AMENDMENT

to

Time and Extent Application

Triclosan USP

Prepared to support the Inclusion of Triclosan into FDA’s Monograph for Topical Acne Drug Products for Over-the-Counter Human Use; Docket No. 81N-0114, (21 CFR 333.301; 56 FR 41008, August 16, 1991; and subsequent amendments)

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Amendment submitted on:
April 22, 2005

Submitted by:
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1. INTRODUCTION

This TEA is being submitted by Ciba Specialty Chemicals Corporation ("Ciba"), Home and Personal Care Business Line. It contains the most current and factual information on the ingredient IRGASAN® DP300 (triclosan) being proposed for inclusion into FDA's Monograph for Topical Acne Drug Products for Over-the-Counter Human Use; 21 CFR 333.301.

Ciba is the pioneer manufacturer of triclosan for topical and oral care applications worldwide. Triclosan has been used safely in human dermal and oral care applications for the past thirty-five years. Triclosan became the United States Adopted Name (USAN) for the drug substance in 1992. The trade name IRGASAN DP300 has historically been used by Ciba to present the dermal applications (i.e., OTC, cosmetic, preservative uses) of triclosan.

Ciba requests that the Agency include triclosan in the Topical Acne Drug Monograph on the basis of the information contained herein. This information was developed by Ciba and contains confidential and commercial trade secret information. Further information is available as necessary.

1.1 BASIC INFORMATION ABOUT THE ACTIVE INGREDIENT (IRGASAN DP300)

1.1.1 Description and Identity

The generic name of the active ingredient is triclosan. Triclosan became the United States Adopted Name (USAN) for the drug substance in 1992. Triclosan is recognized as an official drug substance by the United States Pharmacopeia (USP 28).

The tradename: IRGASAN® DP300 was adopted by Ciba in 1989 to denote the pharmaceutical grade of triclosan, which is manufactured and distributed specifically for use in topical products.

1.1.2 Intended OTC Use

The intended use is as an active ingredient for human OTC acne drug products.

1.1.3 OTC Strength

Proposed concentrations in topical OTC acne drug formulations:

- 0.2 to 0.5% dosage strength in leave-on applications, alone or in combination with other monograph active ingredients, and;
- 0.3 to 1.0% dosage strength in rinse-off applications, alone or in combination with other monograph active ingredients.
1.1.4 Route of Administration

Route of administration would be via topical ointments, creams, gels and wash formulations. Directions for use would fall under FDA’s New Acne Monograph.

1.1.5 Applicable OTC Monograph

Topical Acne Drug Products for Over-the-Counter Human Use; Final Monograph; Docket No. 81N-0114, (21 CFR 333.301; 56 FR 41008).

1.2 PHYSICAL-CHEMICAL CHARACTERISTICS OF ACTIVE INGREDIENT

1.2.1 Chemical Names

2,4,4'-trichloro-2'-hydroxydiphenyl ether
5-chloro-2-(2,4-dichlorophenoxy)phenol

1.2.2 Chemical Abstracts Service Number

3380-34-5

1.2.3 Molecular Weight

289.6

1.2.4 Molecular Formula

C₁₂H₇Cl₃O₂

1.2.5 Molecular Structure

Figure 1. Structure of Triclosan

![Structure of Triclosan](image-url)
1.2.6 Melting Point

57 ± 1° C

1.2.7 Method of Synthesis and Purification

1.2.8 Specifications and Analytical Methods

Specifications for purity are dictated under USP 28 (triclosan). Analytical methods are contained in Ciba’s FDA Type II DMF for triclosan (No. 12097) and also available upon request.
2.0 MATERIAL TIME AND EXTENT DATA

Triclosan (IRGASAN DP300) is currently incorporated into a variety of consumer acne products worldwide. Table 1 presents a summary of 19 diverse countries where Triclosan has been marketed for acne use for a minimum of five (5) continuous years or more.

