CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204096Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	204096
Product Name:	Astagraf XL (tacrolimus extended-release capsules)

PMC #1 Description: Optimize the dissolution method with respect to detection of (b) (4) content, by evaluating the dissolution profiles of 0.5 mg and 5 mg capsules containing (b) (4) under different test conditions· (medium with 0.0%, 0.05% and 0.1% added sodium lauryl sulfate (SLS), at paddle speeds of 50, 75 and 100 rpm).

PMC Schedule Milestones:		
	Final Protocol Submission:	09/21/2013
	Study/Trial Completion:	09/21/2014
	Final Report Submission:	11/21/2014
	Other: Interim Report	03/21/2014

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☒ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

(b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☒ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

Astellas will evaluate the dissolution profiles of Astagraf XL capsules containing (b) (4) under different test conditions (medium with 0.0%, 0.05% and 0.1% added sodium lauryl sulfate (SLS), at paddle speeds of 50, 75 and 100 rpm). Using the most discriminatory method, Astellas will perform a complete assessment of the dissolution method on capsules with and without added (b) (4) content. The dissolution profiles of aged and stressed samples will be evaluated. Regulatory acceptance criteria will be proposed as supported by the data.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MARK R SEGGEL
07/12/2013

ANGELICA DORANTES
07/12/2013

RAPTI D MADURAWE
07/12/2013

PMR/PMC Development Template: Product Quality (CMC)

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NDA/BLA # 204096
Product Name: Astagraf XL (tacrolimus extended-release capsules)

PMC #2 Description: Optimize the acceptance criteria for the regulatory dissolution test method by analyzing the dissolution profile data of all the strength of your product at release and on stability, obtained by collecting data at two-hour intervals until a minimum of (b)(4)% of tacrolimus is released, as well as at the 24 hour time point. Based on these results, propose the revised acceptance criteria for the dissolution test of your product.

PMC Schedule Milestones:		
	Final Protocol Submission:	09/21/2013
	Study/Trial Completion:	09/21/2014
	Final Report Submission:	11/21/2014
	Other: Interim Report	03/21/2014

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☒ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The dissolution test acceptance criteria (sampling time points and/or limits), as proposed, may not be as discriminating as desired. Data from intermediate time points (at suitable intervals) are not currently available. Dissolution testing of all strengths of drug products at release and on stability (including batches already in the stability program) will allow adjustments to the acceptance criteria that may provide increased assurance of product performance characteristics.

2. Describe the particular review issue and the goal of the study.

The goal of the study is to establish potentially more discriminating dissolution test acceptance criteria. Current sampling time points are 0.5, 1.5 and 24 hours (sampling at 7 hours was routinely conducted for release of clinical lots). The proposed acceptance criterion of NLT (b)(4)% at 24 hours is actually reached sometime between 7 hours and 24 hours.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☒ Dissolution testing
   ☐ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   ☐ Other

   Describe the agreed-upon study:

Astellas will conduct dissolution testing on all proposed capsule strengths, at release and on long-term and accelerated stability, using the currently proposed regulatory method. Samples will be withdrawn at short intervals (2-hours). The data will be used to generate dissolution profiles.

5. To be completed by ONDQA/OBP Manager:

   ☒ Does the study meet criteria for PMCs?
   ☒ Are the objectives clear from the description of the PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 204096
Product Name: Astagraf XL (tacrolimus extended-release capsules)

PMC #3 Description: Evaluate the relationship between (b) (4), and dissolution rate under stressed conditions and under long term stability.

PMC Schedule Milestones:		
	Final Protocol Submission:	09/21/2013
	Study/Trial Completion:	09/21/2014
	Final Report Submission:	11/21/2014
	Other: Interim Report	01/21/2014

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☒ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

(b) (4)

. Optimization of the dissolution method will performed as described in PMC #2.

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by ONDQA/OBP Manager:

   - ☒ Does the study meet criteria for PMCs?
   - ☒ Are the objectives clear from the description of the PMC?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 204096
Product Name: Astagraf XL (tacrolimus extended-release capsules)

PMC #4 Description: Characterize the [redacted (b) (4)] in order to confirm the proposed shelf life [redacted (b) (4)], using a validated and appropriately discriminating direct measurement (e.g., ss-NMR, NIR) of [redacted (b) (4)] and using the optimized discriminating dissolution test. Evaluate stressed and aged samples. Compare the [redacted (b) (4)] prior to introduction into manufacture of capsules, to the [redacted (b) (4)] of the resulting capsules.

PMC Schedule Milestones:

Final Protocol Submission:	09/21/2013
Study/Trial Completion:	09/21/2014
Final Report Submission:	11/21/2014
Other: Interim Report	01/21/2014

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☒ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☒ Improvements to methods
- ☒ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

[redacted (b) (4)]. Optimization of a discriminating dissolution method will performed as described in PMC #2.

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

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- ☐ Assay
- ☐ Sterility
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- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
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07/12/2013

RAPTI D MADURAWE
07/12/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 2, 2013

To: Joette Meyer, Pharm.D., Clinical Team Leader
Office of Antimicrobial Products (OAP)/ Division of Transplant and Ophthalmology Products (DTOP)

Ozlem Belen, M.D., MPH, Deputy Director for Safety
OAP/DTOP

From: Christine Corser, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Astagraf XL™ (tacrolimus extended- release capsules)**
NDA 204096

As requested in DTOP's consult dated November 19, 2012, OPDP has reviewed the following proposed letters for Astagraf XL:

- Dear Health Care Provider (DHCP) letter
- Dear Pharmacist letter
- Dear Professional Society letter

OPDP has reviewed the letters, which were received via email from DTOP on June 28, 2013. DTOP also stated in the email that the edits proposed by DTOP in the DHCP letter will also be applied to the Dear Pharmacist and Dear Professional Society letters.

The purpose of these letters is to inform healthcare providers, pharmacists, and professional societies of the risk of medication and dispensing errors associated with Astagraf XL. OPDP offers the following comments:

General Comments

- These letters are considered to be promotional labeling. Therefore, please remind the sponsor, pursuant to 21 CFR 314.81(b)(3)(i), to submit

the final letters under cover of Form FDA 2253 at the time of initial dissemination.

- Please refer the sponsor to 21 CFR § 200.5 (Mailing of important information about drugs) regarding the format for recommended mailing of important information about drugs. We recommend that the distinctive box described in 21 CFR § 200.5 appear on the envelope in addition to the letter.

- If sending the letters electronically, please remind the sponsor to disseminate the letter in accordance with 21 CFR § 200.5 and the FDA's Guidance for Industry on Using Electronic Means to Distribute Certain Product Information (March 2006).

- FDA's Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of Important Safety Information (November 2010) recommends the letter to be concise and not exceed two pages. If possible, we recommend limiting this letter to two pages.

Specific Comments

- The subject line of the letters state, "Important Information Regarding Risk of Medication Errors with Astagraf XL." We note that the Warnings and Precautions section of the PI describe the possibility of medication **and dispensing errors** (emphasis added). Should the subject line include "dispensing errors" as well?

- The first paragraph of each letter includes only part of the indication for Astagraf XL. We recommend including the full indication, including limitations of use, in the body of the letter. We also recommend including a reference to where the complete indication is located in the letter in conjunction with any presentations of the partial indication for Astagraf XL.

- The first paragraph of each letter includes the following statement, "(b) (4) [redacted]" We are concerned that the presentation of this information in the first paragraph detracts from the main purpose of these letters, which is to communicate the risk of medication and dispensing errors. If this information is necessary and pertinent to the risk described in this letter, we recommend revising the letter to communicate this information in a section of the letter after the risks are disclosed.

- The first paragraph of each letter communicates the following, "Astellas would like to inform you of important risk information regarding medication and dispensing errors, including inadvertent or unintentional substitution, between twice-daily immediate-release and Astagraf XL (once-daily

extended-release) tacrolimus formulations." OPDP recommends including additional information to specifically communicate the severity of the issue in this first paragraph, as recommended in FDA's Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of Important Safety Information (November 2010). For example, we recommend including information that these medication errors have led to serious adverse events, including graft rejection.

- The letters include the statement, "For additional copies of the Medication Guide, please visit www.AstagrafXL.com." If these letters are disseminated electronically, we recommend including a direct link to the Medication Guide.

- The letters include the following, (b) (4) [redacted]." We note that Astagraf XL is associated with a Boxed Warning; therefore, we recommend revising to, "Please read the enclosed Astagraf XL Package Insert for full prescribing information, including Boxed Warnings,…"

- The Dear Professional Society letter states, "We are asking you to share this communication with members of your society (b) (4) [redacted]" (emphasis added). The latter part of this sentence suggests that this letter presents all of the benefits and risks associated with Astagraf XL, which is not the case. The purpose of this Important Drug Warning Letter is to present the risk regarding medication errors, and the placement of this statement early in the letter detracts from this purpose. We recommend deleting this statement. Alternatively, we recommend revising the letter to communicate this information in a latter section of the letter, and we also recommend including an adjacent statement similar to, "This letter is not intended to provide a complete description of the risks associated with the use of Astagraf XL. Please refer to the enclosed Full Prescribing Information, including Boxed Warnings, for a complete discussion of the risks associated with Astagraf XL."

Thank you for the opportunity to provide comments on these draft letters. If you have any questions please contact Christine Corser at 6-2653 or Christine.corser@fda.hhs.gov.

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/s/

CHRISTINE G CORSER
07/02/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 17, 2013
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Astagraf XL (Tacrolimus) Extended-release Capsules, 0.5 mg, 1 mg, 5 mg
Application Type/Number:	NDA 204096
Applicant:	Astellas Pharma, Inc
OSE RCM #:	2012-2550 and 2012-2748

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Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, insert labeling, and communication plan including a Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society Letters for Tacrolimus Extended-release (NDA 204096) for areas of vulnerability that could lead to medication errors. For the purposes of this review, tacrolimus extended-release capsules will be referred to as TAC-ER as requested by the Division of Transplant and Ophthalmology Products.

1.1 BACKGROUND

Immediate-release oral and intravenous formulations of tacrolimus are marketed worldwide for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. In the United States, immediate-release oral and intravenous formulations of tacrolimus (Prograf) were originally approved by the FDA in 1994. Prograf, immediate-release tacrolimus capsules, requires twice-daily oral dosing while tacrolimus extended-release was developed as a once-daily capsule formulation of tacrolimus for the prophylaxis of organ rejection after transplantation. Tacrolimus extended-release capsules have been available since April 2007and are approved in 69 countries.

Medication errors involving confusion between tacrolimus extended-release (TAC-ER) and tacrolimus immediate-release capsules have been reported as a result of similarities with their product characteristics. Both products contain the same active ingredient (tacrolimus), share an overlapping dosage form (capsule), route of administration (oral), strengths (0.5 mg, 1 mg, 5 mg), similar indications for use, similar prescribers, as well as a similar patient population. As a result of the confusion between these two products in the international market, particularly in the United Kingdom, where the majority of the reports originated, risk mitigation strategies were implemented in the European Union (EU) in late 2008 and early 2009 including the issuance of a Dear Healthcare Professional Letter, modifications to TAC-ER's and Prograf's package inserts, as well as additional labeling of TAC-ER's outer packaging emphasizing the once-daily dosing regimen. The risk mitigation strategies focused on resolving the knowledge deficit among practitioners concerning the difference between the extended-release and immediate-release formulations, highlighting the differences in dosing regimens, and including a warning in the package insert that medication errors have occurred involving inadvertent, unintentional or unsupervised substitution of immediate-release or extended-release tacrolimus formulations.

In the U.S., the Applicant proposes to differentiate the two formulations (Prograf and TAC-ER) by proposing a unique proprietary name for TAC-ER, utilizing a different shape, size, and cap colors for the bottles, and differentiating the capsule colors, sizes, and imprints. In addition, the Applicant proposes to include a communication plan that includes a Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society Letters for TAC-ER, similar to what was implemented in the EU. Also, a warning statement will be included in the Warnings and Precautions section of TAC-ER's insert labeling regarding medication errors reported with unintentional substitution of Prograf with TAC-ER.

1.2 REGULATORY HISTORY

The Applicant initially submitted three NDAs for this product: NDA 050811 (prevention of rejection in renal transplantation), NDA 050815 (prevention of rejection in liver transplantation), and NDA 050816 (prevention of rejection in heart transplantation). (b) (4)

On January 31, 2012, a Type B Pre-NDA meeting was held between FDA and Astellas followed by a subsequent Pre-NDA CMC meeting held on February 14, 2012 with the Sponsor. On September 20, 2012, the Applicant submitted NDA 204096 with the indication for use in patients receiving kidney transplants and male only patients receiving liver transplants. On February 6, the Applicant withdrew the indication for liver transplants in male only patients. Since the liver indication had been withdrawn and it was determined that the potential for medication errors could be managed outside of a REMS, the Applicant requested to withdraw the REMS from the NDA on April 18, 2013. The Division concurred with the Applicant to withdraw the REMS.

1.3 PRODUCT INFORMATION

The following product information is provided in the June 5, 2013 revised package insert labeling submission.

- Active Ingredient: Tacrolimus
- Indication of Use: Prophylaxis of organ rejection in adult patients receiving kidney transplants
- Route of Administration: Oral
- Dosage Form: Extended-Release Capsules
- Strengths: 0.5 mg, 1 mg, 5 mg
- Dose and Frequency: Once daily oral administration. The dosage of TAC-ER should be titrated based on clinical assessments of rejection and tolerability. Careful and frequent monitoring of tacrolimus trough concentrations is recommended.

Table 1. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Kidney Transplant Recipients

(b) (4)

Table 2. TAC-ER Administration in Black Patients

Time After Transplant	White Patients n=160		Black Patients n=41	
	Dose (mg/kg)	Mean Trough Concentration (ng/mL)	Dose (mg/kg)	Mean Trough Concentration (ng/mL)
Day 7	0.14	10.65	0.14	7.78
Month 1	0.14	11.11	0.17	10.92
Month 6	0.10	7.95	0.13	8.42
Month 12	0.09	7.53	0.12	7.33

- How Supplied: 30-count bottles and 5 blister sheets of 10 capsules

STRENGTHS:	CAPSULE COLORS:
0.5 mg	Light Yellow/Orange
1 mg	White/Orange
5 mg	Grayish-Red/Orange

- Storage: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (USP Controlled Room Temperature)
- Container and Closure System:
  - Bottles: A square high-density polyethylene (HDPE) bottle with a child resistant and tamper evident cap with a desiccant and a coil

STRENGTHS:	CAP COLORS:
0.5 mg	Brown
1 mg	Blue
5 mg	Orange

  - Blister Packs: Blister sheets wrapped in an (b) (4) pouch with a desiccant

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for TAC-ER medication error reports. In addition, we reviewed the 152 foreign post marketing medication error report narratives provided by the Applicant in their submission dated August 6, 2012 under IND 64148. We also reviewed the TAC-ER labels, package insert labeling, and the communication plan which includes a Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society Letters submitted by the Applicant, in addition to the sample bottles for TAC-ER and Prograf.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Dates	April 1, 2007 (date of TAC-ER's approval in the EU) to December 7, 2012
Drug Names	Tacrolimus (active ingredient) Tacrolimus anhydrous (active ingredient)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

152 foreign post marketing medication error report narratives were provided by the Applicant in their submission dated August 6, 2012 and the FAERS database search identified 313 cases.

Each case was reviewed for relevancy and duplication. After individual review, 302 cases were not included in the final analysis for the following reasons:

- Cases not related to tacrolimus extended-release capsules and/or to medication errors involving label and labeling
- Cases not related to a medication error involving confusion between tacrolimus immediate-release and extended-release formulations
- Adverse drug reaction not related to a medication error
- Drug interactions that are documented in the package insert labeling
- Product quality issues, expired drug
- Wrong time of administration error in which patient took dose outside the specified time period
- Overdose due to unspecified cause

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Bottle Container Labels submitted June 5, 2013 (Appendix B)
- Bottle Carton Labeling submitted June 5, 2013 (Appendix C)
- Unit-Dose Blister Foil Labels submitted June 5, 2013 (Appendix D)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Unit-Dose Blister Pouch Labeling submitted June 5, 2013 (Appendix E)
- Unit-Dose Blister Carton Labeling submitted June 5, 2013 (Appendix F)
- Revised Insert Labeling submitted June 5, 2013
- Dear Healthcare Provider, Dear Pharmacist, and a Dear Professional Society Letters submitted September 21, 2012
- Response to January 25, 2013 FDA Request for Information received February 19, 2013.
- Response to February 1, 2013 FDA Request for Information received March 8, 2013 and March 11, 2013
- Sample bottles of TAC-ER (Advagraf) and Prograf provided by the Applicant during the Pre-NDA meeting on January 31, 2012

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed TAC-ER's label and labeling in OSE #2007-2052 on January 23, 2008 and on March 21, 2008. We looked at the reviews to ensure all our recommendations were implemented. Our comments from the January 23, 2008 review were communicated to the Applicant on January 24, 2008 and it appears most of our comments were adequately addressed. It is unclear if our comments pertaining to the blister foil and blister pillow labels from the March 21, 2008 review were communicated to the Applicant, however, it appears all of our comments regarding the blister labels and labeling have thus far been addressed in their latest submission. Additional comments not implemented from the previous reviews will be addressed in this review.

3 MEDICATION ERROR RISK ASSESSMENT

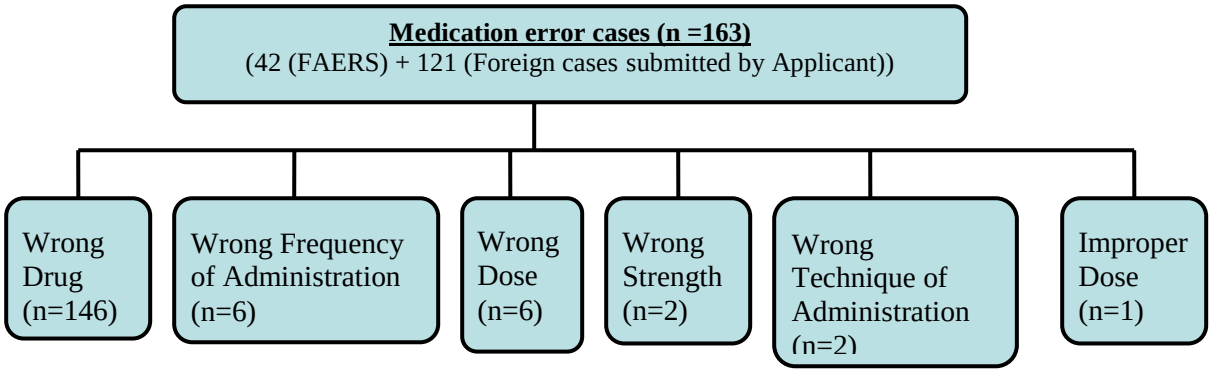
The following sections describe the results of our FAERS search as well as the foreign cases submitted by the Applicant and the risk assessment of the TAC-ER product design in addition to the associated labels and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, forty-two (42) TAC-ER medication error cases identified by the FAERS database remained for our detailed analysis, in addition to the 121 foreign cases submitted by the Applicant. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendices H and I provide listings of all case numbers for the cases summarized in this review.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

Figure 1: TAC-ER medication errors (n = 163) categorized by type of error



3.1.1 Wrong Drug (n=146)

We identified 146 cases of wrong drug error in which 107 cases were due to wrong dispensing and 39 cases due to wrong prescribing in which TAC-ER and Prograf were confused and one drug inadvertently prescribed and/or dispensed for the other.

The wrong dispensing and prescribing errors have resulted in overdose, underdose, graft rejection, as well as other adverse events. The majority of erroneous prescribing and/or dispensing of the unintended formulation originated in the United Kingdom (53 reports from the UK) where prescribing is done primarily with the use of International Nonproprietary Names (INN) (tacrolimus) instead of by proprietary names[2] whereby the specific formulation (immediate-release or extended-release) was not specified. In the Risk Management Plan submitted by the Applicant on September 21, 2012, their analysis of the potential root cause for these medication errors was attributed to a lack of education and awareness, poor communication between healthcare professionals and patient, prescribing by INN, ambiguity of the prescribing, ordering and dispensing computer system, price differences, and also due to possible similarities in the outer-packaging of TAC-ER and Prograf.

One case of wrong drug error (Case #8580520-2) was identified in which a suspension was compounded with TAC-ER instead of Prograf. The outcome was not reported in this case and no root cause was provided as to why the wrong drug was selected to prepare the suspension.

3.1.2 Wrong Frequency of Administration (n=6)

Six wrong frequency of administration errors were identified in which all the patients mistakenly took TAC-ER twice daily instead of once daily due to confusion about their dose. In five of the cases, it mentioned the patient had previously been on Prograf and was switched to TAC-ER and because they were confused about their dose, continued to take TAC-ER twice daily, the same way they had taken Prograf for many years. The sixth case did not provide enough information regarding why they took TAC-ER twice daily. The outcome of these errors was the patients experienced trembling, high

[2] Generics and Biosimilars Initiative (GaBI) . Policies and Legislation Posted 12/08/2011. http://www.gabionline.net/layout/set/print/Country-Focus/United-Kingdom/Policies-and-Legislation

tacrolimus levels, nausea, vomiting, diarrhea, and in one case (#8491096-1) complete graft rejection. The root cause was not provided in any of these cases, but in five of the cases it was stated the patients were confused about their dose after switching from Prograf to TAC-ER which could be a result of patients not receiving adequate counseling from their healthcare professional regarding the proper dosing regimen for TAC-ER.

3.1.3 Wrong Dose (n=6)

Six cases of wrong dose were identified in which the patient mistakenly took the incorrect dose. In two of the cases, the wrong dose error was attributed to noncompliance by the patient. The remaining 4 cases attributed the wrong dose error to the patient self administering the wrong dose due to confusion. The outcomes from these errors include headache, severe tremors, and acute cellular rejection. In one of the four cases (case #2009EU001108), the confusion was attributed to the similarity of the capsule colors between Advagraf 0.5 mg (light yellow and orange) and 1 mg (white and orange). The patient was previously on Prograf but was switched to Advagraf 0.5 mg and 1 mg and possibly due to the similarities in the colors light yellow and white, the patient confused the two strengths and took a suboptimal dose. The patient did not experience any adverse events from this error. The root cause is unknown in the remaining 3 cases.

3.1.4 Wrong Strength (n=2)

We identified 2 cases of wrong strength error. The first case describes a patient who received TAC-ER 0.5 mg instead of 5 mg. No adverse events were reported and the narrative provided no additional information to determine the root cause. The second case involved a wrong strength error in which the patient confused TAC-ER 0.5 mg with 1 mg because of the similarity in package color to Prograf. This case originated from the Netherlands and reports that Prograf 0.5 mg strength is printed in the color green and the 1 mg is printed in the color blue. The case reports that the patient was confused as she received TAC-ER with similar color print strengths to those on the Prograf packaging which caused the patient to confuse TAC-ER 0.5 mg with TAC-ER 1 mg. No further details were provided as to what the colors were for the different strengths of TAC-ER. The patient experienced decreased tacrolimus levels but later recovered.

3.1.5 Wrong Technique of Administration (n=2)

Two wrong technique of administration errors were identified. Both errors involved the nurse opening TAC-ER capsule to administer via nasogastric tube to the patient. No adverse reactions were noted in either of these two cases. We evaluated the insert labeling and note that section 17 (Patient Counseling Information) advises the patient to swallow capsule whole with liquid and to not cut or crush capsules; however, we also found instructions on how to administer TAC-ER to patients who are unable to swallow capsules. The package insert states that a suspension can be prepared from TAC-ER capsules which can then be given by nasogastric tube.

3.1.6 Improper Dose (n=1)

One case of improper dose error (case #2012EU000154) was identified in which a patient inadvertently took 1 addition dose of Advagraf 2 g in the evening after being switched to Advagraf (2 g every morning). The patient did not experience any adverse events. No reason was given as to the root cause of the error, however, it was stated the patient was

switched to Advagraf (most likely from Prograf) and may have been accustomed to taking Prograf twice daily which may have resulted in the patient taking an extra dose of Advagraf in the evening.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The Applicant proposes to implement medication error risk mitigation strategies similar to the strategies implemented in the European Union for tacrolimus extended-release in the United States to help mitigate the confusion between the immediate-release Reference Listed Drug (Prograf) and extended-release formulations. The risk mitigation strategies proposed by the Applicant for the U.S. market to differentiate the two formulations include the following:

1. A unique proprietary name with the modifier 'XL'
2. Different shape and size bottles
3. Different cap colors
4. Different capsule colors, capsule size, capsule imprints
5. A communication plan which includes a Dear Healthcare Providers, Dear Pharmacists, and Dear Professional Societies Letters to inform them of the risk of medication errors
6. A warning statement in the Warnings and Precautions section of the insert labeling for TAC-ER regarding medication errors reported with unintentional substitution of Prograf with TAC-ER.

As the majority of the medication errors identified between tacrolimus immediate-release (Prograf) and tacrolimus extended-release formulations were wrong drug errors as a result of wrong dispensing, wrong prescribing, wrong frequency of administration, wrong dose, and wrong strength, DMEPA anticipates that without mitigation strategies, similar medication errors with the approval of TAC-ER in the U.S. may occur due to the overlapping product characteristics of these two formulations.

Of note, since the approval of the first generic formulation of Prograf in 2009, there has been a gradual increase in the number of prescriptions dispensed and number of patients receiving the generic formulation of tacrolimus. In 2012, approximately (b) (4) of patients receiving a dispensed prescription for oral tacrolimus received the generic formulation compared to approximately (b) (4) who received the brand name.[3] In an attempt to mitigate these potential errors, the Applicant proposes to utilize a unique proprietary name for tacrolimus extended-release. The name will also include the modifier 'XL' to help differentiate between the two formulations. The proposed proprietary name, Astagraf XL, was found acceptable in OSE review #2013-897. In addition, the inclusion of the modifier 'XL' was determined to be appropriate to convey the once-daily dosing frequency for this product.

The Applicant also proposes to provide adequate differentiation between TAC-ER and the Prograf (tacrolimus immediate-release) by using different bottle shapes and sizes as

[3] IMS, Vector One®: National (VONA). Years 2009-2012. Extracted April 01, 2013.

well as statements on the container labels and carton labeling. Furthermore, the strengths of TAC-ER will be differentiated with the use of different color schemes and cap colors that do not overlap with Prograf's cap colors or with the colors within the TAC-ER product line (particularly due to the numeric similarities between the strengths (0.5 mg and 5 mg)) (See Table 1 below). The capsules for TAC-ER and Prograf will also be differentiated by different size, color, and imprint.

