence Interval)	56% (31%-78%)	58% (34%-79%)
Specificity (95% Confidence Interval)	92% (85%-96%)	99% (94%-99.9%)

Sensitivity: the number of true positives (correctly diagnosed sensitive subjects) divided by number of true positives plus the number of false negatives.

Specificity: the number of true negatives divided by the number of true negatives plus the number of false positives.

Study No. 6: This study was conducted to demonstrate the performance of T.R.U.E. TEST panel 3.1 allergens tixocortol-21-pivalate (TIX) and budesonide (BUD) for diagnosing allergic contact dermatitis in a North American patient population. Comparison of allergen reactivity between allergens in T.R.U.E. TEST and allergens in petrolatum were made.

The enrolled test population included consecutive patch-test patients (n=100) with a clinical history consistent with allergic contact dermatitis. Patients with a positive patch test reaction to petrolatum-based TIX (n=9) and BUD (n=19) allergens in the past 5 years and clinical history of allergic contact dermatitis were also recruited. Patients ranged in age from 20 to 83 years (mean age, 51.3 years). Females accounted for 81 (63%) of the 128 patients; 112 were Caucasian, 15 were African-American, and 1 was Asian. Two investigators participated in this study that was completed in approximately 4 months.

T.R.U.E. TEST Panel 3.1 TIX and BUD allergens were applied to the patient's back and remained there for 48 hours. Patch test reactions were evaluated 3-4 days and again 7 days after application using the study endpoints including measurements of positive reaction frequencies, specificity, sensitivity, concordance and discordance as shown in Tables 8 to 10. 21 days after application the patients were examined for late reactions and persistent local responses. No late reactions were observed to any of the patches. 16 persistent reactions (3 erythema (mild), 1 infiltration (mild), 7 hyperpigmentation (4 mild, 3 moderate), 3 pruritus and 2 others (mild)) were observed in 6 subjects. A total of 50 patients experienced from mild (n=37), moderate (n=11) to severe (n=2) itching or burning sensations at Day 2. A total of 51 patients experienced from mild (n=40), moderate (n=10) to strong (n=1) tape irritation at Day 2. A total of 16 adverse events in 14 patients were reported where only 1 of them was related to the test tape (mild pruritus) and the remaining 15 adverse events were not related to the study product. Duration of adverse events was in average 9 days (4 to 14), 4 were ongoing when study was completed. There were no serious adverse events reported. No patients experienced irritation to any of the patches. On six of the consecutive patients the test

tape fell off before the second visit; these patients were withdrawn and are only part of the safety analysis. So in the final efficacy calculation of the results shown in Table 8 – 10 in total 122 patients participated.

Table 8: Positive Reactions Observed to T.R.U.E. TEST TIX and BUD Allergens in Study No. 6

		T.R.U.E. TEST tixocortol-21-pivalate (TIX)	T.R.U.E. TEST budesonide (BUD)
Previously positive patients	Positive to TIX (n=9)	8	3
	Positive to BUD (n=19)	5	12
Consecutive patients (n=94)		3	2
Total Positives (% Frequency, n=122)		16 (13%)	17 (14%)
Frequency 95% Confidence Interval		7%-19%	8%-20%

Reactions were compared between T.R.U.E. TEST TIX and BUD allergens and their corresponding petrolatum-based allergens in all tested patients. As shown in Table 9 below the overall concordance of positive and negative reactions was 95% for TIX and 97% for BUD. The overall discordance of positive and negative reactions was 5% for TIX and 3% for BUD. For TIX, 12 of 14 (86%) positive reactions were concordant between T.R.U.E. TEST and the petrolatum-based allergen. For BUD, 15 of 17 (88%) positive reactions were concordant between T.R.U.E. test and the petrolatum-based allergen.

