CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-753

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 7, 2004 **DATE OF DOCUMENT:** June 25, 2004	**DESIRED COMPLETION DATE:** September 28, 2004 **PDUFA DATE:** February 5, 2005	**ODS CONSULT #:** 04-0224

TO: Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Millie Wright
Project Manager
HFD-540

PRODUCT NAME: **Differin® XP™** (Adapalene Gel) 0.3% **NDA#:** 21-753	**NDA SPONSOR:** Galderma Laboratories

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Differin XP. The safest use of this product may be best managed under the proprietary name Differin. The higher strength (0.3%) should suffice to identify the drug product. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review, in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Differin XP acceptable from a promotional perspective.

4. DMETS recommends a consult be submitted to the Division of Surveillance, Research and Communication Support for review of the patient package insert.

Carol Holquist, RPh
Director, Division of Medication Errors and Technical Support
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Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 7, 2004

NDA# 21-753

NAME OF DRUG: Differin® XP™ (Adapalene Gel) 0.3%

NDA HOLDER: Galderma Laboratories

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) for an assessment of the proprietary name, Differin XP, in regard to potential name confusion with other proprietary or established drug names. Container labels and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Differin is currently marketed in the United States as a 0.1% solution (NDA 20-338), 0.1% gel (NDA 20-380) and 0.1% cream (NDA 20-748). Differin XP contains the same active ingredient of adapalene as Differin, but in an aqueous gel of 0.3%. The drug product is indicated for the topical treatment of acne vulgaris. Adapalene binds to specific retinoic acid nuclear receptors, but the exact mode of action is unknown. The suggested mechanism is the normalization of the differentiation of follicular epithelial cells that results in decreased microcomedone formation. It is recommended that Differin XP be applied to the [ ] skin once daily, at bedtime. A thin film of the gel [ ] should be applied to the skin [ ]. The patient should expect a mild transitory sensation of warmth or slight stinging after the application. The drug product is supplied in 45 gram tubes to be stored at room temperature.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Differin XP to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Differin XP. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Error Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical skill, professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Differin XP acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Differin XP. These products with the available dosage forms and usual dosage are listed in table 1 (see page 4).

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage Form(s), Strength(s), Available dispensing size (if applicable)	Usual adult dose*	Other**
Differin® XP™	Adapalene 0.3% in an Aqueous Gel	Applied to the affected areas of the skin once daily, at bedtime	
Differin®	Adapalene 0.1% Gel, 45 gram tube 0.1% Cream, 45 gram tube 0.1% Solution; 30mL bottle 0.1 % Solution; Pledgettes (60 count)	Apply to affected areas of the skin, once daily at nighttime.	LA/SA
Definity®	Perflutren Lipid Microsphere (lipid-coated microspheres filled with octafluoropropane gas) Injectable Suspension	10 microliters/kilogram by intravenous bolus within 30-60 seconds, followed by 10 milliliter saline flush. 1.3 milliliter added to 50 mL of preservative-free saline for intravenous saline. Initiate infusion at 4 milliliter per minute, but titrate as necessary. Do not exceed 10 milliliter per minute.	SA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Differin XP were captured by the Expert Panel (EPD).

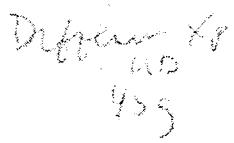
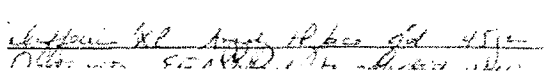
C. POST-MARKETING ADVERSE EVENT REPORTS (AERS DATABASE SEARCH)

As Differin is a currently marketed drug product, a search of the FDA Adverse Event Reporting System (AERS) database was performed to determine if any post-marketing safety reports of medication errors were reported. The drug names, "adapa%" and "diff%" were used to perform the search with no specific MedDRA Terms used, so all reports would be selected. There were no reports found which related to nomenclature, packaging or labeling. However, there were many reports indicating various facial irritations due to product use. The etiology of the reactions were not provided, however some patients used the drug product more often than the approved frequency (twice daily versus daily). There was no indication if this was the result of physician prescribing habits or the patients altering their dosing schedule. DMETS will continue to monitor these deviations from the prescribed dosing interval with Differin.

