

Dyclo9, Inc.
411 Business Center Dr.
Suite 111
Mount Prospect, IL 60056
Tel: (847) 297-2265
Fax: (847) 297-1365
e-mail: ar.unitel@usa.net

2700 101 JUL 15 10:37

7/9/2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Citizen Petition to Reopen Docket No. 81N-0033: Oral Health Care Drug Products for Over the Counter Human Use; Tentative Final Monograph for Over the Counter Relief of Oral Discomfort Drug Products.

Dear Sir or Madam:

Dyclo9, Inc. submits this petition pursuant to 21 C.F.R. 10.30 requesting that the Food and Drug Administration (FDA) reopen the administrative record to allow for the submission and evaluation of additional data to support the Category I efficacy and safety classification of dyclonine hydrochloride (DH) in the Oral Health Care Drug Products for Over-the Counter (OTC) for Human Use Tentative Final Monograph (TFM) for Oral Topical Discomfort Drug Products, 56 FR 48302 (September 24, 1991).

Specifically, in this Citizen's Petition, Dyclo9, Inc. formally requests that the FDA approve the efficacy and safety data contained herein that support Category I safety and efficacy of DH at concentrations of 0.5 to 1.0 %, for Over the Counter Human Use. A summary of the efficacy and safety data being submitted is presented below.

Dyclo9, Inc. believes there is ample data in the docket and additional data to be presented below that establishes DH at a concentration of 0.5 to 1.0% as safe and effective as a Category I Oral Discomfort Drug Product. Dyclo9, Inc. believes the FDA should classify DH, an Oral Topical Anesthetic, as a Category I Oral Discomfort Drug Product.

At the present time, FDA has allowed DH 0.5 to 1.0% as a topical anesthetic in creams and ointments, by external application to the skin, or rectally, and contains no drug limited to prescription sale under the provisions of section 503 (b) (1) of the act. The preparations must contain no more than 1.0% concentration of DH. The above matter has

been revised and approved as of April 1, 2003 (Cite: 21DFR 310. 201), Subpart C, New Drugs Exempted from Prescription-Dispensing Requirements.

I. Data Supporting Safety and Efficacy

In addition to the revised and accepted use of DH at a concentration not more than 1.0%, in externally used creams or rectally used ointments per the above, the following three reports are felt to convey the safety and efficacy on a clinical and practical basis:

Dyclo9, Inc. respectfully submits the following 3 clinical research reports (see attached references), demonstrating the safety, efficacy and performance of DH at concentrations of 0.5 and 1.0%.

The first study undertaken in 1991 and published as "Dyclonine Hydrochloride – A Topical Agent for Managing Pain", in *Clinical Dentistry, Illinois Dental Journal*, 1992; July-August Issue: pp.303-304. The study evaluated the onset and duration of the topical anesthetic DH 1.0% oral rinse, in 35 patients (21 female and 14 male), undergoing local anesthetic injection or scaling and root planning occurring beneath the soft tissue gum line. Onset of anesthesia was reported to be on the average, 1.9 minutes. The average time of anesthesia was 48 minutes. Sixty percent of the patients felt comfortable during either injection or scaling. Twenty percent of patients felt only pressure and the remaining 20 % felt a combination of both pain and pressure together. Absolutely, no adverse clinical signs of hypersensitivity, allergy, or ulceration were observed.

In the second study, a larger group of patients were evaluated, 57 in all. The study, "A Research Study Using Dyclonine Hydrochloride 0.5% as a Topical Anesthetic for Debridement", *Journal of Practical Hygiene, Supplement 1: March/April 1998:1-5.*, studied the topical anesthetic effects of DH 0.5% oral rinse during periodontal scaling procedures.

Average onset and duration of anesthesia was demonstrated at 1.75 minutes and 57.5 minutes, respectively. In the present study, about 77% of patients claimed to be very comfortable during dental scaling and 10.5 % claimed to feel comfortable with pressure, around the gums. Seven percent of the study population claimed to feel pressure and pain together. Again, no signs or claims of adverse side effects were seen including hypersensitivity, allergy or ulceration.