Table 9: Comparison of Reactions between T.R.U.E. TEST and Petrolatum-Based Allergens in Study No. 6

A. Tixocortol-21-pivalate (TIX)

Number of subjects		Petrolatum-based TIX			
		Neg	Pos	Sum	
T.R.U.E. Test	Neg	104	2	106	
	Pos	4	12	16	
TIX		Sum	108	14	122

Concordance (95% Confidence Interval) = 95% (93% - 99%)

Discordance (95% Confidence Interval) = 5% (1% - 9%)

B. Budesonide (BUD)

Number of subjects		Petrolatum-based BUD			
		Neg	Pos	Sum	
T.R.U.E. Test	Neg	103	2	105	
	Pos	2	15	17	
BUD		Sum	105	17	122

Concordance (95% Confidence Interval) = 97% (94% - 99.8%)

Discordance (95% Confidence Interval) = 3% (0.2% - 6%)

As shown in Table 10, the T.R.U.E. TEST TIX and BUD diagnostic sensitivity is 86% and 88%, and specificity is 96% and 98%, respectively. The high sensitivity reported here agrees with the data from the European studies, where the sensitivity for both T.R.U.E. TEST TIX and BUD were 100% in phase II as well as phase III studies.¹⁷

Table 10: Sensitivity and Specificity Estimates for T.R.U.E. TEST TIX and BUD Allergens in Study No. 6

	Tixocortol-21-pivalate (TIX)	Budesonide (BUD)
Sensitivity (95% Confidence Interval)	86% (56%-98%)	88% (62%-98%)
Specificity (95% Confidence Interval)	96% (90%-99%)	98% (93%-99.7%)

Sensitivity: the number of true positives (correctly diagnosed sensitive subjects) divided by number of true positives plus the number of false negatives.

Specificity: the number of true negatives divided by the number of true negatives plus the number of false positives.

These studies demonstrate that T.R.U.E. TEST is a clinically relevant method for diagnosing allergic contact dermatitis. The persistent local responses, as well as the occurrence of late reactions, are within the normal range expected for patch testing. Although there are no specific data, in general, more severe positive reactions can be expected to require longer healing times. Of course, healing time can be influenced by many factors, especially the general health of the patient.

To further demonstrate the clinical relevance of the T.R.U.E. TEST method for diagnosing allergic contact dermatitis, a comparison was made to data in a screening tray recommended by the NACDG.⁸⁻¹³ The frequency of reactivities observed in the first four North American clinical studies have been summarized in Table 11.¹⁷

Also listed in Table 11 are the frequencies of reactivity for allergens⁸ in a screening tray recommended by the NACDG.⁸⁻¹³ These data were collected over 2 years by the NACDG members after testing 3549 patients with suspect contact dermatitis. Thirty-eight percent (38%) of the patients tested were male. The average age of the patients was 46 years (range, 3 to 92 years).⁸

Additional data on allergen reaction frequencies using the T.R.U.E. TEST method have been collected on data collection forms in a postmarketing survey. These reaction frequencies are also included in Table 11 and further support the data from the clinical trials using this method.

These data in Table 11 demonstrate that most allergens have very similar reactivities in the 2 methods. Differences noted are most likely due to patient selection in the clinical trials and to the fact that there is approximately a 10-fold difference in size between the sample populations of the 4 North American clinical studies and the NACDG patients. Nickel sulfate, thimerosal, Quaternium-15, formaldehyde, thiuram mix, and Balsam of Peru are the most commonly reported reactive allergens in both series. Average concordance in clinical studies that tested both the T.R.U.E. TEST method and allergens in petrolatum ranged from 60% to 77%.¹⁷

Table 11: Comparison of Allergen Reactivity Between Allergens in T.R.U.E. TEST and Allergens in Petrolatum

Frequency of Allergen Reactions for T.R.U.E. TEST Panels 1.1 and 2.1				North American Contact Dermatitis Group (NACDG)		
Allergen	Postmarketing Survey (n = 2356)	Four North American Multicenter Studies		Responses to Allergens in Screening Tray ⁸		
	Frequency (%)	n	Frequency (%)	Allergen (% in petrolatum)	n	Frequency (%)
1. Nickel sulfate	17.7	300	19.7	Nickel sulfate, 2.5%	3491	14.3
2. Wool alcohols	2.5	294	1.4	Wool (wax) alcohols, 30%	3528	2.9
3. Neomycin sulfate	7.3	300	4.3	Neomycin sulfate, 20%	3518	9.0
4. Potassium dichromate	5.2	300	1.7	Potassium dichromate, 0.25%	3497	2.0

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Table 11: Comparison of Allergen Reactivity Between Allergens in T.R.U.E. TEST and Allergens in Petrolatum (cont'd)

