The Registration of Generic Topical Corticosteroid Formulations in South Africa

_a report by_

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Topical corticosteroid formulations are used widely for a variety of skin conditions such as psoriasis and eczema. The most commonly used formulation types are cream, ointment, lotion and scalp application, with some mousse formulations being released recently onto the market for scalp application. The type of formulation used depends on the condition being treated. Dry lesions are normally treated with ointments and wet lesions with creams. Cosmetically, cream formulations are more acceptable as they can be rubbed in, thus leaving no residual oiliness. Scalp applications have to be less viscous to allow the formulation to pass through the hair and contact the scalp. Occlusion with plastic wrapping hydrates the stratum corneum and facilitates the passage of the corticosteroid through this barrier to the basal layer where the therapeutic effect is required.

Just over 20 years ago, the patents on the early, most commonly used topical corticosteroids – betamethasone 17-valerate and fluocinolone acetonide – expired and a large number of generic formulations of these two corticosteroids were registered for use worldwide. Currently, the patents on all of the initial topical corticosteroids registered on the South African market have expired, which has produced a large number of generic formulations of these two corticosteroids for use worldwide. The MCC accepts measurement of the blanching effect as a valid comparator for testing the bioequivalence of topical corticosteroid formulations.1 The intensity of blanching also depends on the inherent strength of the topical corticosteroid. The classification table published in various journals that rank topical corticosteroids into the categories of ‘weak’, ‘medium’, ‘strong’ and ‘very strong’ have all been produced from the ability of that particular corticosteroid to produce blanching in human skin using the human skin blanching assay and this ranking mechanism has been validated by the degree of clinical success of the formulations.2

In South Africa, all drugs must be registered with the Medicines Control Council (MCC), the local equivalent of the US Food and Drug Administration (FDA), before they may be released onto the local market. The MCC accepts measurement of the blanching effect as a valid comparator for testing the bioequivalence of topical corticosteroid formulations. The way in which this blanching effect is measured has been something of a debate over the last decade.4

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The methodology of the visually assessed human skin blanching assay has been modified and refined considerably since it was first proposed and has subsequently been shown to be accurate and reproducible.3,5–10

The formulations are applied to the flexor aspects of the forearms of human volunteers. Normally, 12 sites measuring 7mm x 7mm are demarcated on each forearm and 3mg of a preparation is placed on the area and spread with a blunt glass rod. Twelve volunteers are used in any one assessment thus resulting in 288 sites. If two formulations are to be compared, this means that each will occupy 144 sites and, optimally, three trained observers are used to visually grade the degree of blanching. This produces a set of numbers amenable to statistical analysis.

The sites are protected to prevent abrasion of the formulations and they are left in place for six hours. The formulations are then removed, the arms washed and, after one hour, the observations commence. Observations are made every hour for 10 hours after removal of the formulations and then at longer

intervals until the blanching has disappeared. The blanching scores for each formulation on each site of all of the volunteers and observers are summed and are plotted against time to produce a blanching profile. Blanching increases with time, reaches a maximum at about 14 to 16 hours after application, and then decreases and finally disappears after about 48 hours. Weaker corticosteroids, e.g. hydrocortisone, peak earlier and the blanching disappears sooner, whereas the opposite is the case for strong steroids, e.g. clobetasol propionate.

Currently, the patents on all of the initial topical corticosteroids registered on the South African market have expired, which has produced a large number of generic formulations that are available on the local market.

The main discussion about this assay procedure hinges around the method of assessing the degree of whiteness produced in human skin. Originally, the human eye was used to assess the blanching and a simple yes/no scale was used. It was soon realised that the human eye was sensitive enough to grade the blanching and now a scale of zero to four is used to assess the blanching, as follows:

0 = normal skin;
1 = slight blanching of indistinct outline;
2 = more intense blanching;
3 = even blanching with a clear outline of the application site; and
4 = intense blanching.

This is a very subjective method of measurement but studies have shown that, even though different observers score differently, the rank order of the blanching profiles of the different formulations being assessed is always the same.9 The large number of application sites for each formulation is necessary because of the subjectivity of this method of assessment.

The FDA has released a guidance document for the assessment of topical corticosteroid formulations that included a method for the assessment of blanching using a chromameter.11 This instrument measures surface colour by reflectance, thus it is an objective method. The measurements are made by quantification of a xenon light pulse in terms of three indices: the a-scale (red-green), the b-scale (yellow-blue) and the L-scale (light-dark). These three values define a point in three-dimensional space that characterises the colour of the measured surface.

Experiences with the chromameter have demonstrated that the results obtained are far from objective.12–15 Chromameter results are reproducible, accurate and objective for the measurement of flat surface colours; however, when applied to the manual measurement of the colour of human skin, several problems arise, as follows.

• The pressure of the head of the chromameter applied by the investigator to the skin of a volunteer can change the colour of the skin due to vasocompaction.

• The presence of hairs, moles and skin mottling on the forearm can produce artefactual readings.

• The angle at which the investigator presents the chromameter to the skin can cause different values to be recorded at the same site.

• Alignment of the head directly over the formulation application site may be problematic for the small application areas used in clinical trials.

Additionally, use of the chromameter requires a reading of the surrounding unmedicated skin to...
determine whether the colour of the application site is different from normal skin. The human eye is capable of performing this without measurements being made.

The FDA recommends the use of the a-scale values only. The Euclidean distances for all three chromameter indices have been measured and plots of these values show greater similarity to visually obtained blanching profiles than to plots of the individual indices. However, even the Euclidean distance plots show exceptionally large variability about the data points.

The FDA prefers to consider registration submissions for generic topical corticosteroids formulations when the blanching assessments have been performed with a chromameter, even though it has been shown many times that assessment of blanching by the human eye is the most accurate and reproducible and the largest body of published data exists for the visual assessment methodology. The FDA does, however, still accept submissions where visual assessments have been made.

In South Africa, the MCC accepts that the human skin blanching assay is the most reliable method for the assessment of blanching, and generic topical corticosteroid formulations are registered on the basis of this test. The formulation will be registered if the blanching profiles of the generic formulation and the innovator product show no more than a 20% difference.

The most recently utilised technique for the assessment of skin blanching has been the use of digital imaging techniques. The major advantage of digital image analysis is the size of the data set obtained from a high resolution image. A 0.5cm² skin site captured at a resolution of 300 dots per inch typically comprises several thousand image pixels, each of which can be analysed for individual colour parameters.

A skin site may then be described in terms of the three-dimensional colour mode co-ordinates, the mean and scientific data values of which are based on thousands of individual pixel measurements. The improved accuracy, precision and validity of the larger data set appears to be highly desirable. This seems as though it may be a useful technique in the future, but comparison with human eye assessment shows that it still requires refining and optimisation. Until these refinements have been researched, evaluators will continue to use the visual and chromameter-based methods of comparison of topical corticosteroids.

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