Bottle Cap Color Scheme, Size, and Shape for TAC-ER (Advagraf) and Prograf:

Table 1 Advagraf Bottle Presentations

	Advagraf Bottles		Prograf Bottles	
Strength	**Color Scheme**	**Shape**	**Color Scheme**	**Shape**
0.5 mg	brown	short, square plastic bottles	yellow	tall, round plastic bottles
1 mg	blue		white	
5 mg	orange		pink	

Our evaluation of the bottles, bottle caps, container labels, and carton labeling for Prograf and the proposed TAC-ER product found there is adequate differentiation between both products with regard to their bottle shapes (round vs. square), bottle cap colors, and size of the bottle caps (which are not interchangeable between Prograf and TAC-ER). The proposed TAC-ER's container labels and cap colors will be brown, blue and orange compared to Prograf's container labels which are green, blue, and pink and bottle caps which are yellow, white, and pink for the 0.5 mg, 1 mg, and 5 mg strengths, respectively. Although, both TAC-ER and Prograf 1 mg container labels and carton labeling share the same color blue for the strength statement, the use of the color blue on Prograf's container label and carton labeling is only used as the font color for the 1 mg strength statement and for the lines that encircle the strength statement, whereas TAC-ER's strength statement, which is printed in a white font, is encased by a more prominent rectangular shaped blue color block (See Appendix G) which we find to be adequately differentiated. Furthermore, with the existence of multiple Prograf generics in the marketplace (there are currently 6 ANDAs for tacrolimus immediate-release capsules-see above) and (b)(4)% of patients receiving generic Prograf, the similarity of the blue color scheme between the 1 mg strength of the brand Prograf and TAC-ER is therefore a decreased risk.

To further provide distinction between TAC-ER and Prograf which both have similar strengths (0.5 mg, 1 mg, and 5 mg), the Applicant will ensure TAC-ER's capsules are visually distinct in color, imprint, and size from the appearance of Prograf capsules (See Table 2 and Figure 2).

Capsule Color and Imprint for TAC-ER (Advagraf) and Prograf:

Table 2 Advagraf and Prograf Capsule Imprint Information

Strength	Advagraf	Prograf
0.5 mg	Hard capsules. imprinted with red "0.5 mg" on light yellow capsule cap and " 647" on orange capsule body	Hard capsules. light-yellow, imprinted with red "0.5 mg" on the capsule cap and "f 607" on capsule body.
1 mg	Hard capsules. imprinted with red "1 mg" on white capsule cap and " 677" on orange capsule body	Hard capsules. white, imprinted with red "1 mg" on the capsule cap and "f 617" on capsule body.
5 mg	Hard capsules. imprinted with red "5 mg" on grayish red capsule cap and " 687" on orange capsule body	Hard capsules. grayish-red, imprinted with white "5 mg" on the capsule cap and "f 657" on capsule body.

Capsule Appearance and Size for TAC-ER (Advagraf) and Prograf:

Figure 2 Visual Appearance of Advagraf and Prograf Capsules

Although we find the Applicant's attempt to mitigate errors by focusing their efforts on differentiating their proposed extended-release product from Prograf, by use of different color schemes, bottle shapes and sizes, and different capsule sizes, colors, and imprints acceptable for these two products. However, differentiating TAC-ER from only the brand Prograf may not effectively mitigate all medication errors between these two formulations due to the increased use of generic tacrolimus whose label and labeling color schemes and capsule colors are not standardized. The Applicant has also proposed additional strategies to differentiate the extended-release formulation from the immediate-release formulations as described below.

Other strategies to differentiate TAC-ER from the immediate-release formulation include adding the statement "extended-release" to the label and labeling to highlight the different formulation, including the dosing frequency statement "Once-Daily" on the principal display panel of the container labels and carton labeling, proposing a

communication plan to convey to healthcare providers, pharmacists, and professional societies through letters that these formulations are different and not interchangeable and inform them of the risk of medication errors, as well as including a statement in the Warnings and Precautions section of the package insert regarding medication errors reported with inadvertent, unintentional or unsupervised substitution of Prograf with tacrolimus extended-release formulations.

We evaluated the container labels and carton labeling and find the formulation statement, "extended-release," lacks prominence relative to the established name, "tacrolimus." We recommend both the active ingredient, "tacrolimus," and the statement "extended-release" should have equal prominence on the container label and carton labeling to highlight that this is an extended-release product and to help further differentiate it from the tacrolimus immediate-release formulation. Also, we find the dosing frequency "Once-Daily" is stated on the principal display panel of the container label and carton labeling for TAC-ER. However, the placement of the "Once-Daily" statement on the container label is displayed on the same line of text as the strength statement. The customary placement of a frequency statement is not to appear on the same line as the strength statement. Therefore, we recommend relocating "Once-Daily" beneath the strength statement to give equal prominence to both statements. Our evaluation of the insert labeling also finds it clearly states throughout the insert labeling that the product is dosed once daily.

In addition, our evaluation of the communication plan which includes the Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society Letters also found that it states TAC-ER is to be taken once a day. The proposed letters to the different healthcare professions and organizations should be helpful in providing further communication and reinforcing the information that the two formulations are different and are not interchangeable and warn of the potential for confusion between these products. Upon approval of tacrolimus extended-release, we recommend the Applicant revise the Prograf package insert labeling to include a statement in the Warnings and Precautions section regarding reports of medication errors between the immediate-release and extended-release formulations, similar to what was implemented in the EU.

Overall, efforts to differentiate TAC-ER from all tacrolimus immediate-release capsules through risk mitigation strategies that include the use of different color schemes, different bottle shapes and sizes, and different capsule sizes and colors may likely mitigate some errors, particularly with the brand Prograf. However, since the majority of prescriptions dispensed are generics and these strategies are focused on differentiating TAC-ER from the Prograf, we cannot expect all medication errors to be mitigated with these strategies alone. In conjunction with the aforementioned strategies, ensuring the prominence of other features of the label and labeling, such as ensuring the statement "extended-release" is presented with equal prominence with the active ingredient, "tacrolimus" and including the dosing frequency statement "Once-Daily" for the extended-release formulation on the container labels and carton labeling, as well as highlighting the difference in formulations through the use of the modifier 'XL' in the unique proprietary name may further assist in mitigating the confusion between TAC-ER, the RLD Prograf, and other generic immediate-release capsule formulations.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

4.1 COMMENTS TO THE DIVISION

A. Section 2 (Dosage and Administration):

1. Replace the hyphen ("-") within Table 1 and in the last paragraphs of sections 2.1 and 2.5 with the word "to" for improved clarity since hyphens between numbers can be overlooked; for example, resulting in the numbers being read as 517 ng/mL instead of 5 to 17 ng/mL.

4.2 COMMENTS TO THE APPLICANT

A. General Comments

1. Revise the presentation of the proprietary name from all upper case letters to title case to improve readability. For example, "ASTAGRAF" should be revised to read "Astagraf."
2. Although the established name is at least half the size of the proprietary name, the active ingredient "Tacrolimus" is more prominent than the words "extended-release capsules." Ensure the entire established name is displayed with equal prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
3. Revise the highlighted box that encases the strength and the "Once-Daily" statements so that only the strength statement is highlighted on the container labels, carton, and blister pouch labeling. The "Once-Daily" statement should appear outside the highlighted box.
4. Currently, the trade dress for your 5 mg strength is (b) (4) Gray would be an acceptable option for trade dress of the 5 mg strength at this time.

B. Blister Carton Label (All Strengths)

1. Revise the strength statement on the blister carton to read XX mg per Capsule.
2. Revise the net quantity statement on the blister carton to read similar to "50 capsules (5 Blister cards containing 10 capsules each)."

C. Bottle Container Labels (All Strengths)

1. Relocate the "Once-Daily" statement to appear below the strength similar to the proposed presentation on the carton labeling.

2. Relocate the net quantity statement "30 capsules" to appear outside of the highlighted box and place below the statement "Swallow capsule whole. Do not cut, crush, or chew capsule."

3. Decrease the prominence of the statement "Swallow capsule whole. Do not cut, crush, or chew capsule" by presenting this in a smaller font size.

D. Individual Bottle Carton Labels (All Strengths)

1. The strength statement is missing from the top panel which includes the lot number and expiration date. Since it is common practice in a clinical setting to display the box upright, we recommend switching the top panel with the bottom panel to ensure the strength statement is visible when viewed from the top.

E. Accumulated Bottle Carton Labels (All Strengths)

1. The strength statement is missing from the side panel which includes the lot number and expiration date. In order to provide additional differentiation between the different strengths of TAC-ER, include the strength statement on the panel with the lot number and expiration date.

F. Dear Healthcare Provider Letter

1. In the Dear Pharmacist Letter, the section titled (b) (4) However, this information is omitted from the Dear Healthcare Provider Letter. We recommend including this same information in the Dear Healthcare Provider Letter as post marketing data identified wrong drug errors involving wrong prescribing with TAC-ER and this information is also important for warning prescribers of the potential medication errors.

G. Dear Healthcare Provider, Dear Pharmacist, and Dear Professional Society Letters

1. Delete the statement referring to (b) (4) rom the first paragraph of these letters.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

IMS, Vector One: National (VONA) Database

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient’s age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

Appendix B: Bottle Container Labels

Astagraf XL 0.5 mg Bottle

Astagraf XL 1 mg Bottle

Astagraf XL 5 mg Bottle

Appendix C: Bottle Carton Labeling

Astagraf XL 0.5 mg Individual Bottle Carton

Astagraf XL 1 mg Individual Bottle Carton

Astagraf XL 5 mg Individual Bottle Carton

Astagraf XL 0.5 mg Accumulated Bottle Carton

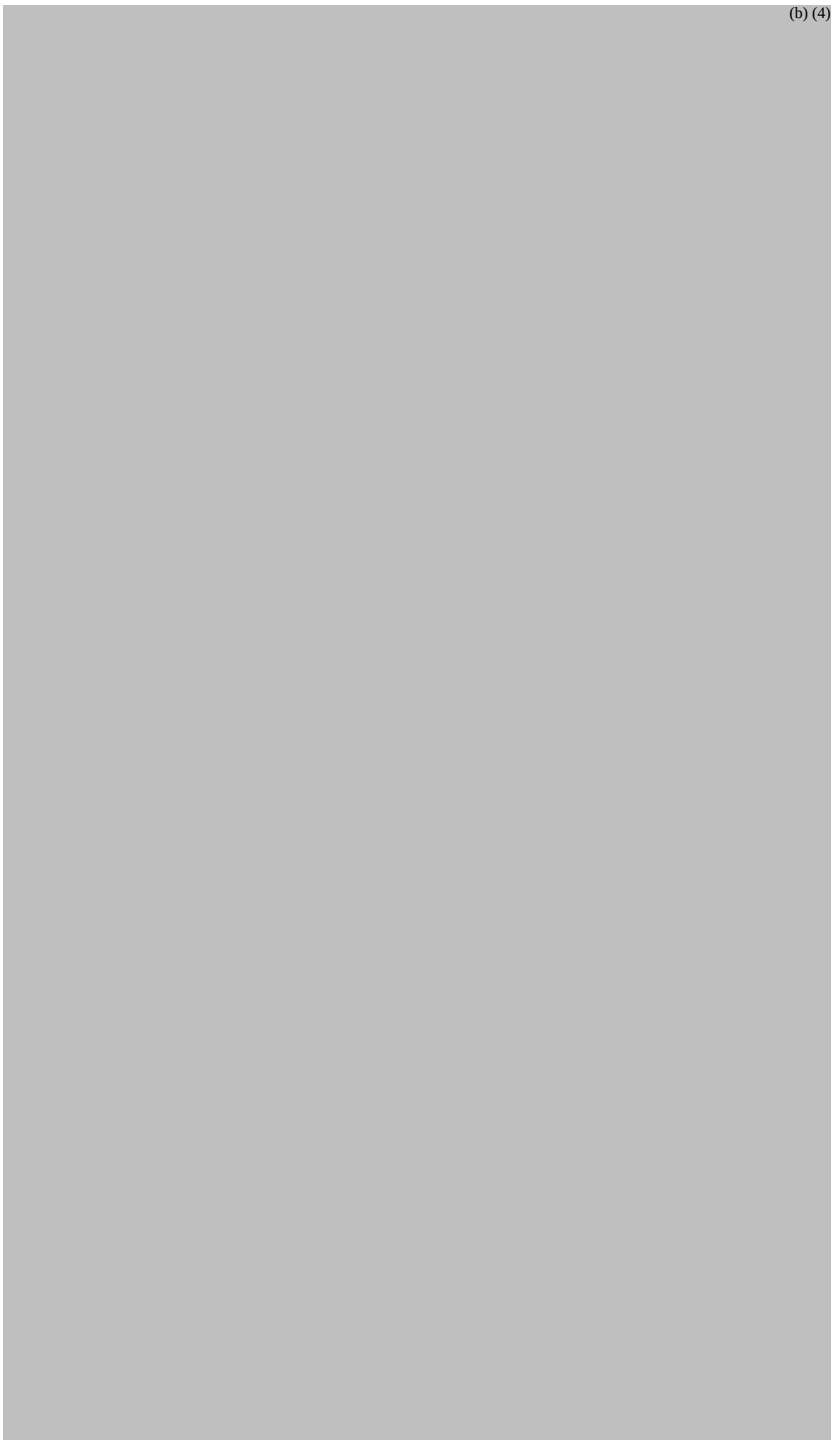
Astagraf XL 1 mg Accumulated Bottle Carton

Astagraf XL 5 mg Accumulated Bottle Carton

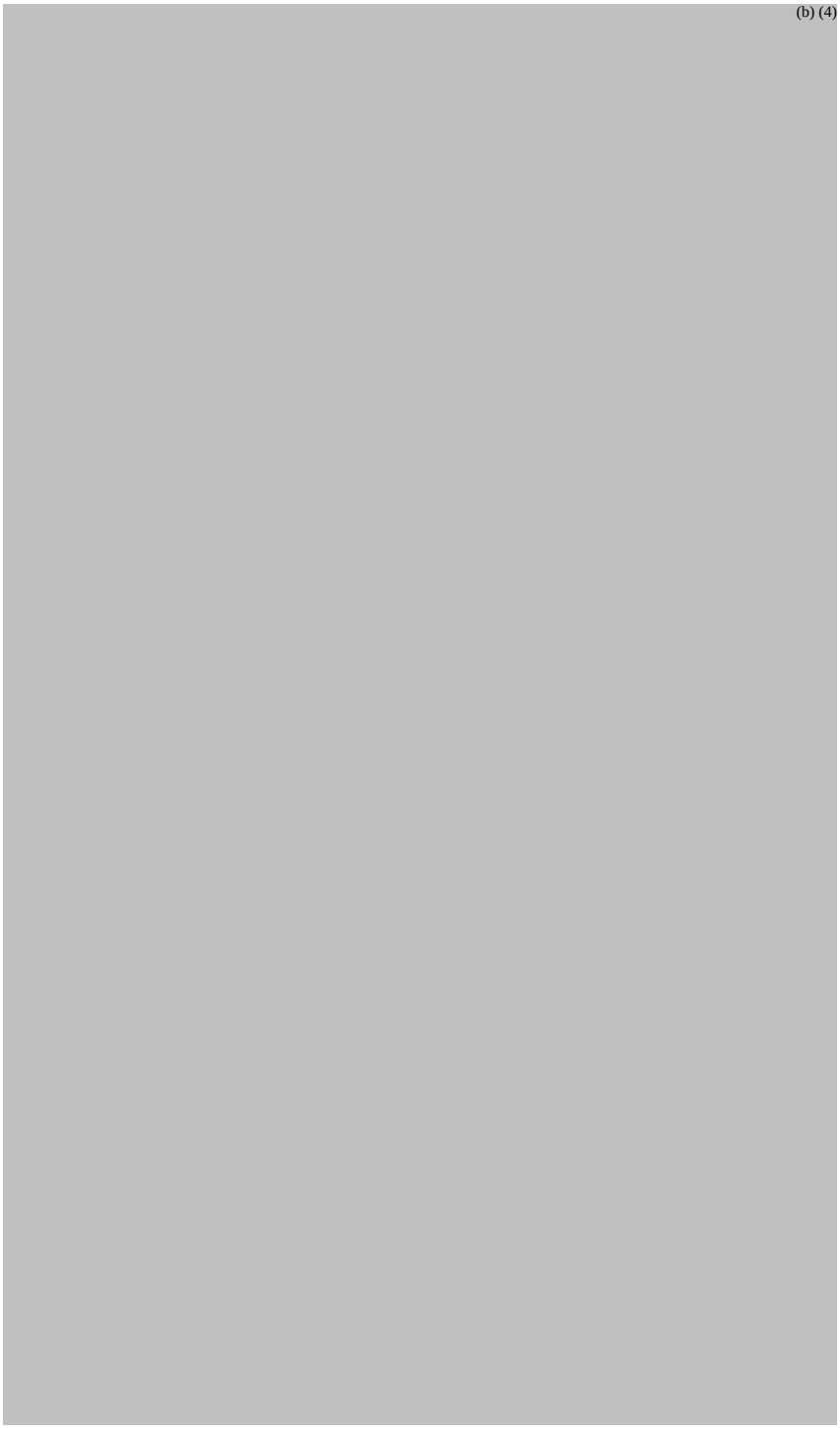
(b) (4)

Appendix D: Unit-Dose Blister Foil Labels

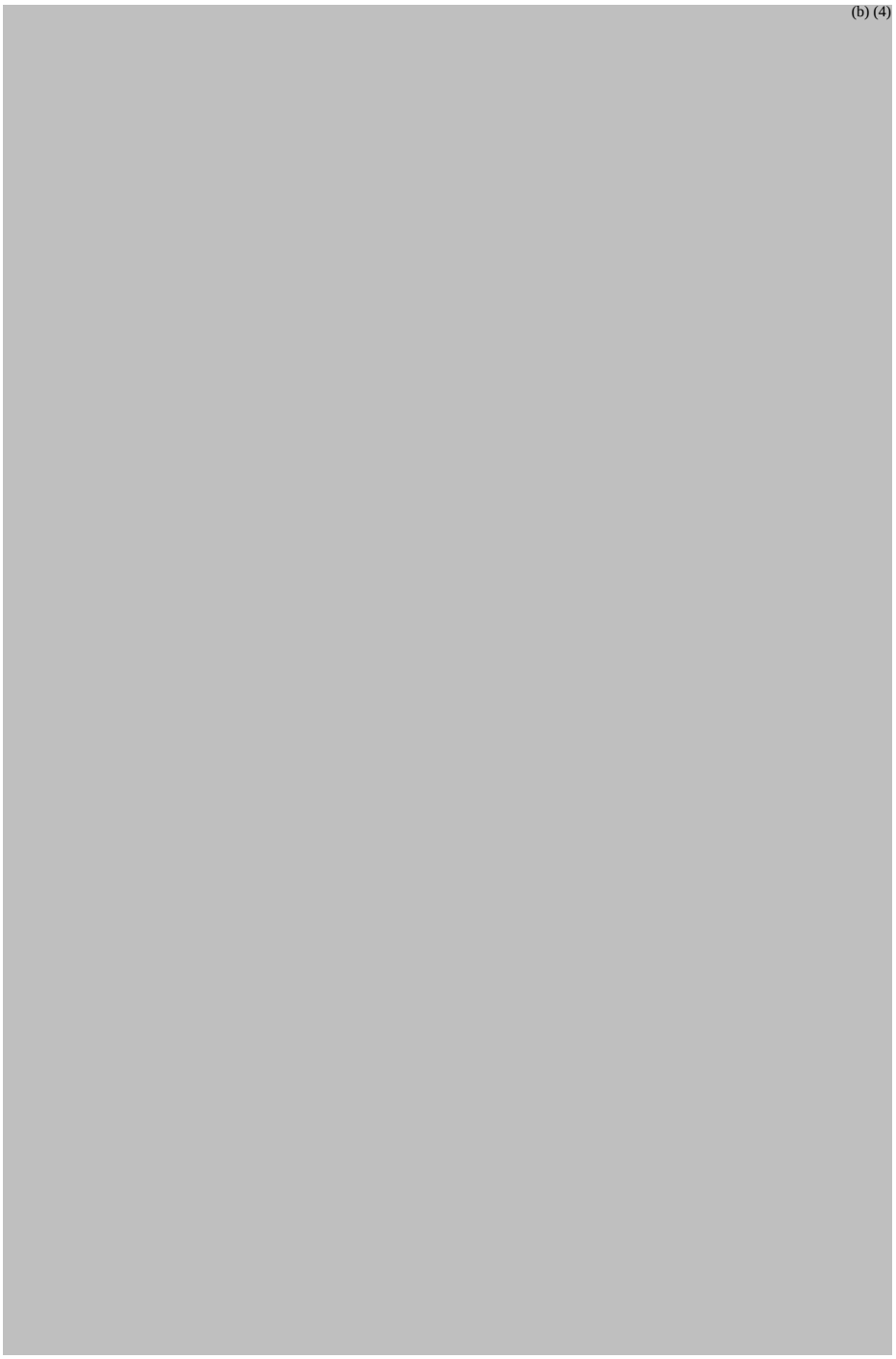
Astagraf XL 0.5 mg Blister Foil



Astagraf XL 1 mg Blister Foil



Astagraf XL 5 mg Blister Foil



Appendix E: Unit-Dose Blister Pouch Labeling

Astagraf XL 0.5 mg Blister Pouch

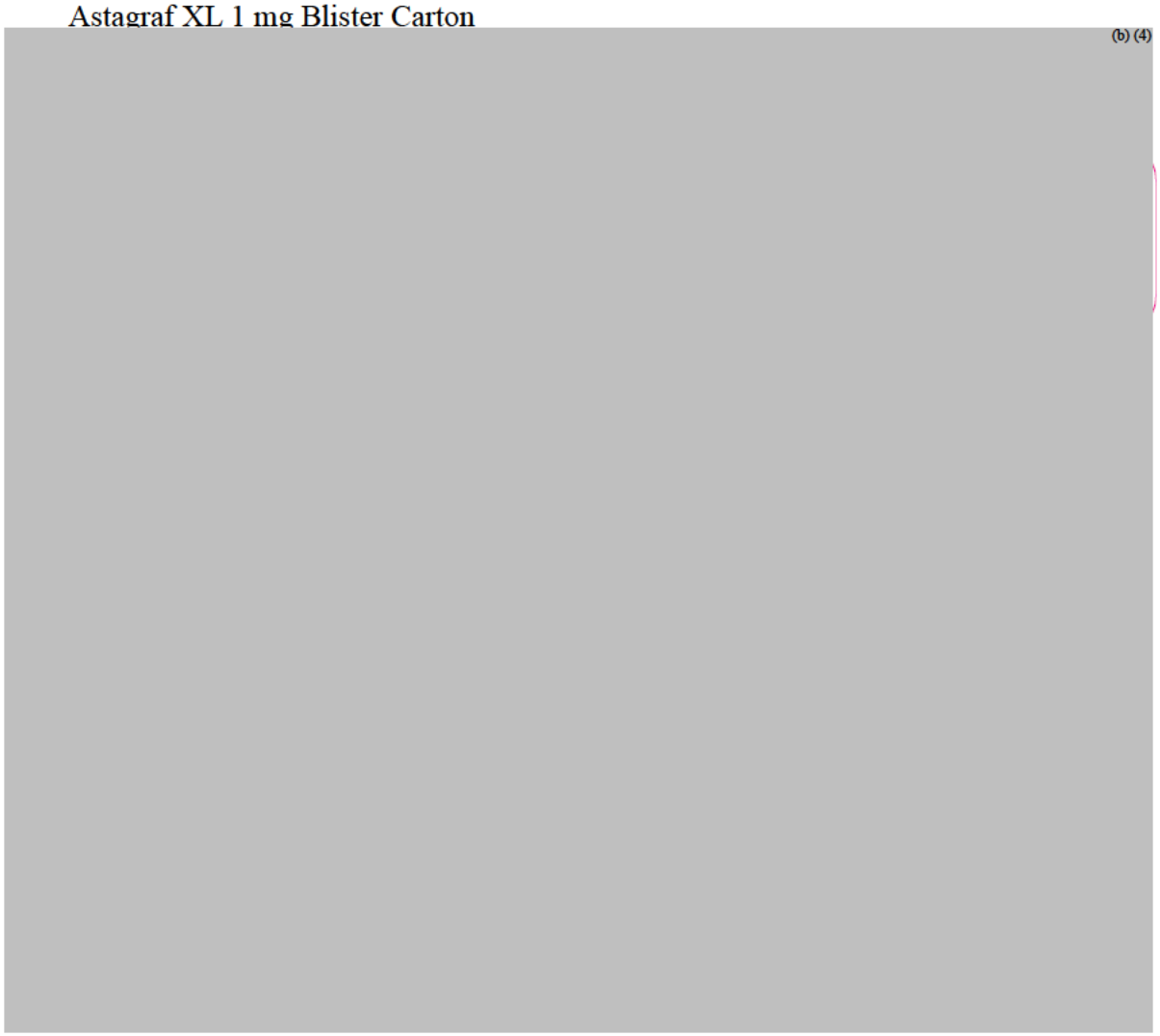
Astagraf XL 1 mg Blister Pouch

Astagraf XL 5 mg Blister Pouch

Appendix F: Unit-Dose Blister Carton Labeling

Astagraf XL 0.5 mg Blister Carton

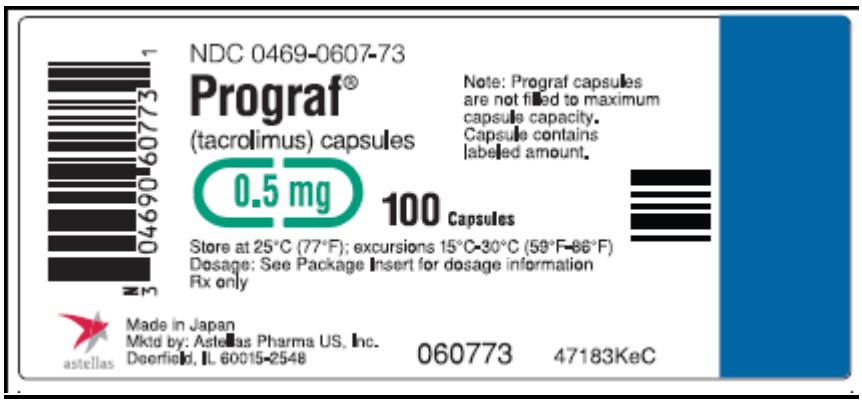
Astagraf XL 1 mg Blister Carton



Astagraf XL 5 mg Blister Carton

Appendix G: Prograf Container Labels

0.5 mg Bottle



1 mg Bottle

5 mg Bottle

Appendix H: FAERS case numbers, medication error type, and narratives discussed in this review

Case Numbers	Medication Error Type	Narratives
6752347-3	Wrong Drug (Dispensing Error)	Advagraf confused with Prograf[Drug dispensing error] high levels of tacrolimus[Drug level increased] diarrhoea[Diarrhoea] vomiting[Vomiting] Increased urea[Blood urea increased] Increased creatinine[Blood creatinine increased] Case Description: Spontaneous REFERENCES: Local ID nr. 4234 UK (E2B Report Duplicate) GB-ASTELLAS-2008E0001634 (E2B Company Number) Astellas paper report ID 2008E0001634 (E2B Report Duplicate) authority case ID GB-MHRA-ADR 20307119 (E2B Report Duplicate) <EVENT INFORMATION #1> VERBATIM TERM: Advagraf confused with Prograf LLT: Drug dispensing error PT: Drug dispensing error ONSET DATE: 11-JUL-2008 OFFSET DATE: 17-JUL-2008 INTENSITY: OUTCOME: Unknown SERIOUSNESS CRITERIA: Medically Significant CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related <EVENT INFORMATION #2> VERBATIM TERM: high levels of tacrolimus LLT: Drug level increased PT: Drug level increased

Case Numbers	Medication Error Type	Narratives
		ONSET DATE: 11-JUL-2008 OFFSET DATE: 17-JUL-2008 INTENSITY: OUTCOME: Unknown SERIOUSNESS CRITERIA: None CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related <EVENT INFORMATION #3> VERBATIM TERM: diarrhoea LLT: Diarrhoea NOS PT: Diarrhoea ONSET DATE: 11-JUL-2008 OFFSET DATE: 17-JUL-2008 INTENSITY: OUTCOME: Unknown SERIOUSNESS CRITERIA: None CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Possible <EVENT INFORMATION #4> VERBATIM TERM: vomiting LLT: Vomiting NOS PT: Vomiting ONSET DATE: 11-JUL-2008 OFFSET DATE: 17-JUL-2008 INTENSITY: OUTCOME: Unknown SERIOUSNESS CRITERIA: None CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Possible <EVENT INFORMATION #5> VERBATIM TERM: Increased urea LLT: Increased urea

Case Numbers	Medication Error Type	Narratives
		PT: Blood urea increased ONSET DATE: OFFSET DATE: INTENSITY: OUTCOME: Unknown SERIOUSNESS CRITERIA: None CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Possible <EVENT INFORMATION #6> VERBATIM TERM: Increased creatinine LLT: Creatinine blood increased PT: Blood creatinine increased ONSET DATE: OFFSET DATE: INTENSITY: OUTCOME: Unknown SERIOUSNESS CRITERIA: None CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Possible Narrative: This spontaneous report, reported by a transplant clinic nurse via a representative, was received on 11AUG2008. A 31 year-old male patient started using tacrolimus (Prograf), 3 mg mane and 2 mg noche, oral in 2001 for prophylaxis of rejection in heart transplant. Patient attended the clinic with unexplained raised trough levels on 11JUL2008. On further investigation the clinic sister asked patient to bring in packet of tacrolimus. The nurse realized that retail pharmacist dispensed Advagraf for Prograf. In addition, patient experienced diarrhea and vomiting and mistakenly believed that he needed to take an extra dose, he took 3 doses of advagraf in 24 hours. Blood tests revealed raised urea and creatinine, which have subsequently reduced, but higher than before adverse event . At time of reporting, outcome of case was unknown. The reporter did not assess the event.