Frequency of Allergen Reactions for T.R.U.E. TEST Panels 1.1 and 2.1				North American Contact Dermatitis Group (NACDG)		
Allergen	Postmarketing Survey (n = 2356)	Four North American Multicenter Studies		Responses to Allergens in Screening Tray ⁸		
	Frequency (%)	n	Frequency (%)	Allergen (% in petrolatum)	n	Frequency (%)
5. Caine mix	3.9	300	2.0	Benzocaine, 5%*	3524	2.2
6. Fragrance mix	6.8	300	7.0	Cinnamic aldehyde, 1%†	3528	2.7
7. Colophony	2.8	300	2.7	Colophony, 20%	3520	1.9
8. Epoxy resin	3.0	300	1.3	Epoxy resin, 1%	3500	1.8
9. Quinoline mix‡	1.8	294	0.68			
10. Balsam of Peru	2.8	300	4.7	Balsam of Peru, 25%	3496	7.5
11. Ethylenediamine dihydrochloride	4.7	300	2.3	Ethylenediamine dihydrochloride, 1%	3525	2.8
12. Cobalt dichloride	5.6	300	7.3			
13. <i>p-tert</i> -Butylphenol formaldehyde resin	3.1	294	3.1	<i>p-tert</i> -Butylphenol formaldehyde resin, 1%	3499	1.7
14. Paraben mix	2.3	294	1.7			
15. Carba mix	5.9	294	2.0	Carba mix, 3%	3524	4.8
16. Black rubber mix	3.1	294	1.7	Black rubber mix (PPD mix 0.6%)	3492	2.1
17. Cl+ Me- Isothiazolinone	4.7	294	2.7			
18. Quaternium-15	11.1	294	6.8	Quaternium-15, 2%	3500	9.6

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Table 11: Comparison of Allergen Reactivity Between Allergens in T.R.U.E. TEST and Allergens in Petrolatum (cont'd)

Frequency of Allergen Reactions for T.R.U.E. TEST Panels 1.1 and 2.1				North American Contact Dermatitis Group (NACDG)		
Allergen	Postmarketing Survey (n = 2356)	Four North American Multicenter Studies		Responses to Allergens in Screening Tray ⁸		
	Frequency (%)	n	Frequency (%)	Allergen (% in petrolatum)	n	Frequency (%)
19. Mercaptobenzothiazole	2.0	294	2.7	Mercaptobenzothiazole, 1%	3525	1.8
20. <i>p</i> -Phenylenediamine [§]	7.6	50	4.0	<i>p</i> -Phenylenediamine, 1%	3515	6.3
21. Formaldehyde [§]	9.0	172	5.8	Formaldehyde, 1% aqueous	3526	7.8
22. Mercapto mix	3.1	294	3.1	Mercapto mix, 1%	3497	2.6
23. Thimerosal	9.5	294	10.5	Thimerosal, 0.1%	3472	10.6
24. Thiuram mix	5.4	300	5.3	Thiuram mix, 1%	3522	7.7
				Imidazolidinyl urea, 2% aq.	3523	1.9

*T.R.U.E. TEST contains caine mix, which is a mixture of benzocaine, dibucaine hydrochloride, and tetracaine hydrochloride.

†Compare with fragrance mix in T.R.U.E. TEST.

‡Quinoline mix has been transferred to panel 3.1 and replaced with a negative control patch in T.R.U.E. TEST panel 1.1.

§Formaldehyde reflects data from studies 3 and 4 and *p*-Phenylenediamine from study 4.

Nickel Use Test: Results from another clinical trial, a nickel use test, are described below.

A study was performed to investigate the relationship between reactions caused by a natural sensitizer, such as nickel-containing costume jewelry, and T.R.U.E. TEST. Nickel is often implicated as a major cause of cutaneous reactions to jewelry.¹⁸

Fifty-one patients with history of cutaneous reactions to jewelry were tested with T.R.U.E. TEST Panel 1.1 (identical to that used in study no. 1). A medallion containing approximately 20% nickel served

as a positive control and a stainless steel earring post was intended to serve as a negative control. It was subsequently discovered that the earring post contained up to 14% nickel on the outer surface.

Patients ranged in age from 16 to 68 years (mean age, 39.3 years). Females accounted for 50 (98%) of the 51 patients and, except for 1 Mexican-American, all were Caucasian. One patient was excluded from the evaluation because of a dislocation of the test. In addition, 12 patients (24%) reported minor problems with the test adhering properly to the skin. This was subsequently attributed to a particular lot of adhesive used to manufacture the clinical test lot. Seven patients (14%) experienced a tape irritation. Thirty-six of the remaining 50 patients (72%) experienced a total of 51 reactions to various T.R.U.E. TEST patches as shown below.