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Differin XP with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Differin XP (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Differin XP Apply to face at bedtime Give 45 gram tube
Inpatient RX: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar or look similar to any currently marketed U.S. product. However, three participants interpreted the leading letters of the name as "ib", which raised a concern regarding the possibility of confusion with Bufferin. Bufferin is a currently marketed buffered aspirin product. See appendix A for the complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Differin XP, the primary concerns related to look-alike and sound-alike confusion with Differin and Definity®. Additionally, DMETS is concerned with the use of the modifier XP. Upon further review of the name Definity, this name will not be reviewed further due to a lack of convincing sound-alike similarities with Differin and numerous differentiating product characteristics such as product strength, indication for use, frequency of administration, route of administration and dosage form.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with

any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Differin XP. However, three participants interpreted the leading letters of the name as "ib", which raised concern regarding the possibility of confusion with Bufferin. This is especially true as the products share the same last six letters ("fferin").

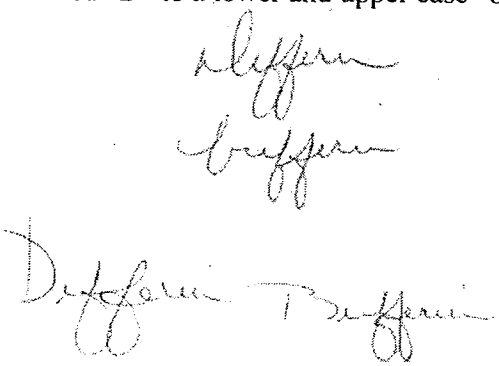
1. Sound-alike/Look-alike concerns

   a. Differin XP is the latest product extension to the Differin product line. The products contain the same active ingredient of adapalene. The names Differin and Differin XP are phonetically identical except for the "XP" modifier. Differin contains 0.1% adapalene in four formulations: gel, solution, Pledgettes and cream. All formulations should be applied once daily at bedtime. The gel and cream formulations are available in a 45 gram tube and the solution is available in a 30 mL bottle or 60 count pledgette. The sponsor has proposed to add the modifier XP to the proprietary name Differin, which is to represent an increased strength of the aqueous gel formulation. This concerns DMETS as it will risk the omission of a modifier; therefore eliminate differentiation of strength. Post-marketing error reports and independent research has indicated that the omission of modifiers continues to cause medication errors. Timothy S. Lesar, Pharm.D, conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms.[5] Detailed analysis of 402 medication errors over a 16 month period (Sept. 1999 to Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled release dosage formulation (280 cases or 69.7%). Studies such as this one, support DMETS concern that healthcare professionals may fail to include a modifier (e.g. XP) on a prescription. Errors due to the omission of the modifier (XP) would be very difficult to detect since there are no differences in the indication of use or dosing interval (use as directed or apply daily) of the two strengths of Differin. In this case, use of the modifier "XP" would unnecessarily introduce an additional component in the product's nomenclature. If the modifier (XP) is not present; the product will be confused with the product Differin. Even when the names are clearly spoken or written, transcription and interpretation of that order may result in omission of the modifier. If the modifier for Differin XP was omitted, the patient would likely receive Differin 0.1% gel. Since the original Differin is of a lower strength (0.1%), the patient would receive a lesser strength, thus a potential continuation or worsening of symptoms could result. The addition of the "XP" modifier does not provide any critical information to the provider in comparison to an inclusion of the actual strength adjacent to the name. In addition, modifiers tend to cause medication errors due to their omission or misinterpretation. The current accepted practice for the addition of a modifier or suffix to an existing proprietary name is to create a unique proprietary name for a modified release dosage formulation. Since this product is merely an increase in strength, DMETS believes the higher strength (0.3%) should be used as a differentiating factor for this product.

   b. Bufferin may resemble Differin when scripted if the modifier is omitted. Bufferin is an over-the-counter buffered aspirin formulation used in the treatment of headaches, minor arthritis pain/inflammation, muscle aches, pain and fever of colds, menstrual pain and toothaches. The available strengths include 325 mg and 500 mg (extra strength). The

[5] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

standard dosing is two tablets every four hours for the 325 mg strength and two tablets every six hours for the 500 mg strength. The resemblance of the names is due to the shared ending of "fferin" when scripted, which is compounded by the similarity of a scripted and capitalized "D" to a lower and upper case "b" (see below).