The third study, "Use of Dyclonine Hydrochloride 0.5% as Anesthetic in Oral Soft Tissue Biopsies", *Journal of Practical Hygiene, Supplement 1: March/April 1998:6-9*, studied as the sole oral topical rinse agent in 2 soft tissue biopsy procedures. During this study 2 different patients underwent incisional and excisional biopsy procedures without the use of an injectable anesthetic. Both patients claimed to be comfortable during each procedure, and no adverse signs of allergy, hypersensitivity or ulceration were observed.

A further report demonstrating safety and efficacy is one of the original reports on DH. In the report, "Dyclonine Hydrochloride as a topical anesthetic in dentistry", *Oral Surgery Oral Medicine Oral Pathology* 1957; 10:623-626 describes the anesthetic as free

of escharotics, caustic and astringent agents and is classified as non-injurious to oral tissues.

Dyclonine hydrochloride is a ketone- based topical anesthetic. According to Adraini, J. et al.: "Topical anesthetics: Use and misuse". Southern Medical Journal; 1985; 78:1224-1229, and Adriani, J. et al.: "Scope and limitations of topical anesthetics in anesthesiology", Anesthesiology Review 1983; 10:10-15, dyclonine hydrochloride is less toxic than the amide or ester type anesthetics and it is a safe topical agent. Furthermore, it does not cause adverse systemic reactions and the duration of its effect has been found to be longer than topical lidocaine.

Previously, DH marketed under the trademark Dyclone, by Astra Pharmaceutical, Co., the Dyclone Product Insert Data states, the topical agent has proven to be an effective tool for debridement, preinjection anesthesia (particularly for hard palate injections), soft tissue biopsies, abscess drainage and demonstrates excellent control of the gag reflex.

Dyclonine hydrochloride has been demonstrated in a clinical study NOT to cause airway irritation or bronchospasm as demonstrated for other topical anesthetics such as lidocaine and ropivacaine. This was demonstrated in a paper entitled, "Airway Anesthesia alone does not explain attenuation of histamine induce bronchospasm by local anesthetics: a comparison of lidocaine, ropivacaine and dyclonine". Groeben H., Grosswendt T., et al. 2001; Anesthesiology; 94:423-428.

Finally, the superiority and safety of DH as a topical local anesthetic has been well documented as the most effective "non-caine" type local anesthetic that is free from acute toxicity. Adriani, J. et al.; Clinical Pharmaceutical Therapeutics; 5:49-62, 1964 and Adriani, J. The Pharmacology of Anesthetic Drugs; a syllabus for Students and Clinicians, 5th Edition, p. 144, Thomas, Springfield, IL. , 1970. In support of the above, is a study titled, "High Performance Liquid Chromatographic determination of Dyclonine Hydrochloride in the Presence of its Degradation Products", Bhagat, H.R. et al., 1995, Department of Chemistry, Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Mass., demonstrated that dyclonine hydrochloride oral spray and gel formulations containing appropriate pharmaceutical excipients such as color and flavor in a formulation of a pH of 1.0 and 2.5 exhibited good chemical stability, with a predicted shelf life of more than 3 years.

II. Information Supporting External Skin vs. Oral Use

Previous report revising and approving the exemption of DH by the FDA, at a concentration of not more than 1.0%, as of April 1, 2003 (Cite: 21 DFR 310.201, Subpart C) for external skin use or rectally does have similarities to oral rinse use, when evaluating the histological aspect and description of the external skin, rectal mucosa and oral mucosal tissues.