Table 12: Allergen Reactions Observed in the Nickel Use Test

Allergen	Reactions	Frequency (%)
Nickel sulfate	31	60.8
Cobalt dichloride	7	13.7
Fragrance mix	2	3.9
p-Phenylenediamine	1	2.0
Neomycin sulfate	3	5.9
Colophony	3	5.9
Epoxy resin	1	2.0
Thiuram mix	2	3.9
Caine mix	1	2.0

These reactions generally resolved within an average of 10 days (range, 2 to 42 days) with the following frequencies: 1 to 10 days (22), 11 to 20 days (9), 21 to 30 days (1), 31 to 45 days (1). The time of resolution for three patients is not available.

A further breakdown of the positive results obtained with the T.R.U.E. TEST nickel sulfate patch, the medallion, and the earring post is presented below.

Table 13: Positive Reactions Observed in the Nickel Use Test

	+	++	+++	Total
T.R.U.E. TEST	13	15	3	31
Medallion	10	11	0	21
Earring Post	2	4	0	6

If the results obtained with the medallion were used as the only basis for determining the presence of contact sensitivity to nickel, then the T.R.U.E. TEST nickel patch would demonstrate the following characteristics:

Table 14: Medallion vs. T.R.U.E. TEST Nickel Patch Comparison

	Medallion			Total
		+	-	
T.R.U.E. TEST	+	20	11	31
Nickel Patch	-	1	18	19
	Total	21	29	50

Sensitivity: 95.2%.

Specificity: 62.1%.

Predictive value of a positive test: 64.5%.

Predictive value of a negative test: 94.7%.

Test efficiency: 76.0%.

In addition, 35.4% of the T.R.U.E. TEST nickel patch positive results would have been considered false positives and 5.3% would have been considered false negatives. However, the results obtained in this study should be interpreted with caution. The metal composition of jewelry can vary greatly from manufacturer to manufacturer and thereby alter the bioavailability of the causative allergen. A different medallion could have produced either a greater or lesser correlation with T.R.U.E. TEST nickel patch. Of the 21 medallion positive patients, 20 also demonstrated a positive response to T.R.U.E. TEST nickel patch and the 1 other patient demonstrated a doubtful (?) T.R.U.E. TEST response. In addition, 18 of the 21 medallion responders (85.7%) experienced reactions with T.R.U.E. TEST greater than or equal to the medallion reaction. T.R.U.E. TEST demonstrated excellent sensitivity in detecting patients who had positive responses to the medallion. The comparatively large number of additional nickel positive results obtained with T.R.U.E. TEST may, in fact, be true positives unresponsive to the particular medallion used in this study, although false-positive reactions cannot be ruled out.

Colophony study: Results from another clinical trial, a colophony bioequivalence study, are described below. A study was performed to evaluate the bioequivalence of a previous formulation of colophony, which used a vehicle of hydroxypropyl cellulose, with the currently marketed formulation of colophony, which uses polyvidone as a vehicle and contains BHA and BHT as antioxidants.

Sixteen patients known to be sensitive to colophony and 112 consecutive patients with suspected allergic contact dermatitis were tested with both formulations of colophony. The study was designed to evaluate the bioequivalence of the new stabilized colophony patch versus previously marketed colophony patch formulation. Two separate batches of stabilized versus nonstabilized colophony were evaluated on each patient.

Patients ranged in age from 18 to 79 years (mean age, 41 years). Females accounted for 87 (68%) of the 128 patients and, except for 1 Hispanic and 1 Asian patient, all were Caucasian. 26 patients reported tape irritation (20.3%), and the tape adhered perfectly in all but 1 patient. A breakdown of the positive responses is presented below.

Table 15: Reactions Observed in Colophony Study

	-	IR/?	+	++	+++
Lot 1	0	0	6	12	0
Lot 1 + BHA/BHT	0	1	9	8	0
Lot 2	1	2	4	11	0
Lot 2 + BHA/BHT	1	3	6	8	0

Several studies have been conducted to demonstrate the clinical reproducibility of results obtained with 3 different production runs of representative allergens. These data are summarized below and demonstrate excellent reproducibility of in vivo responses to different production lots of these allergens. No significant safety concerns were noted in these studies, although no safety data were collected after 21 days.