Table 1. Countries where Triclosan Sold or Marketed in OTC Acne Products

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>On Market for a Minimum of 5 Continuous Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHINA</td>
<td>YES</td>
</tr>
<tr>
<td>FRANCE</td>
<td>YES</td>
</tr>
<tr>
<td>GERMANY</td>
<td>YES</td>
</tr>
<tr>
<td>INDIA</td>
<td>YES</td>
</tr>
<tr>
<td>INDONESIA</td>
<td>YES</td>
</tr>
<tr>
<td>JAPAN</td>
<td>YES</td>
</tr>
<tr>
<td>KOREA</td>
<td>YES</td>
</tr>
<tr>
<td>MALAYSIA</td>
<td>YES</td>
</tr>
<tr>
<td>PHILIPPINES</td>
<td>YES</td>
</tr>
<tr>
<td>SINGAPORE</td>
<td>YES</td>
</tr>
<tr>
<td>SWITZERLAND</td>
<td>YES</td>
</tr>
<tr>
<td>TAIWAN</td>
<td>YES</td>
</tr>
<tr>
<td>THAILAND</td>
<td>YES</td>
</tr>
<tr>
<td>UK</td>
<td>YES</td>
</tr>
<tr>
<td>VIETNAM</td>
<td>YES</td>
</tr>
</tbody>
</table>

Table 1a. Additional countries where Triclosan Sold/Marketed in OTC Acne Products

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>On Market for a Minimum of 5 Continuous Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUSTRALIA</td>
<td>YES</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>YES</td>
</tr>
<tr>
<td>MEXICO</td>
<td>YES</td>
</tr>
<tr>
<td>SOUTH AFRICA</td>
<td>YES</td>
</tr>
</tbody>
</table>

2.1 Marketing Information

2.1.1 Amount of Active Ingredient Sold

Table 2 presents a summary of the amount (Kg) of IRGASAN DP300 (triclosan) sold by country/geographical region in acne products during the past six (6) continuous years.
Table 2. Volume (Kg) of Triclosan Sold for Acne Products by Country and/or Geographical Region

<table>
<thead>
<tr>
<th>Country/Area</th>
<th>Year</th>
<th>Volume (Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 provides a summary of the volume of Triclosan sold in each country for the past six years.

Table 3. Volume (Kg) of Triclosan Sold Continuously in Individual Selected Countries by Year (1999-2004).

Approximately 61,000 kg of IRGASAN DP300 has been sold for use in OTC acne products in 18 diverse countries during the past six years.
2.2 Estimates of Number of Units Sold and Exposed Populations

Table 4 provides an estimate of the total number of acne product units containing triclosan sold in 19 countries and geographical regions during the past 6 continuous years. From the data in Table 4, it is estimated that over 21 million units of acne products containing triclosan have been sold in these select countries during the past six years. These data are based on actual Ciba sales of IRGASAN DP300 for acne product use and are considered proprietary.

The total number of units sold was derived using the following information: A typical unit size contains approximately 100 grams of acne product. Assuming triclosan is incorporated into such products at an average concentration of 0.3%. It is estimated that one kilogram of triclosan yields approximately 350 units (unit weight: 100 grams) at a formulation concentration of 0.3%.

Assuming that the estimates derived from Table 4 can be used a surrogate for potential human exposure, it is estimated that approximately 21 million consumers have been exposed to triclosan in acne products during the past six years in the 19 countries selected.