Case Numbers	Medication Error Type	Narratives
		Correction on case on 30SEP2008 The coded event term was corrected to drug dispensing error. Additional information received on 24SEP2009. The events Blood urea increased and Blood creatinine increased were added to the case. Both levels subsequently reduced although not to pre adverse event levels. The reporter did not assess the causality of these events.
6758541-2	Wrong Drug (Dispensing Error)	Confusion between Advagraf and Prograf[Drug dispensing error] Case Description: Spontaneous REFERENCES: Local Case ID 3812.1 (E2B Report Duplicate) GB-ASTELLAS-2008EU001488 (E2B Company Number) Astellas paper report ID 2008EU001488 (E2B Report Duplicate) <EVENT INFORMATION #I> VERBATIM TERM: Confusion between Advagraf and Prograf LLT: Drug dispensing error PT: Drug dispensing error ONSET DATE: OFFSET DATE: INTENSITY: OUTCOME: Recovered / Resolved w/seq SERIOUSNESS CRITERIA: Medically Significant CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related Narrative: Spontaneous report received from a pharmacist on 22JUL2008. This case concerns a (b) (6) patient who was prescribed tacrolimus (Advagraf once daily). In stead of Advagraf 5mg the patient was dispensed 5mg Prograf. The reporter confirmed that the patient did not take the product wrongly dispensed to her. Reporting pharmacist did

Case Numbers	Medication Error Type	Narratives
		not provide an assessment. Follow-up information received on 24SEP2008. A company representative talked with the pharmacist and she reported that the severe confusion between both Advagraf and Prograf took place within the hospital. Patients on the ward have been prescribed Advagraf instead of Prograf and were given Advagraf two times a day. Most of the liver patients had sky high trough levels because they received Advagraf instead of Prograf. Community errors were also in abundance. Patients were presenting at clinic or on the telephone being prescribed the wrong medication. Part of the confusion was due to transplant ward, being over crowded and there were outliers all over the hospital. They tried to keep them on the renal /hepatology wards. Also the ward is full of bank nurses which rotated so frequently that they were not trained and did have so many other issues to cope with. The hospital has taken immediate action by training the junior doctors on the importance of brand name prescription. They stipulated that tac or tacrolimus must not be written on the drug charts. Also the hospital suggested to develop some posters for around the ward and in the drug trolleys which stipulated that Advagraf is once a day and prograf twice a day. They discussed to educate the staff every three weeks or so, depending on the need. The materials were all centralized again to the transplant ward and for the outliers the materials would be marked with stickers. All pharmacists, dispensers and technicians were asked to query every drug chart with tacrolimus, Prograf or Advagraf. All prescription errors would be documented and reported. Also for the discharge letter it was suggested to prescribe by brand.
6762262-2	Wrong Drug (Dispensing Error)	Advagraf confused with Prograf[Drug dispensing error] Case Description: Spontaneous REFERENCES: Local case ID 2354 UK (E2B Report Duplicate) GB-ASTELLAS-2008EU000699 (E2B Company Number) Astellas paper report ID 2008EU000699 (E2B Report Duplicate) EVENT INFORMATION #1>

Case Numbers	Medication Error Type	Narratives
		VERBATIM TERM: Advagraf confused with Prograf LLT: Drug dispensing error PT: Drug dispensing error ONSET DATE: OFFSET DATE: INTENSITY: OUTCOME: Recovered / Resolved SERIOUSNESS CRITERIA: Medically Significant CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related Narrative: Spontaneous report, reported by a pharmacist received on 04APR2008 A female patient of unknown age started Prograf/tacrolimus for renal transplant Instead of Advagraf/tacrolimus, due to dispensing error at retail pharmacy. This is a medication error. The patient has recovered. The reporting HCP assessed the event as not related to Prograf/tacrolimus treatment. Correction on case on 30SEP2008. The event term was changed from medication error to drug prescribing error. The hospital outpatient took her prescription to the community pharmacy. The prescription was written tacrolimus (generic name) and she should have received Prograf but Advagraf was mistakenly dispensed.
6790776-1	Wrong Drug (Dispensing Error)	Spontaneous report, reported by a pharmacist received on xx APR 2008 A female patient of unknown age started Prograf/tacrolimus for renal transplant instead of Advagraf/tacrolimus, due to dispensing error at retail pharmacy. This is a medication error. The patient has recovered. The reporting HCP assessed the event as not related to Prograf/tacrolimus treatment. Not specified Dispensing error at retail pharmacy Medication Error

Case Numbers	Medication Error Type	Narratives
6790828-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative This case concerns a 79 year old male, liver transplant, patient who came in for a routine hernia operation. In run up to the operation the patient was switched from sirolimus to tacrolimus. Instead of Prograf the patient was actually given Advagraf, twice daily. Reporting pharmacist did not provide an assessment. Patient received Advagraf instead of Prograf Unknown Medication Error
6790829-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative A male caucasian patient born on xx (b) (6) 1979 started tacrolimus (Advagraf) on an unspecified date as part of immunosuppressive therapy after renal transplantation. On xx JUL 2008, by mistake, Prograf was administrated instead of Advagraf. The patient was hospitalized but not in the transplantation unit. No other medication use is reported. The patient has unknown medical history. The reporter pharmacist did not give an assessment of causality. Hospitalization Unknown Medication Error
6790830	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative Spontaneous report received from a pharmacist on xx JUL 2008.

Case Numbers	Medication Error Type	Narratives
		This case concerns a patient who was prescribed tacrolimus (Advagraf once daily). Instead of Advagraf 5 mg the patient was dispensed 5 mg Prograf. The reporter confirmed that the patient did not take the product wrongly dispensed to her. Reporting pharmacist did not provide an assessment. Unknown Unknown Medication Error
6796743-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative A 31 year-old male patient started using tacrolimus (Prograf), 3 mg mane and 2 mg noche, oral in 2001 for prophylaxis of rejection in heart transplant. Patient attended the clinic with unexplained traised trough levels on xx JUL 2008. On further investigation the clinic sister asked patient to bring in packet of tacrolimus. The nurse realized that retail pharmacist dispensed Advagraf for Prograf. In addition, patient experienced diarrhea and vomiting and mistakenly believed that he needed to take an extra dose, he took 3 doses of Advagraf in 24 hours. Blood tests revealed raised urea and creatinine, which have subsequently reduced, but higher than before adverse event. At time of reporting, outcome of case was unknown. The reporter did not assess the event. High levels of tacrolimus, diarrhea, vomiting, raised urea and creatinine Physician prescribed bid Advagraf instead of Prograf Medication Error
6796748-1	Wrong Drug Wrong Drug	Abstracted by FDA Representative This case concerns a male patient who received a renal transplant. He was prescribed

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	tacrolimus 5 mg daily, which suggested Advagraf. The patient actually got 3 mg in the morning and 2 mg in the evening of Prograf. Eventually Advagraf, 5 mg daily (the correct drug) was prescribed. The reporter confirmed that this patient did not take the product wrongly dispensed to him. The reporting pharmacist did not provide an assessment. Patient did not take the product wrongly dispensed Prescribed tacrolimus 5 mg daily, received Prograf (3 mg morning 2 mg night) and not Advagraf Medication Error
6807070-1	Wrong Drug (Dispensing Error)	Spontaneous case received on xxDEC2007. The 51 year old male patient was on Prograf (2 mg bid). The patient was dispensed Advagraf instead of Prograf at the pharmacy. Prescription was written generically for tacrolimus 1 mg. The patient took 4 capsules (2 at nights and 2 the next morning). This happened only once and the patient did not report any disturbances regarding this drug dispensing error. The pharmacist reported that this could have happened maybe due to the information on the screen of the ordering system. No further information could be provided at time of reporting. The reporting physician did not assess the causality for this event in relation with the treatment. Unknown Pharmacy, pharmacist "MEDICATIN ERROR"
6807071-1	Wrong Drug (Dispensing Error)	Spontaneous case received on xxSEP2008. A patient of unknown age and gender (an anaesthesist) was prescribed Prograf but at the community pharmcacy Advagraf was dispensed. No further information could be provided. The reporter did not assess the causality between the drug dispensing error and the tacrolimus treatment. Unknown Community pharmacy dispensed Advagraf instead of Prograf.

Case Numbers	Medication Error Type	Narratives
		"MEDICATION ERROR"
6807072-1	Wrong Drug (Dispensing Error)	Spontaneous case received on xxAUG2008 for a transplant nurse. A female patient born on xx(b) (6) 1939 reveived tacrolimus (Prograf) treatment (2mg bid orally) for immunosuppression after kidney transplantation. In JUL2008 at the retail pharmacy the patient was dispensed Advagraf instead of Prograf. The patient did not take the wrongly dispensed medication. No further information could be provided at time of reporting. The reported did not assess the causality between the event and the tacrolimus treatment. The patient did not take the wrongly dispensed medication. Retail pharmacy "MEDICATION ERROR"
6807246-1	Wrong Drug (Dispensing Error)	Spontaneous report, reported by a nephrologist received on xxSEP2008. The reporter experienced multiple situations of drug dispensing errors between Advagraf and Prograf Case 3: A 39 year old female patient started oral tacrolimus (Advagraf) on an uspecified date for kidney transplant immunosuppression. From the local pharmacy the patient received Prograf instead of Advagraf (on receipt of Advagraf). The patient experienced low trough levels and lower transplant function, the latter was not considered to be related to drug misuse. Concomitant medications were not provided. The patient has a histroy of kidney transplantation. The patient's recovery status is recovered without sequelae. The reporting nephrologist did not assess the relationship for the event of drug misuse and lower levels to the tacrolimus therapy. Administrative correction xxSEP2008: Event changed from drug administration error to drug dispensing error. Administrative correction xxOCT2008:

Case Numbers	Medication Error Type	Narratives
		the events drug dispensing error and drug levels decreased are downgraded to non serious events. The patient experienced low trough levels and lower transplant function. Local pharmacy "MEDICATION ERROR"
6807251-1	Wrong Drug (Dispensing Error)	Spontaneous report, reported by a nephrologist received on xxSEP2008. The physician reported multiple situations of dispensing errors with Advagraf and Prograf Case: 2 A 43 year old male patient started oral tacrolimus (Advagraf) on an unspecified date for kidney transplant immunosuppression. On an unspecified date, the patient received Prograf instead of Advagraf from the hospital pharmacy which was noticed in time. Concomitant medications were not provided. The patient has a history of kidney transplantation. The patients recovery status is recovered wtihout sequela. The reporting nephrologist did not assess the relationship for the event of drug dispensing error and tacrolimus therapy. Unknown Hospital pharmacy Medication Error
6807314-1	Wrong Drug (Dispensing Error)	This spontaneous report, reported by a physician was received on xx-SEP-2008. The physician reported multiple situations of dispensing errors with Advagraf and Prograf. Case 1: The male patient (born on xx (b) (6) 1948) was prescribed ADVAGRAF (tacrolimus) for kidney transplantation immunosuppression. On an unspecified date, the patient was dispensed PROGRAF instead of ADVAGRAF from the pharmacy. The pharmacist did receive instructions for Advagraf use (once daily). The patient experienced no clinical side

Case Numbers	Medication Error Type	Narratives
		effects. The treatment regimen was not reported. The outcome for the event of drug dispensing error was recovered without sequelae. The physician did not provide a causality assessment for the event of drug dispensing error. The patient experienced no clinical side effects. Pharmacist "MEDICATION ERROR"
6807918-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative Spontaneous case received on xxAUG2008 from a transplant nurse. A male patient born on xx (b) (6) 1974 received tacrolimus (Prograf) treatment (3mg bid orally) for immunosuppression after kidney transplantation. In JUL 2008 the patient was dispensed Advagraf in stead of Prograf at the retail pharmacy. The patient did not take the wrongly dispensed medication. No further information could be provided at time of reporting. The reporter did not assess the causality between the event and the tacrolimus treatment. Unknown Retail pharmacy Medication Error
6807919-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative Spontaneous case received from a senior renal pharmacist on xxSEP2008. A patient of unknown age and gender was prescribed Prograf but at the pharmacy Advagraf was dispensed. No further information could be provided. The reporter did not assess the causality between the drug dispensing error and the

Case Numbers	Medication Error Type	Narratives
		tacrolimus treatment. Unknown Pharmacy Medication Error
6807921-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative Spontaneous case received on xxSEP2008 A patient (unknown age or gender) was prescribed tacrolimus (Prograf) for immunosuppression after renal transplantation. At the local pharmacy Advagraf was mistakenly dispensed instead of Prograf. When the patient queried this the chemist told him that was fine and it was the same thing just long acting. The patient phoned the transplant unit to double check. At the outpatient department patient cards are being distributed. After query by the reporter the local pharmacist responded that the GP made the mistake. However, the pharmacist did think Advagraf and Prograf could be interchanged. Attempts will be made to contact the GP. No further information could be provided at time of reporting. The reporter did not assess the causality between the drug dispensing error and the tacrolimus treatment. Unknown Pharmacy, chemist, pharmacist, physician Medication Error
6807923-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative Spontaneous case received on xxAUG2008 from a transplant nurse.

Case Numbers	Medication Error Type	Narratives
		A female patient born on xx(b) (6) 1966 received tacrolimus (Prograf) treatment (4mg bid orally) for immunosuppression after kidney transplantation. In JUL2008 at the retail pharmacy the patient was dispensed Advagraf instead of Prograf. The pharmacist told the patient Advagraf was the same as tacrolimus and insisted she would take it twice a day. Patient refused and phoned transplant unit and got prescription elsewhere. The patient did not take the wrongly dispensed medication. No further information could be provided at time of reporting. The reporter did not assess the causality between the event and the tacrolimus treatment. Unknown Pharmacist, incorrect dosage Medication Error
6807926-1	Wrong Drug (Dispensing Error)	Abstracted by FDA Representative Spontaneous case received on xxSEP2008 from a hospital pharmacist. A 49 year-old female patient was prescribed Prograf as immunosuppressive therapy after renal transplantation. At the pharmacy Advagraf was dispensed. She ended up taking a combination of the two: 1 mg Prograf and 0.5 mg Advagraf. She was admitted to the hospital briefly with an episode of acute rejection. A biopsy was taken which showed acute rejection The patient was discharged from the hospital when she had recovered from the event. She has had no long term problems from the drug dispensing error so far. No further information could be provided at time of reporting. The reporter did not assess the causality between the rejection episode or drug dispensing error and the tacrolimus treatment. Follow up information was received on xxOCT2008 with the complete reporter details which were added. She was admitted to the hospital briefly with an episode of acute rejection. Pharmacy, incorrect dosage

Case Numbers	Medication Error Type	Narratives
		Medication Error
6836764-1	Wrong Drug (Dispensing Error)	Spontaneous case received on xxOCT2008 A patient (unknown age or gender) was prescribed Advagraf. At the local pharmacy the prescription was torn into pieces and the pharmacist told the patient that no Advagraf existed. The patient gave a call to his transplant center which in turn gave a call to the pharmacist advising him to contact the manufacturers local affiliate. No further information could be provided at time of reporting. The reporter did not assess the causality between the drug dispensing error and the tacrolimus treatment. Unknown Drug dispensing error, local pharmacy, pharmacist medication error
6836967-1	Wrong Drug (Dispensing Error)	Spontaneous case received on xxSEP2008 from a renal pharmacist. A patient of unknown age and gender received Prograf treatment for immunosuppression. At the retail/community pharmacy the patient was dispensed Advagraf instead of Prograf. Outcome of the event is unknown. No further information could be provided at time of reporting. The reporter did not assess the causality between the event and the tacrolimus treatment. Unknown Drug dispensing error, retail/community pharmacy medication error
6838503-1	Wrong Drug (Dispensing Error)	Spontaneous case received from a pharmacist on xxSEP2008 A patient (unknown age or gender) was prescribed Advagraf (0.5 mg) but Advagraf was not available at the pharmacy. The phamacist decided to dispense Prograf instead. The

Case Numbers	Medication Error Type	Narratives
		pharmacist had discussed the conversion with the transplant physician, who explained that the patient attended the hospital regularly for check ups and blood tests to measure the trough levels of tacrolimus. The pharmacist said that she would ensure that the patient is not switched back to Advagraf and will remain on Prograf, since there is never a stock problem with Prograf. No further information could be provided at time of reporting. The reporter did not assess the causality between the drug dispensing error and the tacrolimus treatment. Unknown Drug dispensing error, pharmacist medication error
6838504-1	Wrong Drug (Dispensing Error)	Spontaneous case received from a senior renal pharmacist on xxSEP2008. A patient of unknown age and gender was prescribed Prograf but at the pharmacy Advagraf was dispensed. No further information could be provided. The reporter did not assess the causality between the drug dispensing error and the tacrolimus treatment. Unknown Drug dispensing error, pharmacy medication error
6838509-1	Wrong Drug (Dispensing Error)	Spontaneous report, reported by a transplant nurse, received on xxSEP2008. A 34 year old male patient started tacrolimus (Prograf) as an immunosuppressive therapy after transplantation. At an unknown date a drug dispensing error was made and the patient was given Advagraf instead of Prograf. The patient recognized the different boxes and called the hospital back. He was told to go back to his chemist and change it with Prograf which he did successfully. No further information was provided by the reporter at this time. The reporter did not assess the relationship between the drug dispensing error and tacrolimus treatment.

Case Numbers	Medication Error Type	Narratives
		Unknown Drug dispensing error medication error
6838510-1	Wrong Drug (Dispensing Error)	Spontaneous case received on xxSEP2008 from a senior clinical liver pharmacist. A patient of unknown age and gender received Prograf treatment for immunosuppression after liver transplantation. At the community pharmacy the patient was dispensed Advagraf instead of Prograf. Outcome of the event is unknown. No further information could be provided at time of reporting. The reporter did not assess the causality between the event and the tacrolimus treatment. Unknown Community pharmacy medication error
6866627-1	Wrong Drug (Dispensing Error)	Drug prescribing error[Drug prescribing error] acute rejection[Transplant rejection] Case Description: Spontaneous REFERENCES: GB-ASTELLAS-2008EU002113 (E2B Company Number) Astellas paper report ID 2008EO002113 (E2B Report Duplicate) Local ID no. 0004987/UK (E2B Report Duplicate) MHRA paper report ID GB-MHRA-ADR 20326733 (E2B Report Duplicate) <EVENT INFORMATION #1> VERBATIM TERM: Drug prescribing error LLT: Drug dose prescribing error PT: Drug prescribing error

Case Numbers	Medication Error Type	Narratives
		ONSET DATE: OFFSET DATE: INTENSITY: OUTCOME: Not recovered/Not resolved SERIOUSNESS CRITERIA: Hospitalized <Suspect drug #1: Prograf > CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related <Suspect drug #2: Advagraf > CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related <EVENT INFORMATION #2> VERBATIM TERM: acute rejection LLT: Acute graft rejection PT: Transplant rejection ONSET DATE: 26-SEP-2008 OFFSET DATE: INTENSITY: OUTCOME: Not recovered/Not resolved SERIOUSNESS CRITERIA: Hospitalized <Suspect drug #1: Prograf> CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related <Suspect drug #2: Advagraf> CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related Narrative: Spontaneous report, reported by a transplant nurse received on 30SEP2008.

Case Numbers	Medication Error Type	Narratives
		A male patient, born in 1966 started using Prograf as immunosuppressive therapy after transplantation. Patient phoned the Hospital, reporting that he was feeling unwell and he was admitted at the Hospital. On admittance, the patient's medication was checked. A prescribing error was made. Patient should have been taking prograf, 2.5 mg, twice a day, but was taking Advagraf, 2 mg and prograf 0.5 mg, twice a day. On (b) (6), there were early signs indicated acute rejection, which was confirmed after biopsy. At time of reporting, outcome of event was unknown. The reporter did not assess the relationship between the events and the treatment with Prograf/ Advagraf. Follow-up info received by phone on 23OCT2008 from pharmacist: The pharmacist knows patient well. Patient got repeat prescription on 29AUG2008. Pharmacist explained that it is difficult to get hold of prograf. It is often ordered from Astellas as pharmacy they often do not have it in stock. The database of the pharmacy had no info on advagraf to say that it was modified-release. The pharmacist subsequently altered the database, so that it would raise a warning that generic tacrolimus prescriptions should not be issued as advgraf. Subsequently the pharmacy has changed their database and has a disclaimer about details on it. The pharmacist acknowledged that after a drug was prepared, it should be checked by a different pharmacist but time and staff shortage often make this difficult. He did not spot that advagraf was modified-release or a once daily preparation on the packaging. Follow up info received by telephone on 15OCT2008 from transplant nurse: Patient had transplant in 2003. The patient phoned the clinic on 19SEP2008 feeling unwell, and attended the clinic on 22SEP2008. Creatinine level was 489 (normal range 180-210). Through tacrolimus level in clinic was 5.6. Treatment consisted of pulsed Methylpred 0.5 g x 3. Patient had mild chronic allograft nephropathy and acute tubulo interstitial rejection. The local pharmacist has agreed to clarify the circumstances surrounding the dispensing error.
7095144-1	Wrong Drug	Drug administration error[Drug administration error]

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	Case Description: Spontaneous REFERENCES: Local report ID PRG-105 (E2B Report Duplicate) ES-ASTELLAS-2009EU003020 (E2B Company Number) Astellas paper report ID 2009EU003020 (E2B Report Duplicate) <EVENT INFORMATION #1> VERBATIM TERM: Drug administration error LLT: Drug administration error PT: Drug administration error ONSET DATE: OFFSET DATE: INTENSITY: OUTCOME: Unknown SERIOUSNESS CRITERIA: Medically Significant <Suspect drug #1: Prograf> CAUSALITY (INV): Probable CAUSALITY (MFR): Not Related <Suspect drug #2: Advagraf> CAUSALITY (INV): Probable CAUSALITY (MFR): Not Related Narrative: Spontaneous case received on 31JUL2009. A male patient of unknown age started a treatment with tacrolimus (Advagraf 7.5mg/day) after lung transplant. One day on an unknown date the patient received 5 mg Advagraf plus 2.5 mg Prograf which was reported as drug administration error. No further serious events were reported.The reporter notified a pharmacys error due to a mix in tablets. They only noticed generic name instead of trade name.