Table 16: Reaction Frequencies Observed in Lot-to-Lot Consistency Studies

Allergen	Lot no.	-	IR/?	+	++	+++
Nickel sulfate	1	1	0	1	11	0
	2	0	0	2	11	0
	3	1	0	2	10	0
Epoxy resin	1	0	0	3	8	2
	2	0	0	3	7	3
	3	0	0	3	7	3
Balsam of Peru	1	1	0	2	7	1
	2	1	0	2	7	1
	3	1	0	2	7	1
Ethylenediamine dihydrochloride	1	0	0	0	7	6
	2	0	0	0	7	6
	3	0	0	0	7	6
Black rubber mix	1	2	1	4	4	2
	2	2	0	4	5	2
	3	2	0	5	4	2

(continued on next page)

Table 16: Reaction Frequencies Observed in Lot-to-Lot Consistency Studies (cont'd)

Allergen	Lot no.	-	IR/?	+	++	+++
Cl+ Me-Isothiazolinone	1	1	0	1	4	6
	2	1	1	0	4	6
	3	1	0	1	4	6
p-Phenylenediamine	1	1	0	3	4	3
	2	1	0	3	4	3
	3	1	0	2	5	3
Thiuram mix	1	2	0	2	7	1
	2	2	1	1	7	1
	3	2	0	2	7	1
Cobalt dichloride	1	2	0	1	5	1
	2	2	0	2	4	1
	3	2	0	1	5	1

INDICATIONS: T.R.U.E. TEST is indicated primarily as an aid in the diagnosis of allergic contact dermatitis in patients whose histories suggest sensitivity to 1 or more of the substances included on the T.R.U.E. TEST panels. To determine whether sensitization to an allergen may be etiologically important, T.R.U.E. TEST may also be used adjunctively to evaluate other eczemas (atopic, seborrheic, venous, palmar, and plantar hyperkeratotic eczema, vesiculosis, or neurodermatitis) and other dermatologic diseases that do not heal, such as leg ulcers and psoriasis, to determine whether there may be a contact hypersensitivity component.^{3,7,19}

CONTRAINDICATIONS: The minor amount of allergen on each T.R.U.E. TEST patch that penetrates the skin will rarely induce a flare-up of dermatitis. In the case of extensive ongoing contact dermatitis, however, the test should not be applied since it may provoke an intensified reaction on both the present and previously affected sites and may also cause a false-positive test result.

WARNINGS: The use of T.R.U.E. TEST in patients with a known history of severe systemic and/or local reactions to any of the allergen components or inactive substances included in the T.R.U.E. Test panels should be carefully evaluated before application.

Patients should be warned that itching and burning sensations are common occurrences with patch testing and may be severe in extremely sensitive patients. The use of medication may be considered necessary to relieve these itching or burning sensations.

Sensitization to a substance included on the test panel may occur with patch testing but is extremely rare. A test reaction that appears 7 days or later with no preceding reaction may be a sign of contact sensitization.⁷

Dermatitis flare-up may occur in some patients.

Occasionally, hyperpigmentation of the test site occurs during healing. Healing with or without medication normally takes place within 5 days to 2 weeks, although reactions in some individuals may persist longer.

Extremely sensitive patients may exhibit extreme (+++) reactions that may be bullous or ulcerative with pronounced erythema, infiltration, and coalescing vesicles.

Excited skin syndrome (angry back) is a state of hyperreactivity induced by a dermatitis on other parts of the body or by a strong positive skin-test reaction.²⁰

Therefore, test results should be evaluated carefully in patients with multiple, positive, concomitant patch test results. To determine which reactions are false positives, retesting at a later date may be considered.

The safety and efficacy of repetitive testing with T.R.U.E. TEST is unknown. Sensitization or increased reactivity to 1 or more of the allergens may occur. The benefits of repeat testing should therefore be carefully evaluated against the possible risks.

On rare occasions, it may be necessary to remove the test strip from the patient because of severe itching or burning sensations. One patient taking part in the clinical studies removed the test tape after 24 hours because of severe itching.

Formaldehyde is a known carcinogen. Nickel sulfate, potassium dichromate, epoxy resin, cobalt dichloride, and thiuram mix are suspected carcinogens. The potential effects associated with using very low concentrations of these substances for single or multiple applications are currently unknown.^{21,22}

PRECAUTIONS:

General: T.R.U.E. TEST may be applied throughout the year. However, during the summer months, excessive sweating is to be avoided in order to maintain sufficient adhesion to the skin. In addition, exposure to the sun should be minimized in order to prevent a sun-induced skin reaction that may interfere with interpretation of test results.