The external skin of the body is recognized to be a keratinized stratified squamous epithelium. In the same manner, the Oral gingival tissues or gums, and hard palate mucosa is a keratinized stratified squamous epithelium similar to the external skin. The rectal mucosa may be a combination of both keratinized and non-keratinized stratified squamous epithelium. Also, the oral mucosa such as cheeks, soft palate and vestibules are also non-keratinized stratified squamous epithelium. Dyclonine hydrochloride 1.0%, in dentistry, is used as a 1-minute oral rinse and the topical agent is expectorated from the oral cavity and not swallowed in its therapeutic use. Though, it has been shown to be safe and effective if swallowed for anesthetizing the non-keratinized epithelial mucosa of the esophagus, particularly for patients suffering with ulcerations of the esophagus from treatment of radiation for cancerous lesions, in order to eat and swallow comfortably. Point being, with the use of DH 1.0% ointments rectally or on the external skin (which are approved for Over-the Counter) of the body, the absorption would be similar, if absorbed at all, with non-keratinized or keratinized oral mucosa, when DH 0.5 to 1.0% is utilized as an oral rinse and then expectorated. Thus Dyclo9, Inc. claims that DH 0.5% and 1.0 % should be allowed as a Category I Oral discomfort Drug, exempt from prescription status and allowed Over the Counter.

III. Oral Dosage

Dyclo9, Inc. makes this submission for its oral topical anesthetic product. The product discussed above, dyclonine hydrochloride 1.0% active ingredient, delivers 1mg/ml of topical anesthetic to oral mucosal surfaces. Dyclo9, Inc. recommends a 6 to 10 ml, one minute oral rinse followed by expectoration from the oral cavity. Of course, this is a 6 to 10 mg dose only, for mucosal anesthesia. For scientific information, the lethal dose (LD50) of dyclonine hydrochloride is 176mg/kg in female rats and 90mg/kg in female mice, administered orally. Accordingly, the therapeutic recommended dose is far less than any toxic or lethal dose for human use.

Furthermore, in the 1991 Oral Care Drug Products for Over the Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral Discomfort Drugs, the panel cited the following from a scientific paper "Clinical Effectiveness of Drugs Used for Topical Anesthesia", Journal of the American Medical Association, authored by J. Adriani and R. Zepernick, Vol.188:711-716, 1964:

- 1) Compared the potency and effectiveness of dyclonine hydrochloride with other topical anesthetics in man by using electric current delivered by a nerve stimulator.
- 2) The procedure involved quantifying the amount of electric current needed to elicit a response after the topical application of 1 percent dyclonine hydrochloride to an oral mucosal surface.

- 3) Several oral surfaces were tested with the tip of the tongue used for most studies because of its sensitivity, accessibility and production of the most consistent result.
- 4) Duration and effectiveness were considered to result in good depth of anesthesia when dyclonine hydrochloride 1% was compared to 4% lidocaine and 6% hexylcaine, on a milligram for milligram basis.
- 5) The authors specifically mentioned that dyclonine hydrochloride 1% is an effective topical anesthetic that does not have adverse systemic responses characteristic of other local anesthetics.

IV. Proposed Actions

Dyclo9, Inc. desires the change as described in Over the Counter Drug Products – Public Hearing, April 27, 2000, Docket No. 00N-1256, held in the FDA, Department of Health and Human Services, that dyclonine hydrochloride prescription status of 0.5% and 1.0% being changed to OTC status, by the FDA, at the time of the Public Hearing, allow for the above percentages of 0.5 and 1.0% to be written into the document.

V. Environmental Impact

This petition qualifies for a categorical exemption from the requirement of submission of an environmental assessment. 21 CFR 25.31(c).

VI. Economic Impact

The petitioner upon request of the Commissioner 21CFR 10.30(b) will submit information on economic impact.

VII. Certification

The undersigned certifies, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, including representative data.

Sincerely,


Alphonse V. Gangulo, D.D.S., M.S.
Diplomat, American Board of Periodontology
Head, Clinical Research
Dyclo9, Inc.