Case Numbers	Medication Error Type	Narratives
		The patient medical history and concomitant medication were not reported. The outcome of the event was unknown/not applicable. The event of drug administration error was assessed as probably related to tacrolimus (Prograf/Advagraf) treatment.
7097694-2	Wrong Drug (Dispensing Error)	Pharmacy delivered conventional Prograf[Drug dispensing error] Case Description: Spontaneous REFERENCES: Janssen-Cilag paper report ID COL000030709SP CO-ASTELLAS-2009US003040 (E2B Company Number) Astellas paper report ID 2009US003040 (E2B Report Duplicate) <EVENT INFORMATION #1> VERBATIM TERM: Pharmacy delivered conventional Prograf LLT: Drug dispensing error PT: Drug dispensing error ONSET DATE: 01-AUG-2009 OFFSET DATE: INTENSITY: OUTCOME: Recovered / Resolved SERIOUSNESS CRITERIA: Hospitalized <Suspect drug #1: Prograf XL > CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related <Suspect drug #2: Prograf > CAUSALITY (INV): Not Assessed CAUSALITY (MFR): Not Related

Case Numbers	Medication Error Type	Narratives
		Narrative: Initial information received 05-AUG-2009. This spontaneous case was reported by a nurse and forwarded by Janssen-Cilag (COL-0000307-09-SP). The male patient experienced a drug dispensing error with the use of PROGRAF XL (tacrolimus) therapy. Medical history includes kidney transplantation. Co-suspect medications include PROGRAF (tacrolimus). Concomitant medications were not reported. On an unspecified date, the patient began oral PROGRAF XL (dosage information not provided) for kidney transplantation immunosuppression. On 01-AUG-2009, a pharmacy delivered conventional PROGRAF (dosage information unspecified) to the patient instead of the prescribed PROGRAF XL. The patient changed the drug after one week without any symptoms associated. Outcome for the event drug dispensing error was resolved. The reporter did not provide a causal assessment for the drug dispensing error and PROGRAF XL and PROGRAF therapies. Additional information received 27-AUG-2009. It was reported that no further information would be provided.
8392174-4	Wrong Drug (Dispensing Error)	Information was received on 02NOV2011. This is a spontaneous report from a female patient of unknown age and race who experienced adverse drug reaction during Prograf (tacrolimus) treatment. Medical history included primary sclerosing cholangitis for which the patient underwent liver transplant on (b) (6), consumption of alcohol (<10 g/day). No concomitant medications were provided. The patient started taking tacrolimus 8 mg daily from an unknown date for liver transplant. On an unknown date, the patient experienced adverse drug reaction. According to the patient, the adverse drug reactions were disabling.

Case Numbers	Medication Error Type	Narratives
		Trough levels of tacrolimus included 5 ng/ml on 27OCT2011 under Prograf (tacrolimus) 8 mg daily. Action taken with tacrolimus was unknown. The outcome of adverse drug reaction was unknown. The Astellas medical reviewer assessed adverse drug reaction as serious due to disability. ---------- Non-significant follow-up information was received on 07FEB2012. The hepatologist reported that he was not informed about adverse event reported by the patient. There was no medical confirmation. ---------- Follow-up information was received on 21FEB2012. The suspect drug Advagraf (tacrolimus) was added. The event term medication error was added. Concomitant medication included: corticosteroids nos (concomitant with Advagraf treatment) On 27OCT2011 the patient was included in OSIRIS study. On 28OCT2011 the patient started Advagraf 8 mg daily. It was reported that the patient was not treated with Advagraf (tacrolimus) anymore, the patient switched treatment from Advagraf to Prograf because Advagraf was not available in the pharmacy during her trip (This was considered as medication error). On 12JAN2012 trough levels of tacrolimus was 7 ng/ml under Prograf (tacrolimus) 8 mg daily. The patient received Prograf 8 mg daily and corticosteroids 7.5 mg daily. Following consultation Advagraf 8 mg daily and corticosteroids 7.5 mg were prescribed. Action taken on Advagraf was not applicable. The outcome of the event medication error was unknown. The Astellas medical reviewer assessed the event medication error as non serious. ---------- Follow-up information was received on 09MAY2012. The patient did not experience rejection episode since the initiation of Advagraf (tacrolimus). At the time of reporting, the patient was still receiving Advagraf (tacrolimus). He was receiving Advagraf (tacrolimus) 8 mg daily. The prescribed treatment following the consultation was 7 mg daily. Lab data included: Trough level of tacrolimus was 6.8 ng/ml under Prograf 8 mg daily on

Case Numbers	Medication Error Type	Narratives
		26APR2012. ---------- Follow-up information was received on 26SEP2012. The event terms were amended to medication error (Advagraf) and adverse drug reaction (Prograf). The hepatologist specified that the patient was receiving Advagraf (tacrolimus) 8 mg daily and was prescribed 7 mg daily following the consultation for dosage adjustment according to the T0.
8890803-1	Wrong Drug (Dispensing Error)	On 29OCT2012, a spontaneous report was reported by a company representative and a pharmacist regarding a 50 year old male who experienced pulmonary hypertension, nose bleed, green liquid stool and received Prograf (tacrolimus) in error with Advagraf (tacrolimus). On an unspecified date, the patient started Advagraf 8 mg for renal transplant immunosuppression. On an unspecified date, the patient was hospitalized for pulmonary hypertension. On (b) (6), he was transferred to another hospital after being stabilized. On 24OCT2012, his tacrolimus level was 11.2 ng/mL. On 27OCT2012, his Advagraf 8 mg dose was substituted for Prograf 8 mg by a pharmacy technician by accident. The same evening, the patient complained of a nose bleed and green liquid stool. He did not receive a second dose of Prograf. On 28OCT2012, the patient was restarted on Advagraf. On 29OCT2012, another tacrolimus level was drawn and results were pending at the time of this report. Concomitant medications included mycophenolate mofetil, prednisone and warfarin. The outcome of the events was not reported. The reporting pharmacist did not provide a seriousness or causality assessment of the events. An Astellas Medical Reviewer assessed the events of nose bleed, green liquid stool and received Prograf in error as non-serious. No further information was provided.
6807066-1	Wrong Drug (Prescribing Error)	A patient (unknown age or gender) was prescribed 0.5 mg Advagraf instead of Prograf 0.5 mg by a general practitioner twice (linked case ID xx). The first time it was noticed by the pharmacy before it was dispensed and Prograf was dispensed instead. But Advagraf remained on the shelf. Two weeks later the same prescribing error was made at the GP surgery and Advargraf was dispensed to fulfill the script. The error was noticed by the patient's mother and Advagraf was not taken. No further information could be provided at time of reporting. The reported did not assess the causality between the drug dispensing error and the tacrolimus treatment. Advagraf was not taken by patient.

Case Numbers	Medication Error Type	Narratives
		General practitioner, pharmacy "MEDICATION ERROR"
6807068-1	Wrong Drug (Prescribing Error)	Spontaneous case received on xxSEP2008. A patient received tacrolimus (Advagraf) treatment for immunosuppression after kidney transplantation. One time Advagraf was given twice daily because the doctor who was in charge that evening did not know the unique thing about Advagraf (once daily administration). This was a young surgeon and unfortunately the nurse who took the ordination is a newly employed nurse that did not question his decision. The patient did not experience any side effects and when this was noticed the next day the patient got his morning dose and from that on Advagraf was given once daily. No further information could be provided at time of reporting. The patient did not experience any side effects. The reporter did not assess the causal relation of the event with the tacrolimus treatment. Advagraf was given twice daily because the doctor who was in charge did not know that Advagraf is a once daily administration. "MEDICATION ERROR"
6808443-1	Wrong Drug (Prescribing Error)	Spontaneous report, reported by a transplant nurse received on xxSEP2008. A male patient, born in 1966 started using Prograf as immunosuppressive therapy after transplantation. Patient phoned the hospital, reporting that he was feeling unwell and he was admitted at the hospital. On admittance, the patient's medication was checked. A prescribing error was made. Patient should have been taking Prograf, 2.5 mg, twice a day, but was taking Advagraf, 2mg and Prograf 0.5 mg, twice a day. On xxSEP2008, there were early signs indicated acute rejection, which was confirmed after biopsy. At time of reporting, outcome of event was unknown. The reporter did not assess the relationship between the events and the treatment with Prograf/Advagraf. The patient reported that he was feeling unwell. OnxxSEP2008, there were early signs that indicated acute rejection, which was confirmed after biopsy. A prescribing error was made. MEDICATION ERRORS

Case Numbers	Medication Error Type	Narratives
6836892-1	Wrong Drug (Prescribing Error)	Spontaneous case received from a liver specialist on xxSEP2008. A patient (unknown age or gender) was switched from sirolimus to tacrolimus for immunosuppression after liver transplantation 6 weeks prior to surgery due to issues with wound healing. The patient was called back to the hospital to check levels at day 10. The patient had trough levels of 13ng/ml which should have been around 5 mg/nl as the patient was 10 years post-transplantation. The patient had been prescribed Advagraf bid rather than Prograf bid. This error was noted and the patient was switched to Prograf bid. No further information could be provided at time of reporting. The reporter did not assess the causality between the drug prescribing error or high trough levels and the tacrolimus treatment. High drug levels of tacrolimus; the patient had trough levels of 13mg/ml which should have been around 5 mg/ml. Drug prescribing error; the patieint had been prescribed Advagraf bid rather than Prograf bid. medication error
6838507-1	Wrong Drug (Prescribing Error)	A patient of unknown age or gender was prescribed 0.5 mg ADVAGRAF in error instead of PROGRAF 0.5 mg by a general practitioner (country of incidence: United Kingdom). The drug prescribing error was noticed at the pharmacy and ADVAGRAF was not dispensed. Instead, PROGRAF was dispensed. The report indicated that ADVAGRAF remained on the shelf. No adverse event was reported. The report indicated that a pharmacist reported the event and no further information could be provided at the time of reporting. No further information could be provided at the time of reporting. No further information could be provided at the time of reporting. medication error
7192518-3	Wrong Drug	Medication error [Drug prescribing error]

Case Numbers	Medication Error Type	Narratives
	(Prescribing Error)	Case Description: Spontaneous report, reported by a hospital pharmacist received on 02NOV2009. A young female patient started tacrolimus (Prograf) at an unknown date for organ transplant. The patient had recently been moved from Prograf to Advagraf. At an unknown date she was hospitalized due to increased creatinine levels. One of the doctors read her old notes and as a result the patient was put on Prograf instead of Advagraf. This was only one dose a day, for a period of a day. The event was resported as a medication error. No adverse event was reported. The reporting pharmacist did not provide a causality assessment. ---------- Follow-up information received on 23NOV2009 The pharmacist reported that the increased creatinine levels were due to sepsis. The patient received advagraf 8 mg AM at home and prograf 4mg PM at the ward on the same day. The medication error occurred on (b) (6) till (b) (6), the patient was on her regular Advagraf 8mg once daily treatment from the next day (b) (6) which was started from FEB2008. The reporting pharmacist reported that the error was due to the doctor who was confused between two prescriptions and the dispensing pharmacist. ---------- On 28DEC2009, correction awareness. The serious criterium was corrected to non-serious. The patient was not hospitalized for the event drug prescribing error. Evaluator Comment:

Case Numbers	Medication Error Type	Narratives
		Drug prescribing error. Considered unlisted and not related. Relationship of increased creatinine to prescribing error is uncertain. Timelines not assessable. Follow-up information received on 23NOV2009: no change in medical assesment FU correction 28DEC2009: no change to medical assessment. Downgrade
8107077-3	Wrong Drug (Prescribing Error)	Information was received on 25MAY2011. This is a spontaneous case reported by a physician referring to a 12-year-old adolescent female patient who experienced encephalopathy grade III, hyperammonemia, incoherent speech, balance disorders, somnolence, high trough level of tacrolimus and eyelids oedema during Advagraf (tacrolimus) treatment. The patient received Avagraf (tacrolimus) which was considered as off label use as the patient is a child. Medical history included: Liver transplant in 2000 as procedure due to atresia of biliary and Prograf (tacrolimus) as historical drug. No concomitant medication was reported. The patient started Advagraf (tacrolimus) orally unspecified dose for liver transplant from 04MAY2011 to 16MAY2011. On the (b) (6) the patient presented with eyelid oedema and increased trough level of tacrolimus at 30ng/ml. Due to this high level of tacrolimus , the dosage regimen of Advagraf was halved. On the (b) (6) the patient was admitted to emergency care because she had presented with incoherent speech, balance disorders and somnolence. On the (b) (6) the patient also presented with hypeammoniemia. Until the 16MAY2011 the physicians did not suspect tacrolimus in the occurrence of hyperammonemia. On the 16MAY2011 an electroencephalogram was performed which showed encephalopathy grade III. Tacrolimus was then suspected. The patient took her last intake of Advagraf on 16MAY2011. From 16MAY2011 to 19MAY2011, an improvement of the hyperammonemia was noticed. On 19MAY2011, ammoniemia came back to a normal value. On 18MAY2011 the patient did not present with incoherent speech, balance disorders and somnolence anymore. The patient was vigilant. On 20MAY2011, Prograf (tacrolimus) was reintroduced. At the time of reporting, the reporter was waiting of the last result of trough level of tacrolimus. Lab data included: On (b) (6), ammoniemia, 130 g/100 ml, on (b) (6), 191 g/100 ml and on 16MAY201, 490 g/100 ml. On 18MAY2011, the clinical examination of control was normal. Advagraf (tacrolimus) was discontinued and the patient started on Prograf (tacrolimus). The outcome of the event Off

Case Numbers	Medication Error Type	Narratives
		Label use (Advagraf for a children) was not applicable. The outcome of the event Encephalopathy grade III and High trough level of tacrolimus was unknown. The patient recovered without sequelae from the event hyperammonemia on 19MAY2011, incoherent speech balance disorders, somnolence and eyelids oedema in an unspecified date in MAY2011. The reporter assessed the events encephalopathy grade III, hyperammonemia ,incoherent speech, balance disorders, somnolence as serious due to hospitalization, medically significance, high trough level of tacrolimus, eyelids oedema as serious due to medically significance, off label use (Advagraf for a children) as non-serious and the causality for all events to be possibly related to tacrolimus treatment. ---------- ---------- Follow up information was received on 05JUL2011 and 07JUL2011. Medical history included asthma and the patient had allergic diathesis (latex and iodine). In (b) (6) the patient underwent liver transplant due to biliary tract atresia. Concomitant disease included in MAR2006 splenorenal shunting over thrombosis of the primitive portal trunk and stenosis of mesenterico-caval anastomosis in JUL2001. A liver biopsy in JAN2007 was in favour of chronic graft rejection. Concomitant medications included Cellcept (mycophenolate mofetil), Ursolvan (ursodeoxycholic acid), Mopral (omeprazole), Fumafer (ferrous fumarate), Bricanyl (terbutaline) and Seretide (fluticasone propionate/ salmeterol). Before the patient switched to Advagraf (tacrolimus), the patient was treated with Prograf (tacrolimus) 0.4 mg twice daily. By mistake, the patient was switched to Advagraf (tacrolimus) 8 mg daily in one intake instead of 0.8 mg daily. The patient was treated with this dosage regimen during approximately 10 days and again the patient was switched
8314924-1	Wrong Drug (Prescribing Error)	Information was received on 08NOV2011. This is a spontaneous case reported by an physician referring to a female patient (born in (b) (6) 1945) who experienced pyelonephritis during Advagraf (tacrolimus) treatment. In addition, Advagraf was switched to Prograf (tacrolimus) during hospitalization and then it had been forgotten to prescribe Advagraf again after discharge from hospital. This was considered as prescribing error (Prograf). Medical history included occasionally consumption of benzodiazepine as risk factor, kidney transplant due to a hereditary nephropathy with deafness (Alports syndrome) on (b) (6) as procedure. No concomitant medications were reported. On an unspecified date the patient started Advagraf (tacrolimus) oral for kidney transplant. On an unspecified date the patient experienced pyelonephritis and hospitalized. During hospitalization therapy with Advagraf was switched to Prograf (tacrolimus) orally 4 mg daily in (b) (6) due to pyelonephritis but then it had been forgotten to prescribe Advagraf again after discharging the patient. This was considered as prescribing error (Prograf). Therapy with Advagraf

Case Numbers	Medication Error Type	Narratives
		(tacrolimus) was discontinued due to event pyelonephritis. Action taken on Prograf (tacrolimus) was not applicable. On 29SEP2011, the patient started again Advagraf (tacrolimus) 4 mg daily. On 06OCT2011, the patient was included in OSIRIS study. The outcome of the events prescribing error (Prograf) and pyelonephritis (Advagraf) was unknown at the time of this report. The reporting physician assessed the event prescribing error (Prograf) as non serious and pyelonephritis (Advagraf) as serious due to hospitalization. The reporting physician did not assess the causality. ---------- ---------- Follow up information was received on 09DEC2011. The CRA confirmed the prescribing error with Prograf (tacrolimus) and pyelonephritis with Advagraf (tacrolimus). According to the medical record, the patient was treated with Advagraf (tacrolimus) 3.5 mg daily. On an unspecified date, the patient experienced pyelonephritis and was hospitalized during 13 days. During her hospitalization, the patient was treated with Prograf (tacrolimus), Rocephine (ceftriaxone) and Ciflox (ciprofloxacin). On 06MAR2011, the patient was still treated with Prograf (tacrolimus) 5 mg daily. On 23MAR2011, trough level was 10.8 ng/ml under Prograf (tacrolimus) 5 mg daily. The patient recovered from pyelonephritis (Advagraf) and the outcome of prescribing error was not applicable. ---------- ---------- Follow-up information was received on 22DEC2011. Patient initial, date of birth, height and weight were provided. The patient was 64 years old. Further information on medical history included arterial hypertension and hypercholesterolemia as historical conditions. Concomitant medication included Detensiel (bisoprolol) orally at 5 mg for arterial hypertension since 15SEP2009 and was ongoing, Speciafoldine (folic acid) orally at 5 mg daily for anemia since SEP2009 and was ongoing, Uvedose (cholecalciferol) orally at 100 000 UI for vitamin D deficiency every 15 days from 25FEB2010 to 14JUN2011, Phosphoneuros (calcium phosphate dibasic, magnesium glycerophosphate, phosphoric acid, sodium phosphate dibasic) orally at 150 drops daily for hypophosphoraemia from 04MAR2010 to 20MAY2010, Cellcept (mycophenolate mofetil) orally at 1.5 g daily for rejection prevention since 15SEP2009 and was ongoing. The patient was treated with Advagraf for rejection prevention (previously reported as kidney transplant) at 10 mg daily from 15SEP2009 to 05OCT2009, 9 mg daily from 06OCT2009 to 14OCT2009, 8 mg daily from 15OCT2009 to 24OCT2009, 7 mg daily from 25OCT2009 to 16DEC2009, 4 mg daily from 17DEC2009 to 30DEC2009 and 3.5 mg daily from 31DEC2009 to 23FEB2010. The patient was treated with Prograf for rejection prevention at 3 mg (previously reported as 5 mg) daily from 04MAR2010 to 06MAR2010, 4 mg daily from
8714871-2	Wrong Dose	Information was received on 19AUG2011. This is a spontaneous case and was reported by a

Case Numbers	Medication Error Type	Narratives
	(Noncompliance)	consumer via CRO, referring to a male patient born in (b) (6) 1958. Overdose and tremor (hands and fingers) were reported regarding the patient while he was on Advagraf medication. The patient (ID: 270-04) was enrolled in Advagraf study, OSIRIS; Observatory on strategies for the initiation of substained-release tacrolimus (ADVAGRAF) in renal and hepatic transplantation and evaluation of their impact on treatment acceptability and compliance in a targeted population of transplant patients (date of inclusion: 18AUG2011). Medical history included: live and kidney transplant on (b) (6) (context of transplant as elective, waiting time of graft was 4 years, source of graft was a cadaveric donor, initial disease necessitating transplantation was oxalose primitive) as procedure; primary oxalosis as historical condition; alcohol consumption (consumption of benzodiazepines) as risk factor. Concomitant medication included: corticosteroid nos starting on an unspecified date. No therapy details reported. In 2007, the patient started Prograf (tacrolimus) 2 mg daily for liver and kidney transplant. On an unspecified date, the patient developed overdose and tremor (hands and fingers). He recovered from the tremor after the dose of tacrolimus was decreased. According to the patient, the tremor was disabling. However, it was no more disabling at the time of reporting. On 08AUG2011 the patient was involved the study and Advagraf 2 mg daily was initiated. Lab result included: trough levels of tacrolimus 9.200 ng/ml under tacrolimus 2mg per day on 19MAY2011 and 6.260 ng/ml under tacrolimus 2mg per day on 11JUL2011. Action taken with tacrolimus was decreased. The patient recovered from the events overdose and tremor (hands and fingers) on an unspecified date. The reporter assessed the events as non-serious. The reporter did not provide any causality assessment for the event overdose and assessed the event tremor (hands and fingers) possibly related to tacrolimus treatment. ---------- Follow-up information was received on 02AUG2012 from the physician. The report type was changed to sponsored study. The patient (ID: 27007) was enrolled in OSIRIS study. The case refers to a 54-year old male patient. Additional events were reported which included administration error (Advagraf), important irregularity of T0 related to over-consumption of major analgesics (Advagraf) and drug-

Case Numbers	Medication Error Type	Narratives
		drug interaction with analgesics (Prograf, Advagraf) were added as events. The event term was amended to overdosage (Prograf) (previously reported as overdosage) and the event term was amended to tremor (hands and fingers) (Prograf) (previously reported as tremor (hands and fingers). Medical history also included oxalosis muscular pain, opioid dependence related to neurological damage of oxalosis as historical conditions, common bile duct stenosis treated with transhepatic drainage with progressive gradind since 2011 as a current condition. Advagraf was added as a study drug. On an unspecified date, the patient started Advagraf (tacrolimus) (no further details provided). The patient did not respect the dosage regimen prescription of tacrolimus and took only 1 mg of tacrolimus during 2 months from 01SEP2011 to 17NOV2011. This was considered as an administration error (Advagraf).Measures taken included dosage regimen precision and dosage correction. On an unspecified date, there was an important irregularity of T0 related to over-consumption of major analgesics (drug dependency). On 02AUG2010, the patient experienced a drug-drug interaction with analgesics (Prograf, Advagraf). It was reported that since 02AUG2010, the patient had several major analgesics which certainly modified the pharmacokinetic effect of treatment. Measures taken included a therapeutic reduction attempt. On 17NOV2011 during a follow-up visit, it was reported the patient had not
8491096-1	Wrong Frequency of Administration	Information was received on 15MAR2012. This is a spontaneous case reported by a physician referring to a patient of unknown gender and age who had medication error with Prograf (tacrolimus), complete graft rejection with Prograf (tacrolimus) and Poor tolerance with Advagraf (tacrolimus) treatments. No medical history and concomitant medication was provided. On an unknown date, the patient started Advagraf (tacrolimus) for an unknown indication. On an unknown date, patient started Prograf (tacrolimus) once daily instead of twice daily, which was considered as medication error. The treatment with Advagraf (tacrolimus) was switched to Prograf (tacrolimus) due to poor intolerance. On an unknown date, the patient experienced complete rejection of graft. The treatment with Advagraf (tacrolimus) was discontinued on an unknown date and the action taken with Prograf (tacrolimus) was unknown. The outcome of the events was unknown at the time of this report. The reporter did not assess the causality of the events to Advagraf (tacrolimus) and Prograf (tacrolimus) treatments. The Astellas Medical reviewer assessed the event complete graft rejection as medically significant, therefore serious and the events medication error and poor intolerance as non serious. ----------

Case Numbers	Medication Error Type	Narratives
		Follow-up information was received on 20MAR2012. The gender of the patient was provided as female patient. There was no information about the immunosuppressant treatment before Advagraf (tacrolimus) initiation or the cause of medication error. ---------- ---------- Follow-up information was received on 27MAR2012. The case concerns a 60 year-old patient. The event term poor tolerance was amended to digestive disorders (previously reported as poor tolerance (Advagraf)). The patient was initially treated with Prograf (tacrolimus) then she was switched to Advagraf (tacrolimus) for renal transplant on an unspecified date. During her treatment with Advagraf (tacrolimus), the patient presented with digestive disorders and she decided herself without the agreement of a physician to stop Advagraf (tacrolimus) and resume Prograf (tacrolimus),1 intake daily during 1 month leading to complete graft rejection. The reporter reassessed the event of medication error (Prograf) and complete graft rejection (Prograf) as medically significant and assessed the event of digestive disorders to be medically significant as well. The reporter did not provide a causality assessment for the event digestive disorders with Prograf and Advagraf (tacrolimus) treatment. No further information expected
8580520-2	Wrong Drug	On (b) (6) a spontaneous report was received from a physician via an Astellas representative regarding a 7 year old female who was dispensed Advagraf (tacrolimus) instead of Prograf (tacrolimus) suspension and took Advagraf, twice daily. Approximately 6.5 years prior to this report, she started Prograf (tacrolimus) suspension for heart transplant immunosuppression. Co-suspect medication included Advagraf (tacrolimus). On 18APR2012, she was dispensed Advagraf (tacrolimus), twice daily, instead of Prograf (tacrolimus) suspension, twice daily and was hospitalized on an unspecified date. She took Advagraf (tacrolimus) twice daily for 27 days. The outcome of the events and the action taken were not reported. At the time of this report, she remained hospitalized. Concomitant medication included Cellcept (mycophenolate mofetil). The reporting physician did not assess seriousness or causality for the events in relation to Advagraf (tacrolimus) and Prograf (tacrolimus) therapies. An Astellas medical reviewer assessed the event of prescribed Prograf (tacrolimus) suspension as non-serious. No further information was provided. ---------- Additional information was received on 30MAY2012 which indicated the patient was not hospitalized for the events. No further information is expected.