In addition, the "XP" of Differin may be misinterpreted as the extra-strength of Bufferin. However, the products share no overlapping characteristics such as strength (325 mg/500 mg compared with 0.3%), dosing interval (every four to six hours compared with daily), indication of use (pain compared with acne), dosage form (tablets compared with gel), route of administration (oral compared to topical), and prescription status (over-the-counter compared to prescription). The likelihood for confusion is minimal given these differences.

2. Modifier Issues

   a. DMETS is concerned with potential confusion regarding this modifier. The sponsor has chosen to use the "XP" modifier, which represents extra potency. Per the Red Book[6], this modifier is currently used for four marketed products (list in table 1 below). These drug products share the ingredient of guaifenesin. Thus, the "XP" appears to represent the presence of an expectorant.

Table 1: Products with XP in the Proprietary Name

Proprietary name	Formulation	Manufacturer
Genecof XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	PGD, Inc.
Polytussin XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	Poly
Jaycof XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	Pharmkon
Hydro-tussin XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	Ethex

This "XP" modifier also represents an abbreviation for xeroderma pigmentosum, which is rare genetic defect in ultraviolet radiation induced DNA repair mechanisms that results in photosensitivity, pigmentary changes, premature skin aging, and malignant tumor development, which are due to cellular hypersensitivity to ultraviolet radiation resulting from a defect in DNA repair[7]. Although treatment with oral retinoids has been used to decrease the incidence of skin cancer in these patients, DMETS does not believe this drug product will be confused as a treatment for xeroderma pigmentosum.

[6] Thomson Red Book, 2004, pgs 361, 505, 404, and 381.

[7] Horenstein, Marcelo. Xeroderma pigmentosum. E-medicine. www.emedicine.com/DERM/topic462.htm#section~introduction

b. The possibility that the sponsor will develop a higher strength or alternate formulation (e.g. emollient) of this drug product exists. The introduction of the "XP" modifier may restrict the opportunities for naming future Differin drug products; since there would be an increased possibility for error or confusion if two modifiers were to co-exist in the same proprietary name line.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Differin XP. The safest use of this product may be best managed under the proprietary name Differin. The higher strength (0.3%) should suffice to identify the drug product. Additionally, there is concern over the possibility of misinterpretation of the modifier XP.

Differin XP is the latest product extension to the Differin product line. The products contain the same active ingredient of adapalene. The names Differin and Differin XP are phonetically identical except for the "XP" modifier. Differin contains 0.1% adapalene in four formulations: gel, solution, Pledgettes and cream. All formulations should be applied once daily at bedtime. The gel and cream formulations are available in a 45 gram tube and the solution is available in a 30 mL bottle or 60 count pledgette. The sponsor has proposed to add the modifier XP to the proprietary name Differin, which is to represent an increased strength of the aqueous gel formulation. This concerns DMETS as it will risk the omission of a modifier; therefore eliminate differentiation of strength. Post-marketing error reports and independent research has indicated that the omission of modifiers continues to cause medication errors. Timothy S. Lesar, Pharm.D, conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms.[8] Detailed analysis of 402 medication errors over a 16 month period (Sept. 1999 to Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled release dosage formulation (280 cases or 69.7%). Studies such as this one, support DMETS concern that healthcare professionals may fail to include a modifier (e.g. XP) on a prescription. Errors due to the omission of the modifier (XP) would be very difficult to detect since there are no differences in the indication of use or dosing interval (use as directed or apply daily) of the two strengths of Differin. In this case, use of the modifier "XP" would unnecessarily introduce an additional component in the product's nomenclature. If the modifier (XP) is not present; the product will be confused with the product Differin. Even when the names are clearly spoken or written, transcription and interpretation of that order may result in omission of the modifier. If the modifier for Differin XP was omitted, the patient would likely receive Differin 0.1% gel. Since the original Differin is of a lower strength (0.1%), the patient would receive a lesser strength, thus a potential continuation or worsening of symptoms could result. The addition of the "XP" modifier does not provide any critical information to the provider in comparison to an inclusion of the actual strength adjacent to the name. In addition, modifiers tend to cause medication errors due to their omission or misinterpretation. The current accepted practice for the addition of a modifier or suffix to an existing proprietary name is to create a unique proprietary name for a modified release dosage formulation. Since this product is merely an increase in strength, DMETS believes the higher strength (0.3%) should be used as a differentiating factor for this product.