References

1. Department of Health and Human Resources, 21 CFR Parts 356 and 369, Docket No. 81N-0033, Oral Health Care Drug Products for the Over-the-Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral discomfort Drugs, September 24, 1991
2. Department of Health and Human Services, Docket No. 00N-1256; Over-The-Counter Drug Products Public Hearing, April 27, 2000.
3. Department of Health and Human Services, (cite: 21CFR 310.201) Subpart C- New Drugs Exempted from Prescription – Dispensing Requirements., April 1, 2003.
4. Gargiulo, AV, Burns, GM and Huck, CP. "Dyclonine hydrochloride-a topical agent for managing pain." Illinois Dental Journal, July/August 1992, pp. 303-304.
5. Gargiulo, AV, Bianco, CP, Burns, GM and Majcina, L. "A research study using dyclonine hydrochloride 0.5% as a topical anesthetic for debridement." Journal of Practical Hygiene, Special Supplement, March/April, 1998:pp.1-5.
6. Gargiulo, AV, Solt, D. "Use of Dyclonine Hydrochloride 0.5% as anesthetic in Oral soft tissue biopsies". Journal of Practical Hygiene, Special Supplement, March/April, 1998:pp.6-9.
7. Ping, RS, White, JG, Spear, LB. "Dyclonine hydrochloride as a topical anesthetic in dentistry. Oral Surgery Oral Medicine Oral Pathology 1957; 10:623-626.
8. Adriani, J, Beuttler, WA, et al. "Topical anesthetics: Use and misuse." Southern Medical Journal 1985; 78:1224-1229.
9. Adriani, J. et al. "Scope and limitations of topical anesthetics in anesthesiology." Anesthesiology Rev. 1983 10:10-15.
10. Dyclone, Product Insert Data, Astra Pharmaceutical Co. Inc. Westborough, Mass. 01581.
11. Groeben H, Grosswendt T., et al. "Airway anesthesia alone does not explain attenuation of histamine induced bronchospasm by local anesthetics: a comparison of lidocaine, ropivacaine and dyclonine." Anesthesiology 2001; 94:423-428.
12. Bhagat, HR, et al. "High performance liquid chromatographic determination of dyclonine hydrochloride in the presence of its degradation products," Department of Chemistry, Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Mass., 1995.

13. Adriani, J and Zepernick, R. "Clinical effectiveness of drugs used for topical anesthesia." *Journal of the American Medical Association*, 1964; 88:711-716.

Dyclo9, Inc.
411 Business Center Dr.
Suite 111
Mount Prospect, IL 60056
Tel: (847) 297-2265
Fax: (847) 297-1365
e-mail: ar.unitel@usa.net

2004 JUL 13 10:12

7/9/2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Citizen Petition to Reopen Docket No. 81N-0033: Oral Health Care Drug Products for Over the Counter Human Use; Tentative Final Monograph for Over the Counter Relief of Oral Discomfort Drug Products.

Dear Sir or Madam:

Dyclo9, Inc. submits this petition pursuant to 21 C.F.R. 10.30 requesting that the Food and Drug Administration (FDA) reopen the administrative record to allow for the submission and evaluation of additional data to support the Category I efficacy and safety classification of dyclonine hydrochloride (DH) in the Oral Health Care Drug Products for Over-the Counter (OTC) for Human Use Tentative Final Monograph (TFM) for Oral Topical Discomfort Drug Products, 56 FR 48302 (September 24, 1991).

Specifically, in this Citizen's Petition, Dyclo9, Inc. formally requests that the FDA approve the efficacy and safety data contained herein that support Category I safety and efficacy of DH at concentrations of 0.5 to 1.0 %, for Over the Counter Human Use. A summary of the efficacy and safety data being submitted is presented below.

Dyclo9, Inc. believes there is ample data in the docket and additional data to be presented below that establishes DH at a concentration of 0.5 to 1.0% as safe and effective as a Category I Oral Discomfort Drug Product. Dyclo9, Inc. believes the FDA should classify DH, an Oral Topical Anesthetic, as a Category I Oral Discomfort Drug Product.

At the present time, FDA has allowed DH 0.5 to 1.0% as a topical anesthetic in creams and ointments, by external application to the skin, or rectally, and contains no drug limited to prescription sale under the provisions of section 503 (b) (1) of the act. The preparations must contain no more than 1.0% concentration of DH. The above matter has

been revised and approved as of April 1, 2003 (Cite: 21DFR 310. 201), Subpart C, New Drugs Exempted from Prescription-Dispensing Requirements.