Appendix I: Foreign post marketing case numbers discussed in this review

Case Numbers	Medication Error Type	Narratives
2009EU002259	Wrong Drug (Dispensing Error)	A 39-year old male patient, on Prograf 2.5 mg bid, was dispensed Prograf 1 mg and Advagraf 0.5 mg instead of Prograf only. The patient did not experience a reaction. No further information was reported.
2008EU002113	Wrong Drug (Dispensing Error)	A 22-year-old male started Prograf (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. The patient had a history of renal transplantation in 2003. Concomitant medications were not provided. The patient received his repeat Prograf prescription on 29 Aug 2008. On 19 Sep 2008, the patient contacted the clinic as he was feeling unwell. He visited the clinic several days later (22 Sep 2008), at which time his creatinine level was reported as 489 (units not reported, reference range 180-210) and his trough tacrolimus level was reported as 5.6. On (b) (6), the patient was hospitalized after feeling "unwell". Upon admission, the patient's medications were reviewed, at which time it was discovered that the **patient should have been taking Prograf, 2.5 mg twice daily, but was actually taking Advagraf, 2 mg daily and Prograf, 0.5 mg twice daily.** At that time, the patient exhibited **early signs of acute rejection,** which was confirmed by renal biopsy. Renal biopsy revealed acute tubulo-interstitial rejection and mild chronic allograft nephropathy. The patient was treated with pulsed methylprednisolone (0.5 g). **It was noted the computerized database did not indicate that Advagraf was a modified-release formulation. The pharmacist indicated that it was often difficult to obtain Prograf and, although ordered by the pharmacy, often was out of stock.** Patient outcome was not reported. The reporter did not provide a causality assessment.
2008EU002604	Wrong Drug (Dispensing Error)	A 62-year-old male started Prograf, 5 mg, in Oct 2008 (frequency not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, the patient presented with erratic creatinine levels. Upon further investigation, it was determined that both Prograf (5 mg) and Advagraf (1 mg) were dispensed to the patient. The patient's treatment was updated to Prograf alone after which the patient's creatinine levels were reported as normal. The event of increased blood creatinine was considered medically significant. The reporter did not provide a causality assessment.
2010EU000547	Wrong Drug	A male patient of unknown age started tacrolimus in 2001 after renal transplantation.

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	During a week in FEB2010 the patient experienced a medication error, receiving 1 mg Prograf every morning and 0.5 mg Advagraf every night. The patient had admitted to a hospital ward for investigation of possible recurrence of hepatocellular carcinoma. During the check of drug history against the medicines that the patient had brought from home the reporter discovered the medication error. The patient's general practitioner and community pharmacist were informed and changes were made to their computer records. It was reported that there did not seem to be any impact on the patient's liver function tests or tacrolimus levels. The reporter assessed this medication error as non-serious.
2011EU000247	Wrong Drug (Dispensing Error)	A 13-year-old female started a combination of Prograf 1 mg and Advagraf 0.5 mg twice daily on 20 Jun 2008 for an unspecified indication. Medical history and concomitant medications were not provided. The patient was started on a combination of Advagraf 0.5 mg twice daily and Prograf 1 mg twice daily. It was reported that the patient took the combination of Advagraf and Prograf for quite some time. She was monitored by the pediatric hospital and her last tacrolimus levels (AUG 2011) were normal. The reporter was not aware of the difference between tacrolimus MR and tacrolimus. This medication error was brought to attention when a script was faxed by the pharmacist for an order of Advagraf. The reporter stated that the patient needed to see a transplant specialist as soon as possible to have her levels checked. The physician wanted to correct the error and re-issued a new prescription of Prograf 1.5 mg twice daily to streamline the prescription to the same brand name on a twice daily regimen. Treatment with tacrolimus (Advagraf 0.5 mg and Prograf 1 mg) was discontinued. The outcome of the event was unknown. The reporter did not provide any causality for the event with tacrolimus treatment.
2010EU000632	Wrong Drug (Dispensing Error)	A patient of unknown age should have received Prograf from an unknown date for an unspecified indication. It was found later that the patient was prescribed both Advagraf and Prograf. This was considered a medication error. The customer service was contacted to provide the pharmacy with Advagraf, and error was recognized during a check of the scrip, as there was both Prograf and Advagraf on the same prescription. The reporter assessed this medication error as non-serious.
2008EU002385	Wrong Drug (Dispensing Error)	A 45-year-old male began immunosuppression for an unknown indication. Medical history and concomitant medications were not provided. It was reported that the patient received a "mixture" of Advagraf and Prograf for an unspecified duration (initially reported as 2 months duration, but duration was unconfirmed). A drug alert was sent to the pharmacy, after which the pharmacy reviewed the patient's prescription records and discovered the

Case Numbers	Medication Error Type	Narratives
		drug dispensing error. Subsequent unspecified blood tests were reported as normal and no adverse events were reported as a result of the drug dispensing error. The reporter did not provide a causality assessment.
2009EU004755	Wrong Drug (Dispensing Error)	A 13-year old female patient was dispensed a combination of Advagraf and Prograf. The patient took Advagraf 1 mg and Prograf 0.5 mg for kidney transplant (treatment days unspecified). This was a dispensing error as the patient was supposed to be taking Prograf 1.5 mg twice daily. The patient had not experienced any adverse events at the time of reporting of the medication error.
2009EU001974	Wrong Drug (Dispensing Error)	A 67-year old female patient was transplanted around 15 years ago and had been on Prograf for many years. On 10JUN2008 the patient collected the prescription for tacrolimus from a pharmacist who was not the one normally filling the repeat prescription. The patient took 3 x 50 boxes 1 mg capsules. After taking two capsules twice daily for 43 days the patient recognized that she was taking Advagraf instead of Prograf and contacted the pharmacist, who completed a report, and the practice manager at her surgery, reporting the incident. Since an unknown date the patient took Prograf 1 mg a.m. and 1.5 mg p m. onwards. No associated adverse medical events or any other further information were reported.
2008EU002059	Wrong Drug (Dispensing Error)	A 49-year-old female started Prograf (frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. Prograf was prescribed following renal transplantation; however, Advagraf was dispensed. The patient actually administered both medications which included 1 mg of Prograf and 0.5 mg of Advagraf. She was subsequently hospitalized briefly with an episode of acute rejection, which was confirmed via renal biopsy. She recovered from the event on an unspecified date and was discharged. To date, the patient had not experienced any long term problems as a result of the drug dispensing error. The reporter did not provide a causality assessment.
2010EU002624	Wrong Drug (Dispensing Error)	A 40-year-old female started Advagraf (dose and frequency unspecified) on an unspecified date for renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, the patient was dispensed Advagraf instead of Prograf. It was reported that the patient did not take the incorrect medication. The action taken with tacrolimus treatment and event outcome were unknown. The reporting urologist neither provided the seriousness criteria nor assessed the causality for the event.
2010EU001543	Wrong Drug	A female (age unspecified) received Advagraf, 5 mg daily, for renal transplant on an

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	unspecified date. Medical history and concomitant medications were not provided. The reporter stated that Advagraf 5 mg was dispensed in error instead of Prograf 5 mg and the patient was administered the drug.. The outcome of the event was unknown. The reporter assessed the medication error as non-serious and did not assess the causality for tacrolimus.
2010EU000545	Wrong Drug (Dispensing Error)	A 60-year old male patient started Advagraf instead of Prograf twice daily from 29JAN2010 for a kidney transplant, underwent in (b) (6). The patient had been prescribed Prograf 3.5 mg twice daily but was dispensed Advagraf 0.5 mg capsules by a local pharmacy in error. When the medication error was identified, it was corrected within 24-48 hours. It was reported that the tacrolimus levels were only marginally higher as a result of the error, from '9.9' to '10.3' (no units provided), and no serious harm or significant clinical problem happened to the patient. The reporter stated that this had occurred because the sticker was over the once only words on the box. It was reported that the patient had taken Advagraf for two weeks. The patient had stopped Advagraf on 13FEB2010. The error was corrected and the patient was given Prograf. The reporter assessed the event as medically significant.
2009EU004756	Wrong Drug (Dispensing Error)	A 9-year old male patient was dispensed Advagraf instead of Prograf. The boy did not take the incorrect medication, as his mother recognized the error.
2009EU004571	Wrong Drug (Dispensing Error)	A 41-year old male patient started Prograf 3 mg twice daily for a renal transplant on 05OCT2009. No medical history or concomitant medications were reported. On an unspecified date, the patient was dispensed Advagraf 3 mg twice daily instead of Prograf by a community pharmacy. The prescription was generic. The patient was confused with the new medication and showed it to his renal transplant nurse. The patient did not take the incorrect medication.
2009EU001993	Wrong Drug (Dispensing Error)	A male patient of unknown age received oral Advagraf 3 mg twice daily from 09MAY2009 to 15MAY2009 for unspecified transplant. The patient had been stabilized on Prograf 3 mg twice daily. Advagraf was dispensed instead of Prograf on 09MAY2009 on a prescription for tacrolimus 3 mg twice daily for 4 weeks. He developed headaches, tremor and nose bleeds on 14MAY2009. No concomitant mediations were reported. Medical history was not provided. Action taken with tacrolimus was not reported. The patient was reported as recovered from the events. The reporting pharmacist assessed the events as probably related to Advagraf.
2009EU001836	Wrong Drug	A 51-year old female patient returned a bag of unused medication to the hospital outpatients

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	department. Advagraf was noted to be in the bag; however hospital outpatients department was under the assumption that the patient was taking Prograf. An outpatient nurse confirmed that the patient had not received more than one box. The hospital pharmacist contacted the community pharmacist to inform him of the error, and the general practitioners were required to prescribe tacrolimus (Prograf) by brand in the future.
2009EU000342	Wrong Drug (Dispensing Error)	A female patient of unknown age was treated with 1 mg Prograf twice daily after renal transplantation. On 17DEC2008 the patient presented in the clinic with the wrong formulation of tacrolimus (Advagraf), dispensed by error. The patient took Advagraf for 20 days before querying with the transplant coordinator. Trough tacrolimus levels and creatinine levels were checked and shown to be unremarkable. Patient showed no symptoms. The package was from parallel import and the box was covered with 2 labels so the brand name could not be seen. The pharmacist label stated: tacrolimus 1 mg twice daily.
2008EU002827	Wrong Drug (Dispensing Error)	A 31-year old female patient was treated with tacrolimus on unknown dates for immuno-suppression following renal cadaveric transplant, received in APR2006. Medical history included BK virus in urine; transplant biopsy in JUN2008 showed interstitial infiltrate and features of BK virus nephropathy. Concomitant medications included prednisolone, thyroxine, nifedipine, atorvastatin, aspirin, and leflunomide. On an unknown date patient mentioned to the transplant nurse that her tacrolimus box and capsules appeared different. It appears that the patient ordered repeat prescriptions with her general physician online. The patient indicated she had taken the new drug (Advagraf) twice daily for two months (23SEP2008 - 23NOV2008). She had contacted a member of staff at her "GP surgery" and was advised that Prograf and Advagraf are the same drug. It turned out that she took Prograf 2mg twice a day and Advagraf 0.5 mg twice a day (instead of 2.5mg). No associated adverse medical events were reported, and tacrolimus levels were reported to remain stable.
2008EU002660	Wrong Drug (Dispensing Error)	A 14-year old female patient was dispensed Advagraf instead of Prograf on 13NOV2008. On non-specified dates the patient used oral Advagraf 5 mg in the morning and 4 mg in the evening for immunosuppression after renal transplant. No associated adverse medical events, nor any other further information, were reported.
2008EU002658	Wrong Drug (Dispensing Error)	A 17-year-old male started Prograf, 3 mg twice daily (start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On 19 Nov 2008, Advagraf was dispensed rather than Prograf and the patient self-administered Advagraf, 3 mg twice daily. No further details were provided. The reporter did not provide a causality assessment.

Case Numbers	Medication Error Type	Narratives
2008EU002303	Wrong Drug (Dispensing Error)	A 41-year-old male started Advagraf, 2.5 mg twice daily (start date unknown), as immunosuppressive therapy after a renal transplant. Medical history included type 1 diabetes mellitus and blindness (left eye). Concomitant medications included acetylsalicylic acid, atenolol, furosemide, human insulin, mycophenolate mofetil, nifedipine, omeprazole, simvastatin and sodium bicarbonate. The patient's baseline creatinine value was reported as 242 (units not provided) on 11 Sep 2008. On (b) (6) the patient was hospitalized due to an increasing creatinine, reported as 489 (units not provided). It was discovered that the patient had been dispensed Advagraf rather than Prograf. His tacrolimus level was 5.6 (units not provided). Renal biopsy was positive for rejection: acute rejection on background of chronic rejection. The transplant rejection was considered medically significant. The patient was treated with 3 doses of methylprednisolone, followed by oral prednisolone. He was discharged with a reported creatinine of 438 (units not provided) and a glomerular filtration rate of 15 mL/min (approximately 50% loss of function). Prograf was administered and the patient's dose was adjusted to meet therapeutic levels. It was reported that dialysis would be considered if the patient's transplant function did not recover. The patient was reported to be recovering from the events. The reporter did not provide a causality assessment, but the pharmacist who dispensed the medication did mention that the dispensing error could be related to the dispensary computer system.
2008EU002067	Wrong Drug (Dispensing Error)	A male of unreported age started Prograf (dose, frequency, and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. Prograf was prescribed correctly; however, Advagraf was dispensed by the community pharmacy. The patient did not take the Advagraf. It was unknown whether the medication was prescribed using the brand name or generic name. The reporter did not provide a causality assessment.
2008EU002039	Wrong Drug (Dispensing Error)	A 40-year-old male started Advagraf (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history was not provided. Concomitant medications included mycophenolate mofetil. Advagraf was dispensed by the pharmacy from 01 Jul 2008 to 01 Sep 2008 and the patient received 1.5 mg twice daily during this period. Tacrolimus trough levels during this time remained normal at 5 ng/mL. The patient resumed Prograf on 01 Sep 2008. The reporter did not provide a causality assessment.
2008EU002035	Wrong Drug	A patient of unknown age and gender started Advagraf (dose, frequency and start date not

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. Advagraf was mistakenly dispensed by the pharmacy rather than Prograf. No further details were provided. The reporter did not provide a causality assessment.
2008EU002034	Wrong Drug (Dispensing Error)	A 33-year-old male started Prograf, 3 mg twice daily, on an unreported date as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. In Jul 2008, Advagraf was dispensed by the retail pharmacy instead of Prograf; however the patient did not take the Advagraf. The reporter did not provide a causality assessment.
2008EU002033	Wrong Drug (Dispensing Error)	A 55-year-old male started Prograf (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. Advagraf was mistakenly dispensed by the pharmacy rather than Prograf. The patient did not take the dispensed medication as the product packaging appeared different. It was determined that Prograf was prescribed using the brand name. The pharmacist believed the error was due to prescribing physicians using generic medication names and that Advagraf and Prograf appeared in the computerized prescribing system as tacrolimus with only 2 letters differentiating the products. According to the pharmacist, the system usually encourages brand prescriptions for products when a new product is available that replaces another; however, this was not the case for Advagraf and Prograf. The pharmacist's also stated that Advagraf and Prograf packaging and tablets are quite similar. The reporter did not provide a causality assessment.
2008EU002032	Wrong Drug (Dispensing Error)	A male patient of unknown age started Prograf (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, Advagraf was mistakenly dispensed by the local pharmacy rather than Prograf. The patient queried the product dispensed and the pharmacist indicated Advagraf was the same as Prograf, but longer acting. The patient did not take the dispensed medication as the medication did not look the same and contacted the transplantation unit. Following querying by the reporter, the local pharmacist indicated the general practitioner had made the mistake; however, the pharmacist indicated he believed Advagraf and Prograf could be interchanged. It was determined that Prograf was prescribed using the brand name and that the pharmacist was unaware of the difference between Prograf and Advagraf. The reporter did not provide a causality assessment.

Case Numbers	Medication Error Type	Narratives
2008EU002028	Wrong Drug (Dispensing Error)	A 42-year-old female started Prograf, 4 mg twice daily, on an unreported date as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date in Jul 2008, Advagraf was dispensed by the retail pharmacy instead of Prograf; however the patient did not take the Advagraf. The pharmacist told the patient Advagraf was the same as tacrolimus and insisted it should be taken twice daily. The patient refused, obtained her prescription refill elsewhere and contacted the transplant unit. The reporter did not provide a causality assessment.
2008EU002026	Wrong Drug (Dispensing Error)	A 68-year-old female started Prograf, 2 mg twice daily, on an unreported date as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date in Jul 2008, Advagraf was dispensed by the retail pharmacy instead of Prograf; however, the patient did not take the Advagraf. The reporter did not provide a causality assessment.
2008EU001644	Wrong Drug (Dispensing Error)	A male patient of unknown age started tacrolimus, 5 mg daily, as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. The patient was prescribed tacrolimus 5 mg daily, which suggested Advagraf. The patient actually received Prograf, 3 mg in the morning and 2 mg in the evening. Eventually Advagraf, 5 mg daily (the correct medication) was prescribed. The reporter confirmed that the patient did not take the product wrongly dispensed to him. According to the reporter, hospitalized patients were prescribed Advagraf rather than Prograf and were administered Advagraf twice daily. The reporting pharmacist did not provide a causality assessment.
2008EU002196	Wrong Drug (Dispensing Error)	A 34-year-old female started Advagraf, 7 mg daily, on an unreported date as immunosuppressive therapy after an unspecified organ transplant. The patient had a history of restricted vision. Concomitant medications were not reported. On an unspecified date, Advagraf was dispensed in error by the community pharmacist rather than Prograf. Due to her restricted vision, the patient took the Advagraf and the error was discovered by the hospital. Advagraf treatment was discontinued on 16 Sep 2008 and the patient's immunosuppressive therapy was changed to sirolimus. No adverse events were reported as a result of the drug dispensing error. It was unclear whether the drug was prescribed using the brand or generic name. The reporter did not provide a causality assessment.
2008EU002523	Wrong Drug	A 45-year-old female started Advagraf (unknown dose and start date), twice daily as

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	immunosuppressive therapy after a liver transplant. Medical history was not provided. Concomitant medications included mycophenolate mofetil. Prograf was prescribed to the patient by her general practitioner. On an unknown date, the patient was hospitalized with increased tacrolimus levels. Upon investigation, it was discovered that she had been administered Advagraf twice daily instead of Prograf. The event of drug dispensing error was considered medically significant. The drug dispensing error was thought to have occurred due to the generic prescribing of Prograf as tacrolimus. No long term adverse events occurred and the events resolved. The events were considered medically significant. The reporter did not provide a causality assessment.
2008EU002068	Wrong Drug (Dispensing Error)	A patient of unknown age and gender started Advagraf (dose, frequency, and start date not reported) as immunosuppressive therapy after a liver transplant. Medical history and concomitant medications were not provided. Advagraf was dispensed rather than Prograf. Outcome of the event is unknown. The reporter did not provide a causality assessment.
2008EU001490	Wrong Drug (Dispensing Error)	A 79-year-old male started Advagraf twice daily (unknown dose and start date) as immunosuppressive therapy after a liver transplant. Medical history and concomitant medications were not provided. Prior to hospitalization for a routine hernia repair, the patient's medications were changed from sirolimus to tacrolimus. Prograf was prescribed; however, the patient received Advagraf, twice daily. The event was considered medically significant. The reporting pharmacist did not provide a causality assessment.
2009EU004350	Wrong Drug (Dispensing Error)	A 59-year old female patient was given oral Advagraf once daily for immunosuppression (date and dosage not specified). Concomitant medication included oral Prograf 1.5 mg twice daily from 05OCT2009. On an unspecified date a drug dispensing error was reported: the patient was given a prescription of Prograf but was supplied with Advagraf by the pharmacist. The patient did not start Advagraf and reported to the Transplant clinic. No associated adverse medical events or any other further information were reported.
2010EU001238	Wrong Drug (Dispensing Error)	A female patient of unknown age received Advagraf for an unspecified indication from an unknown date. The patient received the drug as dispensing error: Advagraf twice daily had been given instead of Prograf twice daily. After about a month of therapy the patient went to a hospital pre-assessment clinic. She was told that her blood pressure was high, which resulted in a postponement of a planned operation. The pharmacist wanted to know whether the administration of Advagraf could be responsible for the increased blood pressure. The action taken with tacrolimus was not reported. The outcome of the event blood pressure increased was unknown. The reporting pharmacist did not report the events as serious.

Case Numbers	Medication Error Type	Narratives
2009EU002456	Wrong Drug (Dispensing Error)	A 75-year old female patient received treatment with Advagraf. On an unspecified day in DEC2009 tacrolimus was possibly prescribed by generic name. Not the whole quantity prescribed was available for dispensing at presentation, and consequently patient was dispensed some Advagraf and some Prograf. None of the medication was taken as the different product was noted by the patient and changed following questioning and clarification. No other information is available.
2009EU002375	Wrong Drug (Dispensing Error)	A 44-year old male patient received Advagraf treatment since an unknown date for an unspecified indication. The patient was involved in a medication error when he was changed from receiving his tacrolimus from the MRI to the community. No further information was provided.
2009EU001840	Wrong Drug (Dispensing Error)	A 66-year old male patient was prescribed a total daily dose 12 mg (6 mg twice daily) of Prograf. Therapy dates and indication were not provided. On an unspecified date, the patient called the pharmacy to report taking Advagraf. The prescription was believed to be correct, but the patient was dispensed 1 mg of Advagraf and 5 mg of Prograf, and the pharmacy swapped the 1 mg Prograf with Advagraf. The patient took two doses, had no side effects, and an outpatient appointment was made within 3 days of the error. Drug levels were within the expected range.
2009EU001571	Wrong Drug (Dispensing Error)	A patient of unknown age and gender was prescribed therapy with an unspecified dosage of tacrolimus twice daily for an unspecified indication. On an unspecified date, a pharmacist requested more Advagraf for a patient to be taken twice daily; however, the prescription was for tacrolimus twice daily. Medical Information questioned the prescription. The pharmacist called the ordering physician and confirmed that the prescription was for Prograf. The pharmacist thought that the medications were the same. Medical Information informed the pharmacist at that time of the error and provided education to him of the differences between the two formulations. This was a potential dispensing error with Advagraf; however the error was identified before medication was dispensed.
2009EU000277	Wrong Drug (Dispensing Error)	A female patient of unknown age was expected to receive Prograf but was dispensed a mixture of Prograf and Advagraf by her local pharmacy. The prescription came from her general practitioner. All letters sent to the general practitioners by the hospital are branded either Prograf or Advagraf. The patient had noticed there was a different name on the drug, and she did not take any of the drug.
2008EU002504	Wrong Drug	A patient of unknown age and gender started Prograf 1 mg twice daily, on 25 Oct 2008 for

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	an unknown indication. Medical history and concomitant medications were not provided. Prograf, 1 mg twice daily, was prescribed; however, Advagraf was dispensed in error. The pharmacist reported that she thought she had received a parallel import; however, it was Advagraf. From 25 Oct 2008 to 08 Nov 2008, the patient administered Advagraf, 1 mg twice daily (4 in the am, 3 in the evening, units not reported). It was unknown how and by whom the error was discovered. On an unspecified date, the patient's tacrolimus blood levels were reported as "recovering" at 3 mg/mL with a creatine kinase (CK) level reported as 56 (units not reported). At the time of reporting, the patient was back to his/her normal treatment regimen of Prograf. Further information was not reported. The reporter did not provide a causality assessment.
2008EU002281	Wrong Drug (Dispensing Error)	A 32-year-old female started Prograf (dose and start date not reported) for an unknown indication. Medical history and concomitant medications were not provided. On an unspecified date, Advagraf was dispensed rather than Prograf. The patient used 12 (units not reported) Advagraf daily for a few months until it was discontinued on 23 Oct 2008. Advagraf was returned and an alternative medication was provided to the patient by the hospital. No adverse events were reported as a result of the drug dispensing error. The patient reported that she has now observed the warning sign placed in the clinic. The reporter did not provide a causality assessment.
2008EU002195	Wrong Drug (Dispensing Error)	A female patient of unknown age started tacrolimus (dose, frequency, and start date not reported) for an unknown indication. Medical history and concomitant medications were not provided. The patient was prescribed tacrolimus and Advagraf was dispensed in error. The patient noticed the packaging appeared odd, did not take the Advagraf, and planned to replace the Advagraf with Prograf. No adverse events were reported as a result of the drug dispensing error. The reporter did not provide a causality assessment.
2008EU002091	Wrong Drug (Dispensing Error)	A 34-year-old male started Prograf (dose, frequency and start date not reported) as immunosuppressive therapy after an unspecified transplant. Medical history and concomitant medications were not provided. On an unknown date, Advagraf was mistakenly dispensed instead of Prograf. The patient recognized the different packaging and contacted the hospital who instructed him to return to the pharmacist and exchange the Advagraf for Prograf, which he did successfully. No further information was reported. The reporter did not provide a causality assessment.
2008EU002044	Wrong Drug	A patient of unknown age and gender started Prograf (dose, frequency and start date not reported) for an unknown indication. Medical history and concomitant medications were

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	not provided. Prograf, 1 mg capsules, was prescribed; however, Advagraf, 1 mg capsules, was dispensed. The error was noted and the patient did not administer any Advagraf. The reporter did not provide a causality assessment; however, he/she believed the dispensing error could be attributed to the information presented (tacrolimus) on the ordering system screen (Unichem).
2008EU002022	Wrong Drug (Dispensing Error)	A 51-year-old male started Prograf 2 mg twice daily, on an unreported date for an unknown indication. Medical history and concomitant medications were not provided. A prescription for generic tacrolimus, 1 mg was written; however, Advagraf was dispensed instead of Prograf. Thereafter, the patient administered a total of 4 capsules (2 capsules in the evening and 2 capsules the next morning). This occurred only once and the patient did not report any "disturbances" as a result of the drug dispensing error. The pharmacist indicated this may have occurred due to the information presented on the ordering system screen. The reporting physician did not provide a causality assessment.
2009EU002379	Wrong Drug (Dispensing Error)	A 35-year old male patient received Advagraf since an unknown date for an unspecified indication. The patient was involved in a medication error. His pharmacy informed him that he was on Advagraf, asking to check with his transplant unit whether this was correct. His transplant unit informed him he was taking the incorrect dose. No further information was provided.
2009EU003020	Wrong Drug (Dispensing Error)	A male patient of unknown age started a treatment with Advagraf 7.5 mg/day after lung transplant. One day on an unknown date the patient received 5 mg Advagraf plus 2.5 mg Prograf, which was reported as drug dispensing error. No adverse events were reported. The reporter notified a pharmacy's error due to a mix in tablets. They only noticed generic name instead of trade name.
2009EU003953	Wrong Drug (Dispensing Error)	A male patient of unknown age was using Advagraf 5 mg for renal transplant indication and suffered acute rejection. During a routine follow up consultation the specialist discovered that the patient's tacrolimus blood levels were below the therapeutic range. The patient showed renal function deterioration. The rejection took place due to the medication error. It seemed that at the community pharmacy the patient was dispensed tacrolimus 0.5 mg instead of tacrolimus 5 mg. Concomitant medication and the patient's medical history were not provided. The patient was recovering from the events at the time of the report. The reporter assessed the events as probably related to tacrolimus.
2009EU003024	Wrong Drug	A male patient of unknown age started Advagraf treatment for lung transplant indication at