Table 4. Estimation of Units Sold For Six Continuous Years (1999-2004) in Six Geographic Regions (Millions of Units)

<table>
<thead>
<tr>
<th>Country</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
</tr>
<tr>
<td>Australia</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
</tr>
<tr>
<td>Brazil</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
</tr>
<tr>
<td>Europe</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
</tr>
<tr>
<td>Mexico</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
</tr>
<tr>
<td>South Africa</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
<td>⬜⬜</td>
</tr>
<tr>
<td>TOTALS</td>
<td>4.10</td>
<td>4.06</td>
<td>3.99</td>
<td>3.28</td>
<td>3.22</td>
<td>2.83</td>
</tr>
</tbody>
</table>

Cumulative total across all countries: 21.48 Million Units

2.3 Description of Population Demographics

It is expected that the population demographics of the countries where triclosan is sold for acne applications are similar to that of the United States.
2.4 Use Pattern

The use patterns associated with the majority of global acne products utilizing triclosan as an active ingredient are consistent with those that appear in FDA's acne monograph. In most cases, directions for use and claims for these products appear on the product packaging and containers. Examples of specific product brand claims by country (including active ingredient concentrations) for various acne products are presented in Table 5. Actual examples of product labeling are presented in Appendix 1. Ciba certifies that the label translations presented in Appendix 1 are accurate to the best of its knowledge.

Table 5a. Summary of Some Typical Leave-on Acne Products, Claims and Triclosan Content Concentrations

<table>
<thead>
<tr>
<th>Country</th>
<th>Product Description</th>
<th>Active Ingredient</th>
<th>Application Type</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>Dr. Montri Acne Cream</td>
<td>Anti-acne</td>
<td>Leave-on</td>
<td>1.0</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Hazeline Anti-acne cream</td>
<td>Reduces and prevents pimple/acne/ble mishes</td>
<td>Leave-on</td>
<td>0.20</td>
</tr>
<tr>
<td>South Africa</td>
<td>Oxy Medicated Pads</td>
<td>Dries and clears pimples. Helps kill acne-causing bacteria.</td>
<td>Leave-on</td>
<td>0.20</td>
</tr>
<tr>
<td>Germany</td>
<td>Jade Hautklar anti-acne gel</td>
<td>With activity against acne specific claims</td>
<td>Leave on</td>
<td>0.15</td>
</tr>
<tr>
<td>UK</td>
<td>ACT Overnight Prevention Gel</td>
<td>Helps prevent spots</td>
<td>Leave-on</td>
<td>0.10</td>
</tr>
<tr>
<td>South Africa</td>
<td>Clearasil Pimple &amp; Acne Cream</td>
<td>For treatment of pimples, acne, and blackheads</td>
<td>Leave-on</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Table 5b. Summary of Some Typical Rinse-off Acne Products, Claims and Triclosan Content Concentrations

<table>
<thead>
<tr>
<th>Country</th>
<th>Brand Name</th>
<th>Claim</th>
<th>Rinse-off</th>
<th>Triclosan Content Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>pHisoHex</td>
<td>For clearer skin and fewer pimples</td>
<td>Rinse-off</td>
<td>1.0</td>
</tr>
<tr>
<td>Thailand</td>
<td>Dr. Montri Liquid Soap</td>
<td>Anti-acne</td>
<td>Rinse-off</td>
<td>0.40</td>
</tr>
<tr>
<td>Brazil</td>
<td>Clean &amp; Clear Sabonete Liquido Facial</td>
<td>Combats acne causing bacteria</td>
<td>Rinse-off</td>
<td>0.25</td>
</tr>
<tr>
<td>Thailand</td>
<td>Bionic Acne Facial Foam</td>
<td>Anti-acne</td>
<td>Rinse-off</td>
<td>0.20</td>
</tr>
<tr>
<td>Japan</td>
<td>Clear &amp; Clear Moisturising Face Wash</td>
<td>Pimple prevention</td>
<td>Rinse-off</td>
<td>0.20</td>
</tr>
<tr>
<td>South Africa</td>
<td>Gill Gentle Moisturising Face Wash</td>
<td>To protect skin from bacteria which may cause pimples</td>
<td>Rinse-off</td>
<td>0.20</td>
</tr>
<tr>
<td>Mexico</td>
<td>Clean &amp; Clear Jabon Facial</td>
<td>Combats acne causing bacteria</td>
<td>Rinse-off</td>
<td>0.20</td>
</tr>
<tr>
<td>Brazil</td>
<td>Salisoap</td>
<td>Adjuvant for acne</td>
<td>Rinse-off</td>
<td>0.20</td>
</tr>
<tr>
<td>Thailand</td>
<td>Biore Acne Control</td>
<td>Controls acne</td>
<td>Rinse-off</td>
<td>0.05</td>
</tr>
</tbody>
</table>

2.5 Description of Method for Collecting Adverse Drug Experience Data

Most companies selling acne products with triclosan employ a "customer attendance service" system for collecting adverse drug experience data. In general, the systems work as follows.