[8] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

DMETS is concerned with potential confusion regarding this modifier. The sponsor has chosen to use the "XP" modifier, which represents extra potency. Per the Red Book[9], this modifier is currently used for four marketed products (list in table 1 below). These drug products share the ingredient of guaifenesin. Thus, the "XP" appears to represent the presence of an expectorant.

Table 1: Products with XP in the Proprietary Name

Proprietary name	Formulation	Manufacturer
Genecof XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	PGD, Inc.
Polytussin XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	Poly
Jaycof XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	Pharmkon
Hydro-tussin XP	guiafenesin/hydrocodone bitarate/pseudoepedrine	Ethex

This "XP" modifier also represents an abbreviation for xeroderma pigmentosum, which is rare genetic defect in ultraviolet radiation induced DNA repair mechanisms that results in photosensitivity, pigmentary changes, premature skin aging, and malignant tumor development, which are due to cellular hypersensitivity to ultraviolet radiation resulting from a defect in DNA repair[10]. Although treatment with oral retinoids has been used to decrease the incidence of skin cancer in these patients, DMETS does not believe this drug product will be confused as a treatment for xeroderma pigmentosum.

Furthermore, the possibility that the sponsor will develop a higher strength or alternate formulation (e.g. emollient) of this drug product exists. The introduction of the "XP" modifier may restrict the opportunities for naming future Differin drug products; since there would be an increased possibility for error or confusion if two modifiers were to co-exist in the same proprietary name line.

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Since the labels and labeling were presented in draft, it is difficult to properly ascertain and evaluate placement on the carton and container. Please assure the container label and carton labeling is significantly different in presentation (color and design) from the currently marketed Differin 0.1%. This will help practitioners and patients differentiate between the two products and decrease the potential for selection errors.

B. CONTAINER LABEL

1. Please assure the established name is at least one-half the size of the proprietary name as per 21CFR 201.10(g)(2).

[9] Thomson Red Book, 2004, pgs 361, 505, 404, and 381.

[10] Horenstein, Marcelo. Xeroderma pigmentosum. E-medicine. www.emedicine.com/DERM/topic462.htm#section~introduction

C. CARTON LABEL

1. Please reference B1.

D. INSERT LABELING (Package Insert and Patient Package Insert)

1. Dosage and Administration

   a. The package insert and patient package insert (PPI) have different directions for use. The package insert notes the product [redacted]; where the PPI instructs patients that the [redacted] Please assure the instructions for use are the same.

2. Patient Package Insert

   a. In reference to the question of "How should I use Differin XP gel?"

      i. Please consider adding the approved dosing frequency to the first sentence. For example, the recommended dosing for Differin XP is to apply to affected areas of skin once daily, at bedtime or as instructed by your physician.

      ii. Please consider reversing the order of the third and fourth bullet points, so the [redacted] pea size…." is prior to the [redacted] remark for ease of understanding.

      iii. Please specify if Differin XP may be applied to exposed/open [redacted] Since the sixth bullet states that the medicine should be kept away from open wounds.

Appears This Way
On Original

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name, Differin XP. The safest use of this product may be best managed under the proprietary name Differin. The higher strength (0.3%) should suffice to identify the drug product. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review, in order to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name Differin XP acceptable from a promotional perspective.

D. DMETS recommends a consult be submitted to the Division of Surveillance, Research and Communication Support for review of the patient package insert.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kim Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results

Inpatient	Outpatient	Voice
iliffeui XP	Differin XP	Differin SP
Differin XP	Diffllin XP	Differen XP
Differein XP	Differin XP	Differin XP
Differin XP	Differin XP	Diferin XP
Iliffecu XP	Differin XP	Diferen XP
Ibefferin XP	Differin XP	Differin XP
Differen XP	Difplium XP	Differin XP
iliffeui XP	Difolium XP	Diferen XP
Ibiffeuix XP	Differin XP	Diferen XP
Differin XP	Differin XP	Differen XP
Differin XP	Difylium XP	Diferan XP
Differin XP	Differin XP	Differen XP
Differin XP	Differin XP	Differin XP
Differin XP	Diffium XP	Differen XP
Diffececin XP	Differin XP	Differin XP
Differin XP	Differin XP	Giveran XP
Ibifferin XP	Difflium XP	
	Ibbifferi xp	

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/s/

Kimberly Culley
11/17/04 03:14:57 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/17/04 03:56:17 PM
DRUG SAFETY OFFICE REVIEWER