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	a dose of 0.5 mg oral (therapy dates and frequency not reported). On an unspecified date, the patient received Prograf instead of Advagraf. The reporting specialist indicated that the error was made in the hospital pharmacy, as the pharmacist noticed only the generic name and gave Prograf instead of Advagraf. Subsequently the patient was monitored, and dose regulation was made. No serious adverse events were described, but reporter considered the event medically significant. The reporting specialist assessed the relationship between the event and tacrolimus treatment as probable.
2009EU003955	Wrong Drug (Dispensing Error)	A 65-year old male patient started taking Advagraf 5mg daily from 09JUL2009 for renal transplantation, underwent on (b) (6) On an unspecified date the patient experienced a medication error: he was dispensed tacrolimus at a dose of 0.1 mg instead of 5 mg with a start date of 14SEP2009. The patient took the incorrect dosage for about ten days. The patient subsequently developed acute graft rejection grade 1 and renal function deterioration on 01OCT2009 and was hospitalized from (b) (6) to (b) (6). Renal biopsy performed on (b) (6) revealed cellular rejection type I A, C4 d negative. The patient was taking oral mycophenolate sodium for renal transplantation, 720 mg daily from 30JUL2009, which was still ongoing. During a routine follow-up consultation the specialist discovered that the patient's tacrolimus blood levels were below the therapeutic range at 1.1 mg/dl on 30SEP2009. At the time of this report the patient was recovered without sequelae on 08OCT2009. The Investigator assessed the events as probably related to tacrolimus.
2011EU002520	Wrong Drug (Dispensing Error)	A male (age unspecified) inadvertently received Prograf, 1 mg once daily instead of Advagraf 1 mg, for prophylaxis of an unspecified organ transplant. Medical history and concomitant medications were not provided. The patient used Prograf 1 mg twice a day for a while. On an unspecified date, the patient's physician changed the prescription to 1 mg Advagraf once a day, but the pharmacist gave the patient Prograf 1 mg for once a day use. The patient was advised to contact his pharmacist. The action taken with Prograf treatment and the event outcome were not reported.
2008EU001890	Wrong Drug (Dispensing Error)	A 60-year-old male started Prograf (unknown dose, frequency and start date) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, the pharmacist dispensed Prograf rather than the prescribed Advagraf. The pharmacist had received instructions for Advagraf use (once daily). The patient experienced no clinical side effects and recovered from the event without sequelae. The reporting physician did not provide a causality assessment.
2008EU001891	Wrong Drug	A 43-year-old male started Advagraf (unknown dose, frequency and start date) as

Case Numbers	Medication Error Type	Narratives
	(Dispensing Error)	immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, Prograf was dispensed from the hospital pharmacy rather than Advagraf; however, the error was discovered in time. The patient recovered from the event without sequelae. The event was considered medically significant. The reporting physician did not provide a causality assessment.
2008EU001892	Wrong Drug (Dispensing Error)	A 39-year-old female patient started Prograf (unknown dose, frequency and start date) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, Prograf was dispensed from the local pharmacy rather than Advagraf. The patient experienced low tacrolimus trough levels and lower transplant function. The patient recovered from the events without sequelae. The event of graft dysfunction was considered medically significant. The reporting physician did not provide a causality assessment.
2008EU002094	Wrong Drug (Dispensing Error)	A patient of unknown age and gender started Advagraf (dose, frequency, and start date not reported) as immunosuppressive therapy after a liver transplant. Medical history and concomitant medications were not provided. Advagraf was prescribed; however, Prograf was dispensed by the local pharmacy. The patient suspected a drug dispensing error and contacted the transplantation center immediately who, in turn, contacted the pharmacist. The patient was advised to return the Prograf to the pharmacy. The Prograf was not administered. The reporter did not provide a causality assessment.
2008EU002095	Wrong Drug (Dispensing Error)	A patient of unknown age and gender started Advagraf (dose, frequency and start date not reported) as immunosuppressive therapy after a liver transplant. Medical history and concomitant medications were not provided. Advagraf was prescribed and, while attempting to fill the prescription at the local pharmacy, the patient's prescription was torn into pieces. The pharmacist informed the patient that Advagraf didn't exist. Thereafter, the patient contacted the transplantation center who, in turn, contacted the pharmacist and advised him to contact the manufacturer's local affiliate. Further information was not provided. The reporter did not provide a causality assessment.
2008EU002553	Wrong Drug (Dispensing Error)	A female patient of unknown age started Advagraf, 5 mg, (frequency and start date not reported) for an unknown indication. Medical history and concomitant medications were not provided. On an unknown date, Prograf, 5 mg, was dispensed in error rather than Advagraf, 5 mg. The patient took Prograf, 5 mg, for approximately 15 days. No adverse events were reported as a result of the drug dispensing error and the patient continued treatment with Prograf, 2.5 mg twice daily. The patient's tacrolimus level was reported as

Case Numbers	Medication Error Type	Narratives
		"very good" at 8 ng/ml on an unspecified date. The reporter did not provide a causality assessment.
2011EU008895	Wrong Drug (Dispensing Error)	A male patient (age unspecified) started Advagraf 5 mg (frequency unspecified) on an unspecified date for an unspecified transplantation. Medical history and concomitant medications were not provided. On an unknown date, the patient was possibly administered an incorrect tacrolimus dose of 5 mg instead of 0.5 mg. At an unknown time, he experienced tremor and swelling of the feet. It was reported that another pharmacist could have administered an incorrect dose of 5 mg instead of 0.5 mg for about 20 days. This was considered as a possible overdose. The action taken with tacrolimus and event outcome were unknown. The reporter did not assess causality.
2008EU002051	Wrong Drug (Dispensing Error)	A 45-year-old male started Prograf (dose, frequency and start date not reported) for an unknown indication. Medical history and concomitant medications were not provided. Prograf was prescribed; however, Advagraf was dispensed. The patient was very aware and knowledgeable of his medications and noted that the product packaging stated "Advagraf" rather than "Prograf." He notified his transplant nurse who advised him to return the Advagraf to the pharmacy and obtain the correct medication. Prograf was subsequently dispensed. The patient did not take the Advagraf. The reporter did not provide a causality assessment but confirmed that the hospital routine is that all prescriptions are written as Prograf rather than tacrolimus.
2009EU000789	Wrong Drug (Dispensing Error)	A male patient of unknown age was erroneously given Advagraf instead of Prograf on an unspecified date. The medication error resulted in decreased tacrolimus levels. It was noted the prescription showed tacrolimus capsules 0.5 mg. When 0.5 mg tacrolimus was requested *via* the pharmacy computer, the software showed only Advagraf 0.5 mg hard capsules, which were handed over to the patient. The report indicated that Pharmacy Software will be contacted to clarify the error occurred. No associated adverse medical events, nor any other further information, were reported.
2012EU000808	Wrong Drug (Dispensing Error)	A patient (age and gender unspecified) began taking Prograf, 8 mg daily, on an unknown date for liver transplant. Medical history included primary sclerosing cholangitis for which the patient underwent liver transplant on (b) (6) and consumption of alcohol (<10 g/day). Concomitant medications included corticosteroids. On 27 Oct 2011, the patient was included in the OSIRIS study. Trough levels of tacrolimus on 27 Oct 2011 were 5 ng/ml under Prograf (tacrolimus) 8 mg daily. The following day, the patient started Advagraf 8 mg daily. It was reported that the patient was not treated with Advagraf (tacrolimus) anymore

Case Numbers	Medication Error Type	Narratives
		and that the patient switched treatment from Advagraf to Prograf because Advagraf was not available in the pharmacy during her trip (This was considered as medication error). On 12JAN2012 trough levels of tacrolimus was 7 ng/ml under Prograf (tacrolimus) 8 mg daily. The patient received Prograf 8 mg daily and corticosteroids 7.5 mg daily. Following consultation Advagraf 8 mg daily and corticosteroids 7.5 mg were prescribed. On unknown date, the patient experienced an adverse drug reaction (not specified). According to the patient, the adverse drug reaction was disabling. This was not medically confirmed as the hepatologist reported that he was not informed about the adverse event reported by the patient. The action taken with tacrolimus and event outcome were unknown.
2011EU007139	Wrong Drug (Dispensing Error)	A 44-year-old female received oral tacrolimus, 7 mg daily, on an unspecified date for an unspecified indication. Medical history included arterial hypertension and hypercholesterolemia. Concomitant medications included ivabradine hydrochloride, atorvastatin calcium and omeprazole. On an unspecified date the patient started tacrolimus orally 7 mg daily. On an unknown date, the patient received tacrolimus 5 mg once daily instead of 7 mg because she did not have any tacrolimus 1 mg capsules. The following day, it was reported that the patient would be provided with capsules of tacrolimus 1 mg and the patient would resume the 7 mg daily dose. The reporting pharmacist had not seen the patient again and had no other information. The action taken with tacrolimus and event outcome were stated as not applicable. The reporter did not assess the causality of administration error to tacrolimus treatment.
2009US003040	Wrong Drug (Dispensing Error)	A male patient of unknown age experienced a drug dispensing error with the use of Prograf instead of Prograf extended release for kidney transplantation immunosuppression. On 01AUG2009, a pharmacy delivered conventional Prograf (dosage information unspecified) to the patient instead of the prescribed Prograf extended release. The patient changed the drug after one week without any symptoms.
2009US001170	Wrong Drug (Dispensing Error)	A patient of unknown age and gender on an unspecified date began oral Prograf extended release (dosage information not provided) for kidney transplantation immunosuppression. Concomitant medications were not reported. In APR2009 the pharmacy dispensed conventional Prograf instead of Prograf extended release and “blood levels decreased, the last was 5 mg/ml". No other information is available.
2009US001786	Wrong Drug (Dispensing Error)	A 40-year old female on an unspecified date began Prograf therapy (route and dosage information not provided) for kidney transplant immuno-suppression. On an unspecified date, the patient was changed to oral Prograf extended release 7 mg daily. On an

Case Numbers	Medication Error Type	Narratives
		unspecified date, the patient experienced high levels of creatinine. When the physician assessed the patient's clinical history, realized that the patient had continued treatment with conventional Prograf. It was noted that the mistake occurred in the pharmacy. Medical history included kidney transplant. Concomitant medications included mycophenolate, prednisolone and enalapril. The outcome of the event of high levels of creatinine was not reported.
2009US001143	Wrong Drug (Dispensing Error)	A 32-year old female was given conventional Prograf instead of Prograf extended release and experienced very low blood levels of tacrolimus. In DEC2008 the patient began oral Prograf extended release therapy (dose and frequency not reported) for kidney transplant immuno-suppression. In APR2009 tacrolimus blood levels were very low. When the physician examined the medication box he noted that the pharmacy had given conventional Prograf instead of Prograf extended release. A dose adjustment was made and the patient's tacrolimus blood concentration was then within appropriate levels. Concomitant medications included metoprolol.
2010US001276	Wrong Drug (Dispensing Error)	A male (age unspecified) received oral Prograf, 5 mg twice daily, on an unspecified date for unspecified transplant immunosuppression. Medical history and concomitant medications were not provided. The patient's pharmacist mistakenly switched his Prograf with Advagraf 5 mg twice daily. The outcome for the drug administration error was not reported. The reporting pharmacist did not assess the causal relationship for the drug administration error and tacrolimus therapy. The patient had no adverse events associated with taking Prograf. Tacrolimus blood levels were not available, but the patient had other unspecified blood work done and the results were reported as acceptable.
2009US002873	Wrong Drug (Dispensing Error)	A patient of unknown age and gender was dispensed Advagraf on a Prograf prescription. The patient was prescribed oral Prograf (0.5 mg in the morning and 1.0 mg at night) on 24JUL2008 for liver transplant immunosuppression. The patient's tacrolimus level on 25SEP2008 was given as '4.0' and was '4.1' on 10DEC2008 (units not provided). On 27OCT2008, during a clinic visit, it was discovered that the patient had taken Advagraf. There was no significant difference in the levels when the patient was taking Advagraf or Prograf. There were no adverse events resulting from this dispensing error.
2010US000031	Wrong Drug (Dispensing Error)	A female (age unspecified) started oral Advagraf, 10 mg daily, on (b) (6) for living related donor renal transplant immunosuppression. Medical history included Crohns colitis, hypertension and interstitial nephritis. Concomitant medications included basiliximab, mycophenolate mofetil and steroids. Co-suspect medication included amlodipine. Her

Case Numbers	Medication Error Type	Narratives
		postoperative course was unremarkable and she was discharged on [redacted] with a tacrolimus level of 5.5. She was seen in the transplant clinic on [redacted] and no issues were noted. Her blood pressure was 116/70 mmHg and did not change significantly with standing. Her tacrolimus level was 13.5. On [redacted] the patient developed symptoms of unsteadiness, right leg weakness, confusion, blurry vision, headache, but no double vision or speech abnormalities. Her blood pressure fell and she was admitted to the hospital, where she was diagnosed as having a watershed infarction related to hypotension. Magnetic resonance imaging (MRI) showed bilateral cerebral infarcts, more significant on the left side in the anterior choroidal artery/posterior cerebral artery (ACA/PCA) border zone territory. A MRI angiogram showed a distal ACA stenosis in the watershed territory. Time of flight imaging was used to visualize the cerebral circulation. Gandolinium was avoided due to concern related to nephrogenic system fibrosis in light of her reduced glomerular filtration rate (GFR). Her estimated glomerular filtration rate was 33 cc/min/1.73 m2 body surface area (BSA). Flow reduction and caliber irregularity was seen in the distal left anterior cerebral artery. It was noted that the stenosis was too distal to be amenable to any intervention. Amlodipine was discontinued and her blood pressure improved. There was no evidence of thromboembolic sources for the stroke but was started on aspirin. Her renal function was stable throughout her admission. Her creatinine upon discharge was 167. Difficulty ambulating remained and on [redacted] (the night before hospital discharge) she had a minor fall. She was transferred to a rehabilitation facility the next day. Oral Advagraf capsules, 10 mg daily, were ordered for the patient. The pharmacy labeling system at the rehabilitation facility only included the name of the generic medication and strength, which resulted in the technician dispensing oral Prograf, 10 x 1 mg capsules instead of Advagraf capsules. The label read as tacrolimus 10 mg once per day. The dispensing error was discovered on 17 Dec 2009 and it was recognized that the patient had been given Prograf instead of Advagraf. The patient received the Prograf from 28 Nov 2009 to 17 Dec 2009. There were no adverse effects from the Prograf 10 mg daily dosing regimen. Her tacrolimus trough levels were in the therapeutic range. The outcome for the event of stroke was not reported. The reporting pharmacist assessed the causality for the event of stroke as not related to tacrolimus. The reporting pharmacist did not report the serious criteria or causality for the event of Advagraf dispensing error. The outcome for the events of reduced GFR, fall and injury to the lateral aspect of the right hip was not provided. The reporter did not provide the serious criteria or causality for the events of reduced GFR, hypotension, fall and injury to the lateral aspect of the right hip and Advagraf therapy.

Case Numbers	Medication Error Type	Narratives
2011EU001702	Wrong Drug (Dispensing Error)	A 46-year-old male started Advagraf, 3 mg 4 capsules daily, on 03 Mar 2011 for kidney transplant. Medical history and concomitant medications were not reported. On an unspecified date, the **patient was prescribed tacrolimus 4 mg (4 x 1 mg), but he received and used the 3 mg package (4 x 3 mg).** The patient presented with **tremor and an increase in creatine level** from 1.1 to 1.4. His tacrolimus blood level went up to 24.8 ng/ml, but decreased to 5.4 ng/ml a couple of days later after dose adaptation The action taken with tacrolimus treatment was not reported, however the stop date was reported as 14 Mar 2011. The outcome of the events **drug prescription error (Advagraf 4 x 1 mg), dispensing error (3 mg dispensed instead of 1 mg),** tacrolimus blood level went up, tremor and increase in creatine were not reported, while the **patient had recovered from the event overdosing due to medication error** on 14 Mar 2011. The reporter assessed the events as medically significant and the causality as probably related to tacrolimus treatment.
2009US003291	Wrong Drug (Dispensing Error)	A patient of unknown age and gender took Prograf extended release instead of Prograf of immediate release. On an unknown date, the patient experienced abnormal vision, ear pain, increased BUN and increased creatinine after having taken Prograf extended release. The physician noted that the patient still suffered from tinnitus. The outcome for the events abnormal vision, ear pain, increased BUN and increased creatinine was not provided. The reporting physician considered the events to be possibly related to the therapy. The dispensing error occurred because the pharmacist misread the label and the patient did not notice the difference.
2008EU001913	Wrong Drug (Dispensing Error)	A male patient of unspecified age started Advagraf, 5 mg twice daily, on an unreported date for an unknown indication. Medical history was not reported. Co-suspect medications included omeprazole. Concomitant medications included an unspecified corticosteroid. It was reported that Prograf, 5 mg twice daily, was prescribed; however, Advagraf was dispensed in error one month prior to event onset. On 21 Aug 2008, the patient felt ill. Further details and outcome of the events were not reported. The reporting pharmacist did not believe the event of feeling ill was related to Advagraf therapy.
2010EU005745	Wrong Drug (Wrong Prescribing)	A 56-year-old female started the tacrolimus 3 milligrams once daily for kidney transplant on 27 Oct 2010. She was prescribed Prograf 3 mg once daily but erroneously received Advagraf 3 mg once daily for kidney transplant. Medical history included kidney transplant in 1987. Concomitant medications were not provided. The patient was supposed to receive Prograf 3 mg daily, but the general practitioner prescribed Advagraf 3 mg daily instead, which was dispensed by pharmacist. This was the first prescription for the patient. The

Case Numbers	Medication Error Type	Narratives
		general practitioner was later contacted and asked to prescribe Prograf. The patient did not suffer any adverse event due to the medication error. Advagraf was stopped on the first day of treatment. The outcome was unknown. The reporter did not assess the causality to tacrolimus.
2010EU005448	Wrong Drug (Wrong Prescribing)	A 42-year-old female was erroneously prescribed Advagraf, 4 mg twice per day instead of 4 mg once per day, for renal transplantation. Medical history and concomitant medications were not provided. Tacrolimus 4 mg twice per day was dispensed and administered by the patient for 10 days. During this time, the patient experienced high tacrolimus levels. The patient had no adverse events as result of this prescribing error. The error was noticed by the patient's nurse during a routine visit. The error was corrected by a reduction of the dose. The reporting physician assessed the high tacrolimus level as probably related to tacrolimus and did not provide an assessment of causality for the prescribing error.
2008EU002200	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started tacrolimus (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, Advagraf was prescribed in error. It was not reported whether the patient administered the Advagraf. As of the time of reporting, no adverse events were reported as a result of the drug prescribing error. The reporter did not provide a causality assessment.
2008EU002199	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started tacrolimus (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, Advagraf was prescribed in error. It was not reported whether the patient administered the Advagraf. As of the time of reporting, no adverse events were reported as a result of the drug prescribing error. The reporter did not provide a causality assessment.
2008EU002197	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started tacrolimus (dose, frequency, and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On an unspecified date, Advagraf was prescribed in error. It was not reported whether the patient administered the Advagraf. As of the time of reporting, no adverse events were reported as a result of the drug prescribing error. The reporter did not provide a causality assessment.
2008EU002041	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started Advagraf (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and

Case Numbers	Medication Error Type	Narratives
		concomitant medications were not provided. Advagraf was prescribed by the general practitioner (GP) instead of Prograf. The patient insisted the wrong medication was prescribed; however, the GP insisted this was not the case as Advagraf and Prograf were the same according to him. No further details were provided. The reporter did not provide a causality assessment.
2008EU001489	Wrong Drug (Wrong Prescribing)	A 29-year-old male started Advagraf (unknown dose, frequency and start date) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. On (b) (6) Prograf was mistakenly administered rather than Advagraf while the patient was hospitalized on a non-transplantation unit. According to the reporter, hospitalized patients were prescribed Advagraf rather than Prograf and were administered Advagraf twice daily. According to the pharmacist, most of the liver transplantation patients had high trough levels because they received Advagraf instead of Prograf. The event was considered medically significant. The reporting pharmacist did not provide a causality assessment.
2008EU002826	Wrong Drug (Wrong Prescribing)	A 43-year old female patient was treated with tacrolimus for immunosuppression after a kidney/pancreas transplant. By mistake her physician prescribed 0.5 mg tacrolimus extended release tablets (Advagraf) instead of tacrolimus (Prograf) 0.5 mg and therefore the pharmacist dispensed Advagraf. Patient was to have 2.5 mg Prograf twice daily, but due to the error she received 2 mg Prograf twice daily plus 0.5 mg Advagraf twice daily. The mistake was discovered on 19NOV2008 after query by the patient. No associated adverse medical events, nor any other further information, were reported.
2009EU000119	Wrong Drug (Wrong Prescribing)	A female patient of unknown age had been prescribed Advagraf instead of Prograf on an unspecified date for immunosuppression after liver transplant. The prescription was from the general practitioner, and Advagraf had been dispensed by the pharmacist. It is not clear from the report whether patient had used the dispensed Advagraf. No associated adverse medical events, nor any other further information, were reported.
2011EU001541	Wrong Drug (Wrong Prescribing)	A 14-year-old male (born in 1996) erroneously took Advagraf, 3 mg twice per day, for two and a half years prior instead of Prograf following cardiac transplant. Medical history and concomitant medications were not provided. The dose was changed by cardiac transplant team based on the results of the levels taken in community. The GP has prescribed Prograf with the instructions to take as prescribed by transplant team and which has been dispensed by the community pharmacy local to the patient in OCT2008.The GP surgeon changed the prescription to Advagraf (once daily) though the transplant team did not request and were

Case Numbers	Medication Error Type	Narratives
		not unaware of the change. From 29 Oct 2008, the patient had been taking Advagraf twice daily under the impression that his GP was still prescribing Prograf. He was admitted for his MOT (multiorgan transplant) and it was noticed by one of the ward nurses that he had brought Advagraf with him and was talking it twice daily since Oct 2000, but his levels have been in range. After discharge, they were unsure of whether to change to Prograf bid dose, change Advagraf to once daily combining the two doses he was taking currently, or leave him on Advagraf bid dose because his levels were good and he had no adverse effects. The patient has continued on product with no reported adverse events. He was well and his blood levels were fine. The reporter did not provide any causality assessment for the events. The action taken and event outcomes were unknown.
2010EU005591	Wrong Drug (Wrong Prescribing)	A male (age unspecified) had been taking Prograf 2 mg and 3 mg for an unspecified indication. Medical history and concomitant medications were not provided. The physician prescribed Advagraf, 1 mg 2 om and 3 mg 1 om capsules. and the pharmacist had dispensed the Advagraf 1 mg and 3 mg capsules. The patient thought the capsules looked wrong and hence contacted the transplant coordinator who wrote another prescription. The action taken with Advagraf was not reported. The outcome of the event medication error was unknown. The reporter assessed the event as non serious and did not assess the causality.
2010EU001185	Wrong Drug (Wrong Prescribing)	A patient with unknown age and gender was prescribed and dispensed Advagraf instead of Prograf on an unspecified date. The patient noticed the mistake and did not take Advagraf.
2009EU002377	Wrong Drug (Wrong Prescribing)	A female patient of unknown age was prescribed Advagraf twice daily on an unspecified date. The patient recognized that she should be on Prograf twice daily and not on Advagraf. The patient informed her pharmacist. No adverse events were reported.
2009EU001838	Wrong Drug (Wrong Prescribing)	A 51-year old male patient was on therapy with Prograf (therapy dates, dosage, and indication not reported). On an unspecified date the physician wrote an incorrect repeat prescription for tacrolimus MR (Advagraf) instead of Prograf. The patient was scheduled to receive 2 mg Prograf in the morning and 1mg in the evening, however received Advagraf, same dosage and schedule. The patient continued on therapy with Advagraf, pending a review in the clinic, had no reported side effects, and his drug levels were stable.
2009EU001440	Wrong Drug (Wrong Prescribing)	A 44-year old female patient was prescribed Advagraf 1 mg formulation twice daily on an unknown date. The pharmacist noticed that the prescription was incorrect and called Astellas to request whether Advagraf could be taken twice daily. Concomitant therapy included Prograf 5 mg twice daily, oral mycophenolate 720 mg twice daily, alfacalcidol

Case Numbers	Medication Error Type	Narratives
		0.25 mg daily, trandolapril 2 mg daily, acetylsalicylic acid 75 mg daily, simvastatin 40 mg daily, and oral prednisolone 5 mg daily. The patient did not report any adverse events.
2008EU002062	Wrong Drug (Wrong Prescribing)	A male anesthetist of unreported age started Prograf (dose, frequency and start date not reported) for an unknown indication. Medical history and concomitant medications were not provided. Advagraf was prescribed and the patient further clarified via telephone that his GP had prescribed Advagraf as he knew this was not the same medication as Prograf. The patient did not receive the prescribed medication; and, therefore, did not administer it. The reporter did not provide a causality assessment.
2008EU002043	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started Prograf, 0.5 mg (frequency not reported) on 24 Dec 2007 for an unknown indication. Medical history and concomitant medications were not provided. Advagraf, 0.5 mg, was prescribed by the GP rather than Prograf, 0.5 mg. The error was noted prior to dispensing the incorrect medication. The reporter did not provide a causality assessment.
2008EU002042	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started Prograf, 0.5 mg (frequency and start date not reported) for an unknown indication. The patient had previously experienced a prescribing error with Advagraf and Prograf on 24 Dec 2007 (refer to MAH No. 2008EU002043). At that time, the error was noted prior to dispensing the incorrect medication and the patient was dispensed Prograf correctly. Concomitant medications were not provided. Two weeks later, Advagraf, 0.5 mg, was again prescribed by the GP rather than Prograf, 0.5 mg. Advagraf was dispensed at that time; however, the error was discovered during the patient's hospital visit and Advagraf was not administered. The reporter did not provide a causality assessment.
2008EU002031	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started Advagraf, twice daily (dose and start date not reported), as immunosuppressive therapy after a liver transplant. The patient had a history of liver transplantation ten years prior and hepatitis C. Concomitant medications were not reported. Six weeks prior to surgery, the patient was switched from sirolimus to tacrolimus due to issues with wound healing. A trough tacrolimus level of 13 ng/mL was reported 10 days after starting tacrolimus. According to the reporter, the trough tacrolimus reference level should have been approximately 5 ng/mL given the fact that the patient was 10 years post-transplantation. It was determined that Advagraf was prescribed twice daily rather than Prograf twice daily. The patient's medications were subsequently changed to Prograf twice daily. No further tacrolimus levels were reported. The events were considered medically significant. The reporter did not provide a causality assessment.