- Information regarding customer adverse drug experience or information address/telephone number is provided on the product label;
- Acne product company receives a complaint via phone call or mail.
- Company investigates incident and requests that a sample be sent by consumer.
- Sample is analyzed and compared to standard.
- If the sample is okay and without any external interference, company writes a letter to the customer indicating test results with technical information regarding product safety, etc.
- If medical emergency, company provides relevant toxicity information to doctor and pays for doctor to treat the problem. Quality Assurance Department and Customer
Attendance Service Department have all the data related to these complaints in their files to be checked and audited as per GMP.

- Active ingredient manufacturer is advised of serious incidents and follows up accordingly.

To our knowledge, as of the date of this transmittal, there have been no serious or adverse drug experiences filed for any acne products containing IRGASAN DP300 (triclosan).

2.6 Prescription Drug Information

All acne products containing IRGASAN DP300 (triclosan) are sold OTC (directly to the consumer) and not via prescription.

2.7 Marketing Withdrawals

There have been no marketing or product withdrawals in any countries where IRGASAN DP300 is used as an active ingredient in acne formulations.

2.8 Certification

The undersigned certifies that, to the best knowledge and belief, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully Submitted,

Lisa Navarro, Ph.D., D.A.B.T.
Director, Product Safety and Regulatory Affairs
Ciba Specialty Chemicals Corporation
Home & Personal Care Business Line
3.0 APPENDIX: Examples of Acne Product Labels

1. AUSTRALIA
   a. Clean & Clear Facial Cleansing Bar
   b. Neutrogena Acne Sin Cleanser (Bar)
   c. pHisohex Anti-Bacterial Face Wash
   d. Young Solution Cleansing Bar
   e. Young Solution Face Wash
   f. Young Solution Oil Controlling Toner
   g. Young Solution Wash Up

2. BRAZIL
   a. Clean & Clear Facial Soap (Bar)
   b. Clean & Clear Liquid Facial Soap
   c. Salisoap (Bar)

3. CHINA
   a. Clean & Clear Facial Wash

4. FRANCE
   a. Garnier Synergie Pure

5. GERMANY
   a. Jade Hautklar

6. INDONESIA
   a. Biore Antiacne Facial Foam

7. JAPAN
   a. Clearex Face Wash
   b. Clearasil Medicated Face Wash

8. MEXICO
   a. Clean & Clear Facial Soap (Bar)
   b. Axel Facial Bar

9. SOUTH AFRICA
   a. Clean & Clear Facial Cleansing Bar
   b. Clearasil Cream
   c. Cuticura Face Washes
   d. Gill Gentle Moisturising Face Wash
   e. Oxy Face Wash/Medicated Pads
   f. Pond’s Lasting Oil Control Face Wash
   g. Pure SOS Anti-Blemish Pen

10. SWITZERLAND
   a. Antebor N
   b. Louis Widmer Acne Gel
11. THAILAND
   a. Biore Massaging Facial Wash – Acne Control
   b. Bionic Acne Facial Foam
   c. Dr. Montri Acne Cream
   d. Dr. Montri Liquid Soap

12. UK
   a. ACT Overnight Protection Gel
   b. Sainsbury’s Skin Deep Medicated Pads
   c. Skin Clear Face Mask

13. VIETNAM
   a. Hazeline Anti-Acne Cream
   b. Hazeline Anti-Acne Facial Foam