I. Data Supporting Safety and Efficacy

In addition to the revised and accepted use of DH at a concentration not more than 1.0%, in externally used creams or rectally used ointments per the above, the following three reports are felt to convey the safety and efficacy on a clinical and practical basis:

Dyclo9, Inc. respectfully submits the following 3 clinical research reports (see attached references), demonstrating the safety, efficacy and performance of DH at concentrations of 0.5 and 1.0%.

The first study undertaken in 1991 and published as “Dyclonine Hydrochloride – A Topical Agent for Managing Pain”, in *Clinical Dentistry, Illinois Dental Journal*, 1992; July-August Issue: pp.303-304. The study evaluated the onset and duration of the topical anesthetic DH 1.0% oral rinse, in 35 patients (21 female and 14 male), undergoing local anesthetic injection or scaling and root planning occurring beneath the soft tissue gum line. Onset of anesthesia was reported to be on the average, 1.9 minutes. The average time of anesthesia was 48 minutes. Sixty percent of the patients felt comfortable during either injection or scaling. Twenty percent of patients felt only pressure and the remaining 20 % felt a combination of both pain and pressure together. Absolutely, no adverse clinical signs of hypersensitivity, allergy, or ulceration were observed.

In the second study, a larger group of patients were evaluated, 57 in all. The study, “A Research Study Using Dyclonine Hydrochloride 0.5% as a Topical Anesthetic for Debridement”, *Journal of Practical Hygiene, Supplement 1: March/April 1998:1-5.*, studied the topical anesthetic effects of DH 0.5% oral rinse during periodontal scaling procedures.

Average onset and duration of anesthesia was demonstrated at 1.75 minutes and 57.5 minutes, respectively. In the present study, about 77% of patients claimed to be very comfortable during dental scaling and 10.5 % claimed to feel comfortable with pressure, around the gums. Seven percent of the study population claimed to feel pressure and pain together. Again, no signs or claims of adverse side effects were seen including hypersensitivity, allergy or ulceration.

The third study, “Use of Dyclonine Hydrochloride 0.5% as Anesthetic in Oral Soft Tissue Biopsies”, *Journal of Practical Hygiene, Supplement 1: March/April 1998:6-9*, studied as the sole oral topical rinse agent in 2 soft tissue biopsy procedures. During this study 2 different patients underwent incisional and excisional biopsy procedures without the use of an injectable anesthetic. Both patients claimed to be comfortable during each procedure, and no adverse signs of allergy, hypersensitivity or ulceration were observed.

A further report demonstrating safety and efficacy is one of the original reports on DH. In the report, “Dyclonine Hydrochloride as a topical anesthetic in dentistry”, *Oral Surgery Oral Medicine Oral Pathology* 1957: 10:623-626 describes the anesthetic as free

of escharotics, caustic and astringent agents and is classified as non-injurious to oral tissues.

Dyclonine hydrochloride is a ketone- based topical anesthetic. According to Adraini, J. et al.: "Topical anesthetics: Use and misuse". Southern Medical Journal; 1985; 78:1224-1229, and Adriani, J. et al.: "Scope and limitations of topical anesthetics in anesthesiology", Anesthesiology Review 1983; 10:10-15, dyclonine hydrochloride is less toxic than the amide or ester type anesthetics and it is a safe topical agent. Furthermore, it does not cause adverse systemic reactions and the duration of its effect has been found to be longer than topical lidocaine.

Previously, DH marketed under the trademark Dyclone, by Astra Pharmaceutical, Co., the Dyclone Product Insert Data states, the topical agent has proven to be an effective tool for debridement, preinjection anesthesia (particularly for hard palate injections), soft tissue biopsies, abscess drainage and demonstrates excellent control of the gag reflex.