T.R.U.E. TEST should only be applied to healthy skin that is free of acne, scars, dermatitis, or any other condition that may interfere with interpretation of test results.

Since steroids may suppress a positive test reaction, use of topical steroids on the test site or oral steroids (equivalent to 15 mg of prednisolone) should be discontinued for at least 2 weeks prior to testing. Topical steroids on nontest areas may be appropriate.

If a severe patch test reaction develops, the patient may be treated with a topical corticosteroid or, in rare cases, with a systemic corticosteroid.

Information for Patients: Patients should be instructed to avoid extreme physical activity and/or mechanical action that may result in reduced adhesion or actual loss of patch test material. Use appropriate measures to avoid getting the area around the patch wet.

Patients should also be advised that a strong allergic response to 1 or more test allergens can be associated with significant itching, burning, erythema, and vesiculation. Patients who experience intense discomfort should contact their physicians concerning possible removal of the test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies of T.R.U.E. TEST to evaluate carcinogenic potential, mutagenesis, or impairment of fertility have not been performed. Nickel refinery dust, nickel sulfite, and formaldehyde are known carcinogens. Nickel sulfate, potassium dichromate, cobalt dichloride, epoxy resin, and thiuram mix are suspected carcinogens. The potential effects of using very low concentrations of these substances for single or multiple applications are currently unknown.^{21,22} The following components of T.R.U.E. TEST have been reviewed as part of the Cosmetic Ingredient Review and found to be safe or safe with qualifications: those found to be safe are hydroxypropyl cellulose, methylcellulose, wool alcohols, paraben mix, Quaternium-15, and *p*-phenylenediamine and those found to be safe with qualifications are *N*-phenyl-*p*-phenylenediamine, Cl+ Me- isothiazolinone, butylhydroxyanisole, and formaldehyde.²³

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with T.R.U.E. TEST. It is also not known whether T.R.U.E. TEST can cause fetal harm when administered to pregnant women or whether it can affect reproduction capacity. T.R.U.E. TEST should be applied to pregnant women only if clearly needed.

Nursing Mothers: No studies have been performed to evaluate absorption of T.R.U.E. TEST allergens in nursing mothers. It is not known if T.R.U.E. TEST allergens appear in human milk. Because many drugs are excreted in human milk, caution should be exercised when T.R.U.E. TEST is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of T.R.U.E. TEST in children have not been established.

Geriatric Use: Postmarketing clinical studies of T.R.U.E. TEST did not include sufficient numbers of subjects age 65 years and over to determine whether they respond differently from younger subjects.²⁴ However, more frequent patch test responses can be expected in geriatric patients. While no conclusive explanation is available, older patients may exhibit an increased frequency of cutaneous allergies.^{10,12}

ADVERSE REACTIONS: Adverse reactions reported with the use of T.R.U.E. TEST and patch testing in general are normally mild and usually occur only at the site of the test application. Table 17 summarizes the adverse reactions recorded in the 8 clinical studies described in the CLINICAL PHARMACOLOGY section.

Table 17: Adverse Reactions Reported During Patient Follow-Up*

Event Reported	Number of Events Reported							
	Study 1 n† = 33	Study 2 n‡ = 102	Study 3 n‡ = 104	Study 4 n† = 32	Nickel Use n† = 31	Colophony n = 128	Study 5 n† = 21	Study 6 n† = 26
Erythema	2	2	27	2	-	8	-	3
Dermatitis flare	-	-	-	-	-	-	1	-
Hyperpigmentation	9	2	8	6	8	6	-	7
Pruritus	3	1	27	2	-	7	2	4
Scarring	-	-	2	-	-	-	-	-
Urticaria	-	-	-	-	1	-	-	-
Rash	-	-	-	-	-	-	2	-
Delayed reaction (allergen known)	-	-	1§	-	-	-	-	-
Delayed reaction (allergen unknown)	-	2	2	-	-	-	-	-
Sensitization (potential)	-	-	1	-	-	-	-	-
Sensitization (probable)	-	-	1 [¶]	1 [#]	-	-	-	-
Other	-	-	-	-	-	2 ^{**}	-	3 ^{**}

*Patient follow-up was either via telephone or an office visit; time of follow-up ranged from 4 to 80 days after testing.

† Number of patients with positive test results who took part in clinical follow-up.