Case Numbers	Medication Error Type	Narratives
2008EU002049	Wrong Drug (Wrong Prescribing)	A patient of unknown age and gender started Advagraf (dose, frequency and start date not reported) as immunosuppressive therapy after a renal transplant. Medical history and concomitant medications were not provided. While hospitalized, the patient received Advagraf, twice daily (single occurrence) as the hospital physician was not familiar with Advagraf once daily administration. The patient did not experience any adverse effects and received Advagraf once daily the following day (when the error was discovered) and thereafter. The reporter did not provide a causality assessment.
2010EU001500	Wrong Drug (Wrong Prescribing)	A male patient of unknown age underwent kidney transplantation on an unspecified date, and was started with Prograf. The reporter stated that six month post transplantation the patient was switched to Advagraf incurring in a wrong conversion, as a consequence of which the patient had only taken half dose of the drug. The date of medication error was reported as 08JUN2009, and the wrong dose was administered until17JUN2009. There were no adverse events associated with this error. The reporter assessed the administration error as non-serious.
2010EU001502	Wrong Drug (Wrong Prescribing)	An adult Caucasian male (age unspecified) started Advagraf (dose and frequency unspecified) on an unspecified date for kidney transplantation. Medical history was not provided. Concomitant medications included Prograf. On 06 May 2009, after six months post-transplant, the patient was switched to Advagraf. The reporter stated that the conversion was wrong (a 1:1 conversion) and that the patient took a half dose. As per the reporter, this error resolved after two weeks on 20 May 2009 and there was no adverse event associated with this error. Action taken with the suspect drug was not reported. Outcome of the event was reported as unknown. The reporting physician assessed the event of administration error as non-serious and the causality to be probably related to the Advagraf (tacrolimus) treatment.
2010EU001499	Wrong Drug (Wrong Prescribing)	A male patient of unknown age had been receiving Prograf (dose and frequency not specified) after kidney transplant. Six months post transplant the patient was switched to Advagraf: conversion was incorrect and the patient took a double dose. The reporter stated that there were no adverse events associated to this error.
2010EU001503	Wrong Drug (Wrong Prescribing)	A male (age unspecified) started Advagraf (dose and frequency unspecified) on an unspecified date for kidney transplant. Medical history was not provided. Concomitant medication included Prograf. On 01 Sep 2009 (6 months after transplant), the patient was switched to Advagraf. The conversion was wrong (1:1 conversion) and the patient took a

Case Numbers	Medication Error Type	Narratives
		half dose of tacrolimus. There was no adverse event associated with the error. The action taken with tacrolimus was not reported. The error was resolved two weeks later on 10 Sep 2009. The reporting physician considered the event as non serious and causality to be probably related to the tacrolimus treatment.
2011EU009498	Wrong Drug (Wrong Prescribing)	An adult male (age unspecified) started oral tacrolimus, 4 mg daily, on an unknown date for uveitis. Medical history and concomitant medications were not reported. The patient had used Advagraf for six days, and was subsequently being switched over to Prograf as there was a prescription error. The patient was initially prescribed generic tacrolimus, but the patient's physician clarified that the patient should be prescribed Prograf and not generic tacrolimus. The patient was due to finish Advagraf treatment for treatment of uveitis on 20 Dec 2011 and on 21 Dec 2011, and would start oral Prograf 4 mg daily to treat uveitis. The reporter confirmed that the patient did not experience any adverse events while taking Advagraf, adding that the patient was doing very well and found the treatment effective. The action taken with Advagraf and Prograf treatment was not applicable. The outcome of prescribing error was unknown. The reporter did not assess the causality of the events to the Advagraf and Prograf treatment.
2011EU000580	Wrong Drug (Wrong Prescribing)	An 58-year-old adult male received oral Advagraf, 3 mg daily, for heart transplantation. Medical history included heart transplant four years prior. Concomitant medications were not provided. The patient had constant trough tacrolimus levels since starting treatment two years prior to this event. On an unspecified date, the patient asked the physician by mistake to prescribe Prograf instead of Advagraf. The patient subsequently took 1 mg of Advagraf and 1 mg of Prograf in the morning. The patient wanted to continue with the following combination: Advagraf 1 mg and Prograf 1 mg in the morning and Prograf 1 mg in the evening. The patient was advised to not continue with this combination and to contact his transplantation center. No adverse event was reported. Action taken with tacrolimus treatment was unknown. The outcome of the event was not reported.
2008EU002194	Wrong Drug (Wrong Prescribing)	A male patient of unknown age started Advagraf twice daily (dose and start date not reported) as immunosuppressive therapy after a liver transplant. Medical history and concomitant medications were not provided. For approximately 10 days, the patient received Advagraf twice daily rather than once daily. As of the time of reporting, no adverse events were reported as a result of the drug administration error. The reporter did not provide a causality assessment.
2010EU000498	Wrong Drug (Wrong Prescribing)	A 56-year old male patient was treated with Prograf for renal transplant from JUL2002 to

Case Numbers	Medication Error Type	Narratives
		23SEP2009 before the switch to Advagraf. The patient was treated with Advagraf 5 mg from 13OCT2009 to 13JAN2010. Thereafter the patient received again Prograf from 05FEB2010 to 22JUL2010. On the last prescription, the patient received a prescription for Advagraf 3 mg (prescription error). On 08FEB2010, the pharmacist received a call from the patient's wife explaining that the patient had been prescribed Advagraf 0.3 mg. The prescription for Advagraf 3 mg was considered a prescribing error (formulation strength not yet marketed in the country). As the patient preferred to take treatment with Prograf again, the transplant specialist called back the pharmacy to modify the prescription from Advagraf 3 mg to Prograf at a dose of 2.5 mg twice daily. No Concomitant medications were reported. The reporting pharmacist assessed the event of medication error as non-serious.
2010EU002323	Wrong Drug (Wrong Prescribing)	A 19-year-old female started oral Advagraf, 3.5 mg once daily, for renal transplant on an unspecified date. Medical history and concomitant medications were not reported. The patient's tacrolimus dosage regimen was adapted via trough tacrolimus levels, resulting in a prescribed dose of 3.3 mg daily. It was reported that a 0.1 mg capsule of Advagraf does not exist. The event was reported as a prescribing error. The pharmacist informed the patient's physician that it was a prescribing error. Her physician subsequently reduced her tacrolimus dose from 3.3 mg to 3 mg. The outcome of the event was reported as unknown. The reporter assessed the as non serious but did not provide causality for tacrolimus treatment.
2011EU003161	Wrong Drug (Wrong Prescribing)	A 12-year-old female received varying doses (0.4 mg to 8 mg) of Advagraf and Prograf for liver transplant rejection prevention. Medical history included liver transplant in (b) (6) 2000 due to atresia of the biliary tract, asthma, allergic diathesis (latex and iodine), splenorenal shunting over thrombosis of the primitive portal trunk and stenosis of mesenterico-caval anastomosis in Jul 2011. Liver biopsy in Jan 2007 was in favor of chronic graft rejection. Concomitant medications included mycophenolate mofetil, ursodeoxycholic acid, omeprazole, ferrous fumarate, terbutaline and fluticasone propionate/ salmeterol. The patient was initially treated with Prograf 0.4 mg twice daily until 04 May 2011. By mistake, she was switched to Advagraf 8 mg daily instead of 0.8 mg daily. She was treated with 8 mg from 04 May 2011 to 12 May 2011. On 12 May 2011 she presented with eyelid oedema and an increased trough tacrolimus level of 30 ng/ml. Again by mistake, she was switched to Prograf 4 mg twice daily (instead of 0.4 mg twice daily) from 12 May 2011 to 16 May 2011. On (b) (6) she was admitted to emergency care with incoherent speech, balance disorders, somnolence, and hyperammonemia. The physician did not suspect tacrolimus overdose due to the presence of hyperammonemia until 16 May 2011 when electroencephalogram revealed encephalopathy grade III. From 16 May 2011 to 19 May

Case Numbers	Medication Error Type	Narratives
		2011, the hyperammonemia improved and normalized. The incoherent speech, balance disorders and somnolence resolved by 18 May 2011. On 20 May 2011, Prograf was reintroduced at 4 mg twice daily. On 27 May 2011, she presented with tacrolimus overdose (T0 = 52.5). Also at [redacted] (b) (6) she was hospitalized for asthma. Again on 03 Jun 2011 her T0 was 58.8. She continued to receive Prograf 4 mg until the end of Jun 2011. The dose was reduced to 0.4 mg twice daily after the mistake was discovered, after which time her trough tacrolimus levels normalized. On 04 Jun 2011, she developed acute renal failure, which resolved by 09 Jun 2011. The outcome of encephalopathy grade III and high trough level of tacrolimus was resolved. The outcome of overdosage and asthma was recovered. The outcome of hyperammonemia was not recovered. The reporter assessed the encephalopathy grade III as serious due to significant disability or incapacity, and acute renal insufficiency and asthma as serious due to hospitalization or prolongation of hospitalization. The reporter assessed the causality of the liver encephalopathy and acute renal failure as probably related to tacrolimus, and the asthma as not related. According to the reporter, it was probable that concomitant diseases played a role in the occurrence of the adverse events reported. The reporter did not assess the seriousness criteria for medication error and overdosage. The reporter did not assess the causality for the other events in relation to tacrolimus.
2009US002461	Wrong Drug (Wrong Prescribing)	A female patient of unknown age began oral Prograf extended release therapy (5 mg tablet daily) for kidney transplantation immunosuppression, and on an unspecified date experienced polyneuropathy, myalgia, parasthesis and cramps in the proximal upper limbs. Serum tacrolimus concentration was given as '30' (units not provided). Later it was learned that the patient had been taking Prograf extended release as if it was the immediate release formulation. Medical history included kidney transplantation on 21DEC2008 and recurrent urinary tract infection. Concomitant medications include mycophe-nolate mofetil, prednisone, simvastatin, nifedipine, unspecified calcium supplements, and unspecified antibiotics. Treatment was changed to everolimus. Forty-eight hours later the events of polyneuropathy, myalgia, parasthesis and cramps in the proximal upper limbs were dramatically improved. The reporter did not provide a causal assessment for any of the reported adverse events.
2009US003744	Wrong Dose	A patient (unknown age and gender) began Advagraf 1 mg daily, ten days post-transplant for kidney transplant immunosuppression. The Advagraf dose was then increased to 8 x 1 mg capsules daily until 02OCT2009. On 02OCT2009, the patient's dose was subsequently adjusted to 10 X 1 mg capsules daily. The retail pharmacist dispensed Advagraf 5 mg

Case Numbers	Medication Error Type	Narratives
		capsules and instructed the patient to take 2 capsules daily for a total dose of 10 mg daily. On 03OCT2009, the patient took Advagraf 8 x 1 mg capsules (the remaining dose in his possession) plus 2 x 5 mg capsules, for a total dose of 18 mg. On 04OCT2009, the patient took a total dose of 50 mg of Advagraf. On 05-OCT-2009, the patient went to the clinic and the transplant nurse advised the patient to hold the Advagraf. Renal function was investigated and no changes were noticed at the time. The patient was trained in the hospital to take a specific number of Advagraf capsules: 8 or 10 x 1 mg daily. With the change to Advagraf 5 mg capsules (as dispensed by the out-pharmacist) the patient was confused. On unspecified dates, the patient experienced headache and severe tremors. The patient's trough tacrolimus level was reported as '11.2' (units not provided). The outcome for the events of headache and severe tremors was not provided. The reporter did not provide a causal relationship.
2008EU002045	Wrong Dose	A 39-year-old male started Prograf, 2.5 mg twice daily, as immunosuppressive therapy after a renal transplant. Medical history was not provided. Concomitant medications included mycophenolate mofetil and prednisone. The patient initially received Prograf, 2.5 mg in the morning and 2.5 mg in the evening daily. On 11 Apr 2008, the patient's medication was changed from Prograf to Advagraf, 5 mg once daily. The same day, the patient mistakenly self-administered 5 tablets of Advagraf in 1 day (25 mg) rather than 1 tablet daily (5 mg). This was a single occurrence and the patient did not report any disturbances as a result of the drug administration error. Reported tacrolimus levels included (specific dates were not reported): 5.6 – 10.3 ng/mL (prior to medication change), 24.6 ng/mL (after medication change), and 7.4 ng/mL (after medication change). The reporting physician did not provide a causality assessment.
2010EU005289	Wrong Dose	A 55-year-old female started oral Prograf, 2 mg twice daily, as initial immunosuppressive treatment after liver transplantation on (b) (6) Medical history included arterial hypertension, hepatitis C and urinary stomy. Concomitant medications included mycophenolate mofetil for liver transplantation, valganciclovir, sulfamethoxazole trimethoprim, interferon alfa-2B, ribavirin and isradipine for arterial hypertension. The patient initially received Prograf 2 mg twice daily as initial immunosuppressive treatment. On 04 Sep 2010, the patient started Advagraf 1 mg three dosage forms (DF) for liver transplantation until 30 Sep 2010. The pharmacist then ordered boxes of Advagraf 3 mg and instructed the patient to take only 1 capsule per day. Mistakenly, the patient took 3 mg 3 DF daily from 01 Oct 2010 to 02 Oct 2010. On 01 Oct 2010 in the afternoon following morning intake of Advagraf 3 mg 3 DF, the patient developed a headache. On 02 Oct 2010, the

Case Numbers	Medication Error Type	Narratives
		patient reported the headache to the pharmacist and noted that the new box of Advagraf had another color. While speaking with the pharmacist she understood that she had made a mistake. The pharmacist informed the transplant specialist via the nurse who took care of the patient. As of 03 Oct 2010, the patient resumed the correct dose of tacrolimus 3 mg daily and the headache resolved without sequelae. The outcome of the event medication error was reported as not applicable. The reporting pharmacist assessed the event headache as non-serious and the causality to be possibly related to tacrolimus, but did not provide any seriousness criteria or causality for the event medication error.
2009EU001108	Wrong Dose	A 62-year-old male started Advagraf, 4.5 mg daily, on an unknown date as immunosuppressive therapy after a liver transplant. Medical history and concomitant medications were not provided. The patient had switched from Prograf to Advagraf on an unknown date. Initially the patient was treated with Prograf for immunosuppressive therapy at a dose of 4.5 mg daily (four 1 mg capsules and one 0.5 mg capsule). The Advagraf 1 mg and 0.5 mg capsules colors (white and light yellow) confused the patient and led to a sub-dosage. He took four 0.5 mg capsules and one 1 mg capsule (3 mg in total) daily instead of 4.5 mg daily. At the time of the report, the patient had not experienced any consequences resulting from the medication error. The outcome of the event was unknown. The reporter did not provide a causality assessment.
2011EU005906	Wrong Dose	A 28-year-old Mongolian male who began Prograf (Sep 2009 to Apr 2011) for renal transplantation and who then had the formulation changed to Advagraf, received too low a dose. Medical history included Lupus nephritis in 1995 and renal transplant in (b) (6) Concomitant medication included mycophenolate mofetil 6 mg oral once daily and azathioprine sodium 25 mg once daily for renal transplant. In Apr 2011, the patient switched from Prograf to Advagraf but reportedly received a too low dose. The dose was reduced by the patient by mistake in Jun 2011 to Advagraf 1 mg once daily. On 11 Jul 2011, the patient experienced acute cellular rejection. The rejection was attributed to the patient's non-compliance with medication. Tacrolimus was discontinued on 18 Jul 2011. The patient recovered with sequelae on 19 Jul 2011. The reporting physician assessed the acute cellular rejection as serious as it resulted in persistent/significant disability or incapacity, and causality as probably related to tacrolimus treatment.
2009US000169	Wrong Frequency of Administration	A female patient of unknown age experienced an overdose and a cytomegalovirus (CMV) infection with the use of Prograf. Medical history includes transplantation and viral meningitis. Co-suspect medication includes Prograf extended release. Concomitant

Case Numbers	Medication Error Type	Narratives
		medications were not provided. On an unspecified date, the patient began oral Prograf therapy (3 mg every 12 hours) for an unspecified transplantation. On an unspecified date, the patient was converted to Prograf extended release. The patient kept taking the capsules every 12 hours, and then occurred in overdose. Her tacrolimus levels were increased (exact level was unknown). The patient also experienced a CMV infection. The outcome for the events of overdose and CMV infection was not provided. The reporting health professional did not assess the causal relationship for the events.
2011US005399	Wrong Frequency of Administration	A patient (age and gender unspecified) started tacrolimus, 2.5 mg daily, on an unspecified date for an unspecified indication. Medical history and concomitant medications were not provided. On an unspecified date, the patient made an error by taking 1 mg in the morning and 1.5 mg in the evening (split dose). The outcome of the event was not provided. The reporting pharmacist did not provide a seriousness or causality assessment of the event. No further information was provided.
2008EU002046	Wrong Frequency of Administration	A patient of unknown age and gender started Prograf (dose, frequency, and start date not reported) for an unknown indication. Medical history and concomitant medications were not provided. On an unspecified date, the patient's medication was changed from Prograf to Advagraf for ease of management. While at home, following the medication change, the patient was unsure of his understanding regarding the frequency of administration of once daily Advagraf as he had for years self administered Prograf twice daily. He took Advagraf twice daily. He began to tremble and contacted his internist, who advised him of the correct dose and frequency for Advagraf. Patient outcome was not reported. The events were considered medically significant. The reporting physician did not provide a causality assessment.
2010EU005374	Wrong Frequency of Administration	A 21-year-old female was prescribed Advagraf (dose unspecified) once daily on an unspecified date for an unknown indication. Medical history and concomitant medications were not provided. On an unspecified date, the patient was prescribed tacrolimus once daily but reportedly took it twice daily. This was noted by the hospital within 24 hours and the patient experienced no side effects. The action taken with tacrolimus treatment and event outcome were unknown. The reporter did not provide the causality of the event to tacrolimus treatment.
2008EU001922	Wrong Frequency of Administration	A 34-year-old female started Advagraf, 3 mg twice daily, on 02 Aug 2008 as immunosuppressive therapy after a renal transplant. Medical history included renal transplant on (b) (6) Concomitant medications included mycophenolate sodium,

Case Numbers	Medication Error Type	Narratives
		prednisolone, atorvastatin, furosemide, ferrous sulfate, escitalopram, carvedilol, lansoprazole, ranitidine, candesartan, alfacalcidol, and epoetin. Of note, Advagraf was prescribed using the brand name Advagraf. From 02 Aug 2008 to 12 Aug 2008, the patient took Advagraf, 3 mg twice daily instead of 3 mg once daily. The drug administration error was noted at the patient's first control visit when the doses were checked. On 03Aug 2008, she developed nausea, vomiting, tremor, and diarrhea. On (b) (6) the patient was hospitalized with diarrhea and vomiting. Stool cultures performed on (b) (6) were positive for *C. difficile*. The patient recovered from all events on (b) (6) Per patient request, immunosuppressive therapy was changed from Advagraf to Prograf on (b) (6) . The patient was discharged from the hospital on (b) (6) The reporting physician assessed the events as possibly related to tacrolimus therapy.
2008EU002047	Wrong Frequency of Administration	A patient of unknown age and gender started Prograf (dose, frequency and start date not reported) for an unknown indication. Medical history and concomitant medications were not provided. On an unspecified date, the patient's medication was changed from Prograf to Advagraf for ease of management. While at home following the medication change, the patient was unsure of his understanding regarding the frequency and self-administered Advagraf twice daily, as he had for years with Prograf, rather than once daily. He began to tremble and contacted his internist, who advised him of the correct dose and frequency for Advagraf. Patient outcome was not reported. The events were considered medically significant. The reporting physician did not provide a causality assessment.
2012EU000768	Wrong Strength	An adult male (age unspecified) reportedly took Advagraf, 0.5 mg instead of 5 mg, for kidney transplant. Medical history and concomitant medications were not provided. On an unspecified date 14 days post-transplant, the patient took tacrolimus oral 5 mg for kidney transplant. A medication error occurred on unknown date when the patient was administered tacrolimus 0.5 mg instead of tacrolimus 5 mg (though the reporter did not confirm that the patient was administered tacrolimus treatment). At the time of the report, the patient was on day 14 post-transplant. No adverse event occurred. The action taken with tacrolimus was not applicable. The outcome of the event was unknown. The reporting physician did not provide any seriousness criterion of the event and did not provide any causality assessment.
2011EU000647	Wrong Strength	A female (age unspecified) started oral Prograf (dose and frequency unspecified) on an unknown date for renal transplantation. Medical history and concomitant medications were not provided. The patient was on Prograf capsules for an unreported amount of time. It was

Case Numbers	Medication Error Type	Narratives
		reported that the packaging of Prograf capsules was recognizable by distinctly different title of strength but also by the color printing of 0.5 mg in green and 1 mg in blue. On an unspecified date, the patient was confused as she received Advagraf with similar color print strengths to those on the Prograf packaging, which caused the patient to mistake tacrolimus 0.5 mg with 1 mg. On an unspecified date, blood levels of tacrolimus were decreased. No rejection or other complaints occurred during decreased tacrolimus blood level. According to the patient, her tacrolimus blood level increased to normal after administration of the right strength. The action taken with tacrolimus was unknown. The outcome for medication error was reported as recovered, and the outcome for the other event was unknown.
2010EU000160	Wrong Technique of Adminsitration	A 10-year old male patient started Advagraf via naso-gastric tube for a renal transplant in DEC2009. The patient was initially treated with Prograf via naso-gastric tube by opening the capsules. In DEC2009 the patient was switched to Advagraf, and those capsules were also opened to be administered by naso-gastric tube. The kinetics monitoring was good under both Prograf and Advagraf. The patient did not experience any adverse events.
2009EU004924	Wrong Technique of Adminsitration	A male patient of unknown age started Advagraf on an unspecified date and dosage. The patient had been hospitalized in another hospital in the neurosurgery unit. In this hospital tacrolimus was administered via naso-gastric tubing after opening capsules. When the patient was transferred, it was decided to continue the same administration modality of tacrolimus, as the patient was well stabilized under this treatment. No adverse events have been reported.
2012EU000154	Improper Dose	A 64-year-old male started Advagraf, 2 mg daily, on an unspecified date (Sep - Oct 2011 as immunosuppressive therapy after a liver transplant. Medical history included liver transplant in (b) (6) 2011 and prior Prograf use. Concomitant medications included mycophenolate mofetil, 1 gram twice daily. On an unspecified date, the patient switched to Advagraf, 2 mg daily (am). On 05 Jan 2012, the patient inadvertently took 1 additional dose of Advagraf (2 mg in the evening) and additional mycophenolate mofetil (2 grams instead of 1 gram as evening dose). The patient did not take tacrolimus on 06 Jan 2012. It was planned with the pharmacist to resume Advagraf on 07 Jan 2012 (am) with the usual dosage regimen. The patient did not experience any adverse events. Since the intake error, the patient was seen in consultation several times with the hepatologist and the diabetologist without any particular problems. The reporter did not provide a causality assessment.

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/s/

JUNG E LEE
06/17/2013

JAMIE C WILKINS PARKER
06/17/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 7, 2013

To: Jacquelyn Smith, RPM
Office of Antimicrobial Products (OAP)/ Division of Transplant and Ophthalmology Products (DTOP)

From: Christine Corser, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: TRADENAME XL™ (tacrolimus) extended-release capsules, for oral use

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As requested in DTOP's consult dated November 19, 2012 OPDP has reviewed the draft PI for TRADENAME XL™ (tacrolimus) extended-release capsules, for oral use. OPDP reviewed the proposed, clean, substantially complete version of the PI titled, "tacrolimus-xl-Kidney Only-march-2013.doc" received via email from DTOP on June 3, 2013.

OPDP's comments are provided in the attached clean version of the labeling. OPDP notes that several areas of the label include notes to include additional language, data, and presentations (i.e. tables) within the PI. This information was not provided within this version of the label; therefore, OPDP was unable to review and comment on these proposed presentations. If additional information is added to the label, please consult OPDP regarding these revisions.

Thank you for the opportunity to review these materials. If there are any questions, please contact me at 301-796-2653 or Christine.corser@fda.hhs.gov

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/s/

CHRISTINE G CORSER
06/07/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 6, 2013

TO: Jacquelyn Smith, Project Manager
Joette Meyer, Medical Team Leader
Division of Transplant and Ophthalmology Products

FROM: Kassa Ayalew, Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 204096/ IND 64148

APPLICANT: Astellas Pharma US, Inc.

DRUG: Tacrolimus extended-release capsules, 0.5 mg, 1 mg, and 5 mg / Modified release (MR4) tacrolimus

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS:

- Prophylaxis of organ rejection in adult patients receiving kidney transplants.
- Prophylaxis of organ rejection in adult male patients receiving liver transplants (withdrawn)

CONSULTATION REQUEST DATE: November 19, 2012

DIVISION ACTION GOAL DATE: July 21, 2013

INSPECTION SUMMARY GOAL DATE: June 20, 2013

PDUFA DATE: July 21, 2013

I. BACKGROUND:

The Applicant, Astellas Pharma US, Inc. submitted a new drug application (NDA 204096) for Tacrolimus extended-release capsules, 0.5 mg, 1 mg, and 5 mg strengths / Modified release (MR4) tacrolimus requesting approval for prophylaxis of organ rejection in adult patients receiving kidney transplants and in adult male patients receiving liver transplants. The Applicant later withdrew the liver indication from NDA 204096. The immediate-release oral and intravenous formulations of tacrolimus (Prograf®) were originally approved by the FDA in 1994 for prophylaxis of organ rejection in recipients of allogeneic kidney and liver transplants. Tacrolimus as Prograf capsules requires twice-daily oral dosing.

To support the approval, the Applicant has provided data from multiple studies which they believe provide sufficient evidence to support the indication of Tacrolimus extended-release capsules, 0.5 mg, 1 mg and 5 mg strengths / Modified release (MR4) tacrolimus for prophylaxis of organ rejection in adult patients receiving kidney transplants. Brief descriptions of the studies, to support the indication of prophylaxis of organ rejection in adult patients receiving kidney transplant (Studies 02-0-158 and FG-506E-12-03) and de novo liver transplant (Studies FG-506E-11-03), selected for audit, are provided in the following sections:

> **Study 02-0-158**: A Phase 3, Randomized, Open-Label, Comparative, Multi-Center Study to Assess the Safety and Efficacy of Prograf® (Tacrolimus)/MMF, Modified Release (MR4) Tacrolimus/MMF, and Neoral® (Cyclosporine)/MMF in De Novo Kidney Transplant Recipients. The above study was conducted at 60 centers in the U.S., Canada, and Brazil to evaluate the efficacy and safety of Prograf-based immunosuppression and Advagraf-based immunosuppression, each in comparison to cyclosporine (cyclosporine modified, Neoral) - based immunosuppression, in de novo kidney transplant recipients.