Dyclonine hydrochloride has been demonstrated in a clinical study NOT to cause airway irritation or bronchospasm as demonstrated for other topical anesthetics such as lidocaine and ropivacaine. This was demonstrated in a paper entitled, "Airway Anesthesia alone does not explain attenuation of histamine induce bronchospasm by local anesthetics: a comparison of lidocaine, ropivacaine and dyclonine". Groeben H., Grosswendt T., et al. 2001; Anesthesiology; 94:423-428.

Finally, the superiority and safety of DH as a topical local anesthetic has been well documented as the most effective "non-caine" type local anesthetic that is free from acute toxicity. Adriani, J. et al.; Clinical Pharmaceutical Therapeutics; 5:49-62, 1964 and Adriani, J. The Pharmacology of Anesthetic Drugs; a syllabus for Students and Clinicians, 5th Edition, p. 144, Thomas, Springfield, IL. , 1970. In support of the above, is a study titled, "High Performance Liquid Chromatographic determination of Dyclonine Hydrochloride in the Presence of its Degradation Products", Bhagat, H.R. et al., 1995, Department of Chemistry, Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Mass., demonstrated that dyclonine hydrochloride oral spray and gel formulations containing appropriate pharmaceutical excipients such as color and flavor in a formulation of a pH of 1.0 and 2.5 exhibited good chemical stability, with a predicted shelf life of more than 3 years.

II. Information Supporting External Skin vs. Oral Use

Previous report revising and approving the exemption of DH by the FDA, at a concentration of not more than 1.0%, as of April 1, 2003 (Cite: 21 DFR 310.201, Subpart C) for external skin use or rectally does have similarities to oral rinse use, when evaluating the histological aspect and description of the external skin, rectal mucosa and oral mucosal tissues.

The external skin of the body is recognized to be a keratinized stratified squamous epithelium. In the same manner, the Oral gingival tissues or gums, and hard palate mucosa is a keratinized stratified squamous epithelium similar to the external skin. The rectal mucosa may be a combination of both keratinized and non-keratinized stratified squamous epithelium. Also, the oral mucosa such as cheeks, soft palate and vestibules are also non-keratinized stratified squamous epithelium. Dyclonine hydrochloride 1.0%, in dentistry, is used as a 1-minute oral rinse and the topical agent is expectorated from the oral cavity and not swallowed in its therapeutic use. Though, it has been shown to be safe and effective if swallowed for anesthetizing the non-keratinized epithelial mucosa of the esophagus, particularly for patients suffering with ulcerations of the esophagus from treatment of radiation for cancerous lesions, in order to eat and swallow comfortably. Point being, with the use of DH 1.0% ointments rectally or on the external skin (which are approved for Over-the Counter) of the body, the absorption would be similar, if absorbed at all, with non-keratinized or keratinized oral mucosa, when DH 0.5 to 1.0% is utilized as an oral rinse and then expectorated. Thus Dyclo9, Inc. claims that DH 0.5% and 1.0 % should be allowed as a Category I Oral discomfort Drug, exempt from prescription status and allowed Over the Counter.

III. Oral Dosage

Dyclo9, Inc. makes this submission for its oral topical anesthetic product. The product discussed above, dyclonine hydrochloride 1.0% active ingredient, delivers 1mg/ml of topical anesthetic to oral mucosal surfaces. Dyclo9, Inc. recommends a 6 to 10 ml, one minute oral rinse followed by expectoration from the oral cavity. Of course, this is a 6 to 10 mg dose only, for mucosal anesthesia. For scientific information, the lethal dose (LD50) of dyclonine hydrochloride is 176mg/kg in female rats and 90mg/kg in female mice, administered orally. Accordingly, the therapeutic recommended dose is far less than any toxic or lethal dose for human use.

Furthermore, in the 1991 Oral Care Drug Products for Over the Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral Discomfort Drugs, the panel cited the following from a scientific paper "Clinical Effectiveness of Drugs Used for Topical Anesthesia", Journal of the American Medical Association, authored by J. Adriani and R. Zepernick, Vol.188:711-716, 1964:

- 1) Compared the potency and effectiveness of dyclonine hydrochloride with other topical anesthetics in man by using electric current delivered by a nerve stimulator.
- 2) The procedure involved quantifying the amount of electric current needed to elicit a response after the topical application of 1 percent dyclonine hydrochloride to an oral mucosal surface.