‡ Number of total patients who took part in the clinical follow-up.

§ Neomycin sulfate.

|| Wool alcohols.

¶ *p-tert*-Butylphenol formaldehyde resin.

#Cl+ Me- Isothiazolinone.

** Infiltration, skin thinning, and others.

In some cases, allergenic responses may be delayed in onset. One type of delayed reaction is a sensitization, which is not well defined in the literature but is described as a positive reaction observed at 10 to 14 days after application or later and at 2 to 4 days after the test is repeated.⁷ The positive reaction should meet the criteria for an allergic reaction (papular or vesicular erythema and infiltration) in order to distinguish between a false-positive result and a sensitization.

In clinical studies conducted with T.R.U.E. TEST, there have been 3 reports of delayed reactions occurring at 21 days or later. None of these patients were retested to verify a sensitization reaction. There are enough data for only 2 of these patients to indicate probable sensitization. For more details of these reactions, refer to summaries of studies no. 3 and no. 4 in the CLINICAL PHARMACOLOGY section. There are reports of other adverse reactions associated with patch testing. These include keloids, sarcoid infiltrates, vitiligo spots, edema, crusting, and sensitization.^{3,7,25,26}

Table 18 below shows data on itching and burning events from the 8 clinical studies described in the CLINICAL PHARMACOLOGY section. A number of patients in the study groups were prescribed medication to either promote healing or to relieve itching and/or burning sensations. Itching and burning sensations are commonly associated with patch testing. Treatment may be required and the more severe reactions can be expected to require longer times to heal.

In addition, the adhesive tape may also cause an irritation at the test site. Reports of tape irritation are infrequent, usually mild in nature, and self-limiting in clinical studies conducted with T.R.U.E. TEST, though no data were collected in these studies beyond a day 21 safety visit. In the nickel use test study and in a Panel 2.1 clinical study (study no. 2), problems with tape adhesion were observed. 24% and 11%, respectively, of the patients in these studies reported poor tape adhesion. (See CLINICAL PHARMACOLOGY section for complete descriptions of these studies.) In both studies, the problem was subsequently attributed to the lot of adhesive tape used to produce the clinical test samples. No adhesion problems have been reported in other studies, except for study no. 5 and 6 where on 1 (0.8%) and 6 (4.7%) of the patients, respectively, the test tape for unknown reasons fell off.

Table 18: Incidences of Itching and Burning Sensations Reported by Patients at the Time of Patch Test Removal

Event Reported	Number of Events Reported							
	Study 1 n* = 128	Study 2 n* = 122	Study 3 n* = 122	Study 4 n* = 50	Nickel Use n* = 50	Colophony n* = 128	Study 5 n* = 130	Study 6 n* = 128
Itching								
Mild	31	23	48	14	30	49	34	37
Moderate	-	-	-	2	-	12	15	11
Strong	21	5	17		24	6	1	2
Burning sensations								
Mild	7	4	8	14	24	49	34	37
Moderate	-	-	-	2	-	12	15	11
Strong	5	2	1	-	28	6	1	2
Total events	64	34	74	32	66	134	50	50

*Total number of patients in study.

Note that individual patients may exhibit 1 or both symptoms.

DOSAGE AND ADMINISTRATION:

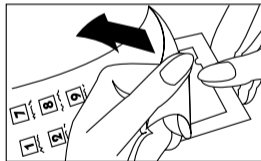
Dosage: A concentration for each allergen has been established that is high enough to evoke a reaction even in weakly sensitive patients, yet low enough to minimize the risk of irritant reactions. Please refer to the DESCRIPTION section for labeled amounts of allergen.

Administration: Please refer to the WARNINGS section prior to administration.

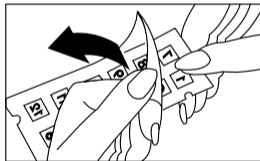
Physicians may either apply T.R.U.E. TEST patches taken directly from the refrigerator or allow them to come to room temperature (15 to 20 minutes) prior to application, as best benefits their practice.

T.R.U.E. TEST Application Instructions:

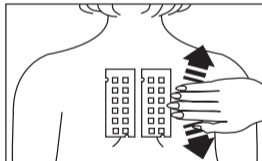
1. Peel open the package and remove test Panel 1.1 (Figure 1).