Study FG-506E-12-03: A Multicenter, 1:1 Randomized, Double Blind Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus FK506 (MR4) vs. Tacrolimus FK506 in Combination with MMF (Cellcept®) and Steroids in Patients Undergoing Kidney Transplantation.This study was performed in 74 centers in 22 countries (Europe, Australia, Canada, Argentina, Brazil, Mexico, and South Africa) and 680 patients (340 patients per treatment arm) in approximately 80 centers were enrolled.

Protocol FG-506E-11-03: A Multicenter, 1:1 Randomized, Double Blind Two Arm Parallel Group Study to Evaluate and Compare the Efficacy and Safety of Modified Release Tacrolimus FK506 (MR4) vs. Tacrolimus FK506 in Combination with Steroids in Patients Undergoing Primary Liver Transplantation

The Office of Scientific Investigation received a consult from the Division of Ophthalmic and Transplant Products to conduct clinical inspections of Study 02-0-158, FG-506E-12-03 and FG-506E-11-03. The above studies for which audits have been requested are considered pivotal and inspections of the above sites are essential to verify the quality of conduct of the study for this application. The data in support this NDA application was obtained primarily from studies that were conducted at foreign clinical investigator (CI) sites. The sites for inspection were selected due to enrollment of large numbers of study subjects, and/or the CI's previous inspectional history. Five foreign clinical sites and one domestic site were chosen for inspection. One of the five sites which was to be inspected in Prague, CZ (Dr. Pavel Trunecka, Site #CZ002), mainly participated in the liver transplantation study (FG-506E-11-03), and was cancelled because the sponsor withdrew the liver indication from the NDA. Therefore, four clinical sites (three foreign and one domestic) were inspected.

II. RESULTS (by Site):

Name of CI/Address/contact information/Site #	Protocol #/ Numbers of Subjects	Inspection Date	Final Classification
Kraemer, Bernhard, M.D. Klinik und Poliklinik fuer Innere Medizin II -Nephrologie, Franz-Josef-Strauß-Allee 11 Regensburg, 93042, Germany Site # DE052	FG-506E-12-03 N=34	February 25- March 1, 2013	VAI
Backman, Lars, M.D., Ph.D. SU/Sahlgrenska University Hospital, Dept of Transplantation and Liver Surgery Gothenburg, 41345, Sweden Site # SE002 **Current Address:** Akademiska Sjukhuset, SE-751 85	FG-506E-12-03 N=22 9463-CL-2101 N=7	February 25- March 1, 2013	VAI

Uppsala Sweden			
Silva, Jr., Helio Tedesco, M.D. Hospital do Rim E Hipertensa Fundacao Oswaldo Ramos, Rua Borges Lagoa, 960, 11o. andar Villa Clementino São Paulo, SP 04038-002, Brazil Site # 1020	02-0-158 N=42	February 25-March 1, 2013	VAI
Yang, Harold, M.D., Ph.D. Pinnacle Health at Harrisburg 205 South Front Street, Brady 8 Harrisburg, PA 17105-8700 Site# 1093	02-0-158 N=36	March 22-28, 2013	VAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Kraemer, Bernhard, M.D.**
   Klinik und Poliklinik fuer
   Innere Medizin II
   Franz-Josef-Strauß-Allee 11
   Regensburg, 93042
   Germany

   a. What was inspected:
   This inspection was conducted in accordance with Compliance Program 7348.811. There were no INDs associated with the inspected entity in CDER's database, and the CI had no prior inspections. This inspection was performed as a data audit for Study FG-506E-12-03.

   There were a total of 47 subjects screened, 34 subjects were randomized, 14 subjects withdrew from the study and 20 subjects completed the study. An in depth audit of the study records for 34 subjects was conducted.

   Review of records for both protocols included, but was not limited to, verification of data line listings for efficacy endpoint data, adverse event reporting, and subject discontinuations, subject eligibility, informed consent documentation, test article accountability/disposition, Ethics Committee approvals; monitoring records, case report forms, concomitant medication usage, and adherence to protocol-specified procedures for

blinding and randomization. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable.

b. General observations/commentary:

There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. There were no SAE's recorded at this site. In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued for failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically:

i) Serious adverse events in six patients were not reported to the sponsor according to the protocol (within 24 hours after the investigator becoming aware of events): Subject H3805 (PROGRAF+MMF)-increased creatinine/acute kidney failure; Subject H3808 (MR4+MMF)-hospitalization for parathyroidectomy; Subject H3831 (MR4+MMF)-right radius fracture ; Subject H3803 (MR4+MMF)-basalioma on nose; Subject H3802 (MR4+MMF)-creatinine increased; Subject H3801 (PROGRAF+MMF)-CMV infection.

OSI Reviewer Comments: *The CI should have reported serious adverse events to the sponsor within 24 hours after the investigator becoming aware of the events. Although the CI failed to report the above SAEs to the sponsor within 24 hours of after the investigator becoming aware of the events, the above mentioned protocol deviation were reported to the sponsor and are noted in the data listings submitted by the sponsor. The SAEs are in the data listings, so the violations due not effect data reliability. Based on the CI's response dated March 13, 2013, the CI acknowledged the delay in reporting SAEs and has indicated that he has implemented corrective actions and procedures to prevent delay in SAE reporting.*

ii) Two female patients with childbearing potential (Subjects H3821 (PROGRAF+MMF) and H3824 (MR4+MMF)) did not receive a pregnancy test at the study entry.

OSI Reviewer Comments: *A urine or serum pregnancy test (β-HCG) was to be performed in females of childbearing potential at Visit 1 and at Visit 11.The CI should have done a pregnancy test at the study entry and completion. There were no pregnancies during the study. The violation was isolated in nature, and it is unlikely that it would affect subject safety or data reliability. Based on the CI's response dated March 13, 2013, the CI indicated that he has implemented corrective actions.*

iii) Proper version of informed consent was not used in one subject (Subject H3804 (PROGRAF+MMF)).

OSI Reviewer Comments: *The CI should have used the most recent version of the Informed Consent form for the subject. Although the clinical investigator failed to*

use the most recent version of the Informed Consent Form for the subject according to the investigational plan, which is a regulatory violation, the form that was used to obtain informed consent from the subject was not significantly different from the most recent version. In addition, this finding was isolated in nature and is unlikely to impact data reliability, nor compromise the rights, safety and welfare of subjects in the study. In a response letter dated March 13, 2013, the CI indicated that he has implemented corrective actions.

iv) Three patients received prohibited medications (Subject H3821 (PROGRAF+MMF) received Myofortic (mycophenolic acid) and Bayotensin (Nitrendipin), and Subjects H3832 (MR4+MMF) and H3829 (PROGRAF+MMF) both received Bayotensin (nitrendipin).

OSI Reviewer Comments: *Although the clinical investigator administered the above prohibited antihypertensive and immunosuppressant medications, which are regulatory violations, the above mentioned protocol deviations were reported to the sponsor and are noted in the data listings submitted by the sponsor. In addition, the findings were isolated in nature and unlikely to impact data reliability, nor compromise the rights, safety and welfare of subjects in the study. In the CI's response dated March 13, 2013, he stated that the above items occurred because the subjects had received treatment in the ICU or with a personal physician.*

v) One patient mistakenly received more than one dose of study drug at one time. Subject H3829 (PROGRAF+MMF) received 2 doses of 6 mg FK506.

OSI Reviewer Comments: *Although the patient mistakenly received more than one dose of study drug, the patient reportedly did not develop any adverse reactions from the extra dose. The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability.*

vi) Two patients, Subject H3825 (PROGRAF+MMF) and Subject H3826 (MR4+MMF), mistakenly received study medication ≤ 2 hours before it should have been administered.

OSI Reviewer Comments: *The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability.*

vii) The protocol requires that subjects who receive a kidney transplant from a cadaveric donor or a living non-HLA identical donor receive a kidney from a donor who is between 5 and 65 years of age with compatible ABO blood type. Subject H3818 (PROGRAF+MMF), received a kidney from a living donor aged 69 years.

OSI Reviewer Comments: *The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability.*

c. Assessment of data integrity:
In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. Although regulatory violations were noted, it is unlikely, based on the nature of the violations, that they significantly affect overall reliability of safety and efficacy data from the site. The data derived from Dr. Bernhard Kraemer's site are considered reliable.

2. Backman, Lars, M.D., Ph.D.
SU/Sahlgrenska University Hospital,
Dept of Transplantation and Liver Surgery
Gothenburg, 41345, Sweden
Site # SE002
Current Address:
Akademiska Sjukhuset, SE-751 85
Uppsala
Sweden

a. What was inspected:
This inspection was conducted in accordance with Compliance Program 7348.811. There was (b) (4) associated with the inspected entity in CDER's database, and the CI had no prior inspection. This inspection was performed as a data audit for Study FG-506E-12-03 and Study FG-506E 11-03.

At this site, for Study FG-506E-12-03, 22 subjects were screened and randomized, 5 subjects discontinued, and 17 subjects completed the study. An audit of 22 subjects' records was conducted. For Study FG-506E 11-03, seven subjects were screened and enrolled in the study, three subjects discontinued due to adverse events, and four subjects completed the study. An audit of seven subjects' records was conducted.

Review of records for both protocols included, but was not limited to, verification of data line listings for efficacy endpoint data, adverse event reporting, and subject discontinuations; subject eligibility, informed consent documentation, test article accountability/disposition, Ethics Committee approvals, monitoring records, case report forms, concomitant medication usage, and adherence to protocol-specified procedures for blinding and randomization. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable.

b. General observations/commentary:
There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. There were no SAE's recorded at this site. In general, the study was conducted appropriately. A Form FDA 483, Inspectional Observations, was issued to this

investigator for failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically:

i) Study FG-506E-12-03, Amendment I of the protocol requires a blood sample to be collected and analyzed for tacrolimus whole blood trough levels during Visit 2, Day 1 of the study. Eight subjects did not have tacrolimus whole blood trough levels performed during Visit 2, Day 1 per protocol (Subjects #H4101 (PROGRAF+MMF) , H4104 (MR4+MMF), H4108 (PROGRAF+MMF), H4109 (PROGRAF+MMF), H4111 (MR4+MMF), H4114 (PROGRAF+MMF), H4115 (MR4+MMF), H4120 (MR4+MMF)

OSI Reviewer Comments: *Although the clinical investigator failed to draw baseline tacrolimus whole blood trough levels according to the protocol , the observed violation is isolated and unlikely to affect subject safety and data reliability. The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability. Based on the CI's response dated March 16, 2013, the CI has provided assurance to identify subjects who would need redrawing of a blood specimen in a timely manner.*

ii) Protocol FG-506E-12-03, Section 9.3.3, requires that the clinical investigator perform a 12-lead ECG at Visit 1, Visit 9 and Visit 11/EOS. The CI failed to performs ECG at Visit 1, Visit 9, and Visit 11/EOS as required per protocol for five subjects: (Subjects # H4106 (MR4+MMF), H4109 (PROGRAF+MMF), H4110 (MR4+MMF), and H4119 (PROGRAF+MMF), at Visit 9; Subject # H4120 (MR4+MMF) at Visit 11).

OSI Reviewer Comments: *The clinical investigator failed to perform ECG assessment at specified study visits per protocol. This is a regulatory violation. The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability. Based on the CI's response dated March 16, 2013, the CI has indicated that he has implemented corrective actions.*

iii) The Protocol FG-506E 11-03, Section 7 "Treatment", requires the dosing to be administered as follows: 0.2 mg/kg FK506E (MR4)-Placebo in the morning and 0.2 mg/kg FK506D (MR4) in the evening was to be administered. In addition, a dose of 0.05 mg/kg FK506 in the morning and 0.05 mg/kg FK506-Placebo in the evening (a ratio of 1:0.5. Three subjects (Subjects G4701 (PROGRAF), G4702 (PROGRAF), and G4705 (MR4)) did not receive doses of study medications as required per protocol at a ratio of 1:0.5 for the time period of 6/25/2005-6/26/2005. Instead they were given doses of the study drugs at ratio close to 1:1.

OSI Reviewer Comments: *Doses of study medications should have been provided per protocol in three subjects. The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability.*

iv) Protocol FG-506E 11-03 requires a blood sample to be collected and analyzed for tacrolimus whole blood trough levels on Visit 2, Day 1 of the study. Two subjects did not have blood analyzed for tacrolimus whole blood trough levels as required per protocol: Subject G4704 (MR4) and Subject G4706 (PROGRAF) did not have a trough level on Visit 2, Day 1.

OSI Reviewer Comments: *Tacrolimus whole blood trough levels should have been drawn during Visit 2, Day I according to the investigational plan. This is a regulatory violation. The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability. Based on the CI's response dated March 16, 2013, the CI has indicated that he has implemented corrective actions.*

v) Protocol FG-506E 11-03 Section 9.3.3, requires that the CI perform a 12-lead ECG at Visit 1, Visit 9, and Visit 11/EOS. Three subjects did not have an ECG assessment performed at specified study visits per protocol (Subject G4701 (PROGRAF) at Visit 9 and Subjects #G4705 (MR4) and H4707 (PROGRAF) at Visit 11)

OSI Reviewer Comments: *The CI failed to perform ECG assessment at specified study visits per protocol. This is a regulatory violation. The above-mentioned protocol deviation was noted in the data listings submitted by the sponsor and was isolated in nature, and it is unlikely that it would affect subject safety or data reliability. Although the clinical investigator failed to obtain ECG according to the protocol, the observed violation is isolated and unlikely to affect subject safety and data reliability. Based on the CI's response dated March 16, 2013, the CI has indicated that he has implemented corrective actions.*

c. Assessment of data integrity:

In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. Although regulatory violations were noted, it is unlikely, based on the nature of the violations, that they significantly affect overall reliability of safety and efficacy data from the site. The data derived from Dr. Backman's site are considered reliable.

3. Silva, Jr., Helio Tedesco, Jr, M.D.

Hospital do Rim e Hipertensao
Fundacao Oswaldo Ramos
Rua Borges Lagoa 960
Sao Paulo, SP 04038-002
Brazil

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811. There were no INDs associated with the inspected entity in CDER's database, and the CI had no prior inspections. This inspection was performed as a data audit for Study 02-0-158.

At this site, 44 subjects were screened; 42 subjects were randomized, and 38 subjects completed the study. An audit of 20 subjects' records was conducted. Review of records included, but was not limited to, verification of data line listings for efficacy endpoint data, adverse event reporting, and subject discontinuations; subject eligibility, informed consent documentation, test article accountability/disposition, Ethics Committee approvals, monitoring records, case report forms, concomitant medication usage, and adherence to protocol-specified procedures for blinding and randomization. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable.

b. General observations/commentary:

There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. A Form FDA 483, Inspectional Observations, was issued to this investigator because of failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically"

> The associates and employees who assisted in the conduct of the study conducted additional duties other than those listed in the Delegation of Authority Log. Several employees performed Informed Consent Administration for the Extension phase of the study, that were not authorized on the Delegation of Authority Log. Out of 38 subjects informed of the Extension phase, 28 informed consent documents were completed with the unauthorized employee, and the CI signed on a later date.
>
> *OSI Reviewer Comments: Although the clinical investigator failed to use only associates and employees listed in the Delegation of Authority Log to obtain informed consent (IC) from some patients, there was documentation that all associates and employees who administered informed consent and who were not listed in the Delegation of Authority Log to administer IC had general Good Clinical Practice (GCP) training that also covers the procedure on how to administer IC. On the CI's response dated March 6, 2013, the CI indicated that he has implemented corrective actions to ensure that all authorized tasks are delegated to fully trained research members prior to the research members performing study related procedures and that the delegation of authority log is updated after each new employee begins or ends participation in a study. Although the observation is a regulatory violation, we do not think it significantly affects overall reliability of efficacy and safety data from the site. We also do not think it significantly affects the rights, safety, and welfare of the subjects under his care, because the study coordinators who administered informed consent during this trial had GCP training.*

Dr. Tedesco-Silva adequately responded to the inspectional findings in a letter dated March 6, 2013.

c. Assessment of data integrity:
While the FDA inspection revealed regulatory violations of clinical investigator obligations in the conduct of the study, these are considered isolated in nature and unlikely to significantly impact data reliability. The data derived from Dr. Tedesco-Silva 's site appear reliable in support of the NDA.

4. Harold Yang, M.D., Ph. D.
Brady Building 8th Floor
Pinnacle Health
205 South Front Street
Harrisburg, PA 17105-8700

a. What was inspected:
This inspection was conducted in accordance with Compliance Program 7348.811. There were no INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection. This inspection was performed as a data audit for Study 02-0-158.

At this site, 36 subjects were screened; 36 subjects were randomized, and 26 subjects completed the study. An audit of 12 subjects' records was conducted.

Review of records included, but was not limited to, verification of data line listings for efficacy endpoint data, adverse event reporting, and subject discontinuations; subject eligibility, informed consent documentation, test article accountability/disposition, Ethics Committee approvals, monitoring records, case report forms, concomitant medication usage, and adherence to protocol-specified procedures for blinding and randomization. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable.

b. General observations/commentary:
There was no evidence of under reporting of adverse events. The primary efficacy endpoint data were verifiable. There were no SAE's recorded at this site. In general, the study was conducted appropriately. A Form FDA 483, Inspectional Observations, was issued to this investigator because of failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically:

i) Failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically, the protocol indicates which adverse events are considered serious and requires reporting to the sponsor within 48 hours. The CI failed to report Serious Adverse Events (SAEs) in 6 patients: (Subject 1017 (NEORAL+MMF) - renovascular hypertension, Subject 1012 (PROGRAF+MMF) - pneumonia and pleural effusion, Subject 4002 (MR4+MMF) - cytomegalovirus infection, Subject 1009 (NEORAL+MMF) - septicemia, pneumonia, acute respiratory failure and possible ureteral obstruction,

Subject 1003 (NEORAL+MMF) - back pain and abdominal pain, and Subject 2003 (NEORAL+MMF) -community-acquired pneumonia, bleeding).

OSI Reviewer Comments: Although the CI failed to report SAE's to the sponsor in accordance with the study protocol within 48 hours, which is regulatory violation, all SAE's were reported to the sponsor at a later dates.

Dr. Yang's written response (submitted on April 08, 2013) to the observations made by the field inspector acknowledged the violations and states that he has taken measures to improve communication and written standard operation procedures for serious adverse event reporting both to the sponsor and to the IRB.

ii) Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others. Specifically, the CI failed to report promptly to the IRB all unanticipated problems involving risk to human subjects in two patients: (Subject # 1017 (NEORAL+MMF) - renovascular hypertension, and Subject #1009 (NEORAL+MMF) - SAE of septicemia, pneumonia, acute respiratory failure and possible ureteral obstruction).

OSI Reviewer Comments: All adverse events were reported to the IRB and the sponsor but were reported outside the timeframe that was required by the protocol.

Dr. Yang's written response (submitted on April 08, 2013) to the observations made by the field inspector acknowledged the violations and states that he has taken measures to improve communication and written standard operation procedures for serious adverse event reporting both to the sponsor and to the IRB.

c. Assessment of data integrity:

In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. Although regulatory violations were noted, it is unlikely, based on the nature of the violations, that they significantly affect overall reliability of safety and efficacy data from the site. The data derived from Dr. Yang's site are considered reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigators, Drs. Kraemer, Backman, Silva, Jr., and Yang, were inspected for this application. The final classification for all clinical investigator inspections is Voluntary Action Indicated (VAI). The studies from all four sites appear to have been conducted adequately, and the data generated may be used in support of the application.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

KASSA AYALEW
06/10/2013

SUSAN D THOMPSON
06/10/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 06, 2013
To:	Renata Albrecht, MD Director **Division of Transplant and Ophthalmology Products (DTOP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Christine Corser, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TRADENAME XL (tacrolimus)
Dosage Form and Route:	Extended-Release Capsules, for Oral Use
Application Type/Number:	NDA 204-096
Applicant:	Astellas Pharmaceuticals US Inc.

1 INTRODUCTION

On September 20, 2013, Astellas Pharmaceuticals US Inc., submitted for the Agency's review a New Drug Application (NDA-204096) for TRADENAME XL (tacrolimus) extended-release tablets, indicated for the prophylaxis of organ rejection in adult patients receiving kidney transplants with concomitant use of mycophenolate mofetil (MME) and adrenal corticosteroids.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Transplant and Ophthalmology Products (DTOP) on November 19, 2012, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME XL (tacrolimus) extended-release capsules.

2 MATERIAL REVIEWED

- Draft TRADENAME XL (tacrolimus) MG received on September 21, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on June 03, 2013.
- Draft TRADENAME XL (tacrolimus) MG received on September 21, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 3, 2013.
- Draft TRADENAME XL (tacrolimus) Prescribing Information (PI) received on September 21, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on June 03, 2013.
- Draft TRADENAME XL (tacrolimus) Prescribing Information (PI) received on September 21, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on June 3, 2013.
- Approved PROGRAF (tacrolimus) comparator labeling dated August 14, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
06/06/2013

MELISSA I HULETT
06/06/2013

LASHAWN M GRIFFITHS
06/06/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 204096

Application Type: New NDA

Name of Drug: Tacrolimus extended-release capsules, 0.5 mg, 1 mg, 5 mg

Applicant: Astellas Pharma US, Inc

Submission Date: September 20, 2012

Receipt Date: September 21, 2012

1.0 Regulatory History and Applicant's Main Proposals

PROPOSED INDICATION(S):

- Prophylaxis of organ rejection in adult patients receiving kidney transplants.
- Prophylaxis of organ rejection in adult male patients receiving liver transplants.

BACKGROUND: Immediate-release oral and intravenous formulations of tacrolimus are marketed worldwide for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants. In the United States, immediate-release oral and intravenous formulations of tacrolimus (Prograf®) were originally approved by the FDA in 1994. Tacrolimus as Prograf capsules requires twice-daily oral dosing. Advagraf was developed as a once-daily capsule formulation of tacrolimus for the prophylaxis of organ rejection after transplantation and is now approved in 69 countries including Japan, the European Union and Canada.

Astellas submitted an NDA on December 19, 2005 proposing the use of Advagraf for once-daily dosing in the prophylaxis of organ rejection following kidney, liver or heart transplantation. The Agency administratively split the NDA into three separate NDA numbers for each indication: NDA 50811 (kidney), NDA 50815 (liver) and NDA 50816 (heart). On January 19, 2007, the Agency issued an approvable letter for kidney and liver indications and a non-approvable letter for the heart indication. (b) (4)

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 14, 2013. The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment: *White space is not available between the headings.*

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *Revision date must be added.*

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Need subheading for boxed warning*

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *Need to have title for boxed warning*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

NO 42. All text is **bolded**.

Comment: *All text not bolded*

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *need to use the first bullet statement*

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/s/

HYUN J SON
12/04/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204096 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Advagraf Established/Proper Name: Tacrolimus extended-release capsules Dosage Form: Oral, capsules Strengths: 0.5 mg, 1 mg and 5 mg		
Applicant: Astellas Pharma US Inc. Agent for Applicant (if applicable): Glen Spears Ph.D.		
Date of Application: September 20, 2012 Date of Receipt: September 21, 2012 Date clock started after UN:		
PDUFA Goal Date: July 21, 2013	Action Goal Date (if different):	
Filing Date: November 20, 2012	Date of Filing Meeting: November 5, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Prophylaxis of organ rejection in adult patients receiving kidney transplants and male patients receiving liver transplants.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 64148	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	X			ODE: Orphan Drug Exclusivity

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
50708	Prograf	ODE	March 29, 2013
50709	Prograf	ODE	March 29, 2013

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?				
• If yes, were all of them submitted on time?				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?				
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***		X		Electronic submission

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				Not sure, will check and if not will request in 74 day letter.
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined?				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** January 31, 2012 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 5, 2012

BLA/NDA/Supp #: 204096

PROPRIETARY NAME: Advagraf

ESTABLISHED/PROPER NAME: Tacrolimus extended-release

DOSAGE FORM/STRENGTH: Capsules, 0.5 mg, 1 mg and 5 mg

APPLICANT: Astellas Pharma US, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- Prophylaxis of organ rejection in adult patients receiving kidney transplants.
- Prophylaxis of organ rejection in adult male patients receiving liver transplants.

BACKGROUND: Immediate-release oral and intravenous formulations of tacrolimus are marketed worldwide for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants. In the United States, immediate-release oral and intravenous formulations of tacrolimus (Prograf®) were originally approved by the FDA in 1994. Tacrolimus as Prograf capsules requires twice-daily oral dosing. Advagraf was developed as a once-daily capsule formulation of tacrolimus for the prophylaxis of organ rejection after transplantation and is now approved in 69 countries including Japan, the European Union and Canada.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Hyun Son	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Joette Meyer		Y
Clinical	Reviewer:	Marc Cavaille-Coll (Kidney) Ergun Velidedeoglu (Liver)	Y
	TL:	Joette Meyer	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Shukal Bala	Y

	TL:	Renata Albrecht	Y

Clinical Pharmacology	Reviewer:	Gerlie Gieser	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Joy Mele	Y
	TL:	Karen Higgins	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Aaron Ruhland	Y
	TL:	Lori Kotch	Y
Product Quality (CMC)	Reviewer:	Mark Seggel	Y
	TL:	Balajee Shanmugam	Y
Facility Review/Inspection	Reviewer:	Kassa Ayalew	Y
	TL:	Susan Liebenhaut	N
OSE/DMEPA (proprietary name)	Reviewer:	Jung Lee	Y
	TL:	Jamie Wilkins-Parker	Y
OSE/DRISK (REMS)	Reviewer:	TBD	
	TL:	Cynthia LaCivita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Kendra Biddick	Y
	TL:		

Other reviewers	Mary Dempsey	Y
Other attendees	Elizabeth Maloney	Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO

• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: ☐ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY	☐ Not Applicable

Comments:	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)?	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Comments:	
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Renata Albrecht

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing.

	Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYUN J SON
11/16/2012