- 3) Several oral surfaces were tested with the tip of the tongue used for most studies because of its sensitivity, accessibility and production of the most consistent result.
- 4) Duration and effectiveness were considered to result in good depth of anesthesia when dyclonine hydrochloride 1% was compared to 4% lidocaine and 6% hexylcaine, on a milligram for milligram basis.
- 5) The authors specifically mentioned that dyclonine hydrochloride 1% is an effective topical anesthetic that does not have adverse systemic responses characteristic of other local anesthetics.

IV. Proposed Actions

Dyclo9, Inc. desires the change as described in Over the Counter Drug Products – Public Hearing, April 27, 2000, Docket No. 00N-1256, held in the FDA, Department of Health and Human Services, that dyclonine hydrochloride prescription status of 0.5% and 1.0% being changed to OTC status, by the FDA, at the time of the Public Hearing, allow for the above percentages of 0.5 and 1.0% to be written into the document.

V. Environmental Impact

This petition qualifies for a categorical exemption from the requirement of submission of an environmental assessment. 21 CFR 25.31(c).

VI. Economic Impact

The petitioner upon request of the Commissioner 21CFR 10.30(b) will submit information on economic impact.

VII. Certification

The undersigned certifies, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, including representative data.

Sincerely,

Alphonse V. Garigulo, D.D.S., M.S.
Diplomat, American Board of Periodontology
Head, Clinical Research
Dyclo9, Inc.

References

1. Department of Health and Human Resources, 21 CFR Parts 356 and 369, Docket No. 81N-0033, Oral Health Care Drug Products for the Over-the-Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral discomfort Drugs. September 24, 1991
2. Department of Health and Human Services, Docket No. 00N-1256; Over-The-Counter Drug Products Public Hearing, April 27, 2000.
3. Department of Health and Human Services, (cite: 21CFR 310.201) Subpart C- New Drugs Exempted from Prescription – Dispensing Requirements., April 1, 2003.
4. Gargiulo, AV, Burns, GM and Huck, CP. “Dyclonine hydrochloride-a topical agent for managing pain.” Illinois Dental Journal, July/August 1992, pp. 303-304.
5. Gargiulo, AV, Bianco, CP, Burns, GM and Majcina, L. “A research study using dyclonine hydrochloride 0.5% as a topical anesthetic for debridement.” Journal of Practical Hygiene, Special Supplement, March/April, 1998:pp.1-5.
6. Gargiulo, AV, Solt, D. “Use of Dyclonine Hydrochloride 0.5% as anesthetic in Oral soft tissue biopsies”. Journal of Practical Hygiene, Special Supplement, March/April, 1998:pp.6-9.
7. Ping, RS, White, JG, Spear, LB. “Dyclonine hydrochloride as a topical anesthetic in dentistry. Oral Surgery Oral Medicine Oral Pathology 1957; 10:623-626.
8. Adriani, J, Beuttler, WA, et al. “Topical anesthetics: Use and misuse.” Southern Medical Journal 1985; 78:1224-1229.
9. Adriani, J. et al. “Scope and limitations of topical anesthetics in anesthesiology.” Anesthesiology Rev. 1983 10:10-15.
10. Dyclone, Product Insert Data, Astra Pharmaceutical Co. Inc. Westborough, Mass. 01581.
11. Groeben H. Grosswendt T., et al. “Airway anesthesia alone des not explain attenuation of histamine induced bronchospasm by local anesthetics: a comparison of lidocaine, ropivacaine and dyclonine.” Anesthesiology 2001; 94:423-428.
12. Bhagat, HR. et al. “High performance liquid chromatographic determination of dyclonine hydrochloride in the presence of its degradation products,” Department of Chemistry, Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Mass., 1995.

13. Adriani, J and Zepernick, R. "Clinical effectiveness of drugs used for topical anesthesia." *Journal of the American Medical Association*, 1964; 88:711-716.