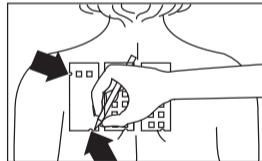
2. Remove the protective plastic covering from the test surface of the panel (Figure 2). Be careful not to touch the test substances.



3. Position the test on the upper left side of the patients back (just beside the midline) so that no. 1 allergen is in the upper left corner. Avoid applying the test on the margin of the scapula. From the center of the panel, smooth outward toward the edges, making sure each allergen makes firm contact with the skin (Figure 3).



4. With a medical marking pen, indicate on the skin the location of the 2 notches on the panel (Figure 4).



5. Repeat the process with test panel 2.1. Position the test on the upper right side of the patients back so that no. 13 allergen is in the upper left corner.

6. Repeat the process with panel 3.1. Position the test just beside panel 1, on the left side of the patients back so that no. 25 allergen is in the upper left corner.

The test should only be applied to healthy skin that is free of acne, scars, dermatitis, or any other condition that might interfere with the interpretation of results (see PRECAUTIONS).

The test is best applied on the upper part of the back, about 5 cm from the midline.

The patient should wear T.R.U.E. TEST for a minimum of 48 hours before it is removed.

Interpretation: The reaction should be read at 72 to 96 hours, when allergic reactions are fully developed and mild irritant reactions have faded. If reading at 48 hours is considered, another reading at 72 to 96 hours is recommended. Patients should be advised to report reactions occurring after 7 days to detect potential sensitizations.

It is important to note that p-phenylenediamine may turn the patch test area black on some patients. However, this is because the allergen is a dye and does not represent an allergic reaction. This discoloration may remain for up to approximately 2 weeks.

Neomycin sulfate and p-phenylenediamine sometimes cause reactions that may not appear until 4 to 5 days (or later) after the application. Patients should be instructed to report this. If appropriate, an additional office visit will verify a late reaction.

An identification template is provided for quick identification of any allergen that causes a reaction. To assure correct positioning, marks on the skin should correlate with the notches on the template.

The interpretation method, similar to the one recommended by the International Contact Dermatitis Research Group, is as follows.⁷

- ? Doubtful reaction:
 - faint macular erythema only
- + Weak (nonvesicular) positive reaction:
 - erythema
 - infiltration
 - possibly papules
- ++ Strong (vesicular) positive reaction:
 - erythema
 - infiltration
 - papules
 - vesicles

- +++ Extreme positive reaction:
bullous reaction
- Negative reaction
- IR Irritant reaction of different types:
Pustules as well as patchy follicular or homogeneous erythema without infiltrations are usually signs of irritation and do not indicate allergy.

False Negatives: False-negative results may be due to insufficient patch contact with the skin, sensitization to a substance not present in the test panel, and/or premature evaluation of the test. Retesting may be indicated. The effect of repetitive testing with T.R.U.E. TEST is unknown (see WARNINGS).

False Positives: A false-positive result may occur when an irritant reaction cannot be differentiated from an allergic reaction. Pustules as well as patchy follicular or homogeneous erythema without infiltration are usually signs of irritation and do not indicate allergy.

A positive test reaction should meet the criteria for an allergic reaction (papular or vesicular erythema and infiltration).

If an irritant reaction cannot be distinguished from a true positive reaction or if a doubtful reaction is present, a retest may be considered in a few weeks or months.

It is important when evaluating a positive test result not only to consider the intensity of the reaction but also to consider whether it is relevant to the patient's existing condition either as a primary cause or an aggravating factor.

Excited skin syndrome (angry back) consists of a hyperreactive state of the skin in which false-positive patch test reactions concur with dermatitis at a distant body site or with adjacent strong positive skin test reactions.²⁷ This rare state of hyperreactivity is not well understood clinically. There has only been 1 reported case of suspected angry back in a patient that was being tested with T.R.U.E. TEST. This patient had the standard screening allergens and a special shoe series on his back and also had T.R.U.E. TEST on his thigh. He displayed symptoms of angry back on his back but not on his thigh. This patient was retested 1 month after complete cure and an accurate diagnosis was made using the standard series and T.R.U.E. TEST.²⁸

There are several publications available that further describe the reading and interpretation of patch test reactions.^{3,7,25}

HOW SUPPLIED: T.R.U.E. TEST is supplied in multipack cartons of 5 units.

Store between 2°C and 8°C (36° and 46°F). Refrigeration required. The expiration date is stated on the package; data available currently support a 24-month dating period.

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