

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201917Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 5, 2011; *Revised April 25, 2011*

To: Debra Birnkrant, M.D., Director
Division of Antiviral Products (DAVP)

Through: Claudia B. Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)

Reviewers: Carolyn L. Yancey, M.D., F.A.A.P.,
Senior Medical Officer, Risk Management Analyst, DRISK

Kendra Worthy, Pharm.D., Team Leader, DRISK

Subject: Rationale for Not Requiring a Risk Evaluation and
Mitigation Strategy (REMS) for [REDACTED]^{(b)(4)} (submission
dated November 23, 2010)

Drug Name: INCIVEK (originally proposed as [REDACTED]^{(b)(4)}) [telaprevir in
combination with Peg-interferon (Peg-IFN) alpha and
ribavirin (RBV)]

Therapeutic Class: Direct-Acting Antiviral Agent as a
Hepatitis C Virus NS3-4A Protease Inhibitor

Dosage and Route: Film-Coated Tablets for Oral Use (350 mg); 750 mg every
7 to 9 hours (with food) for 12 weeks.

Application Type/Number: NDA 201-917

Applicant: Vertex Pharmacetucials Incorporated (Vertex)

OSE RCM #: 2010-2558

*** This document contains proprietary and confidential information that should not be released to the public.***

EXECUTIVE SUMMARY	3
1 INTRODUCTION	4
1.1 Background and Regulatory History.....	4
2 MATERIAL REVIEWED.....	5
2.1 Data and Information	5
3 RESULTS OF REVIEW	5
3.1 Overview of Clinical Program	6
3.2 Safety Concerns	6
3.2.1 Adverse Events of Special Interest.....	6
3.2.1.1 Skin Reactions.....	7
3.2.1.2 Anemia	8
4 APPLICANT’S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY FOR TELAPREVIR.....	8
4.1 Goals	8
4.2 Medication Guide.....	8
4.3 Communication Plan.....	9
4.4 Timetable for Submission of Assessments	9
5 DISCUSSION.....	10
6 CONCLUSION.....	11
7 RECOMMENDATIONS.....	11

EXECUTIVE SUMMARY

The Division of Antiviral Products (DAVP) requested that the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE) review the telaprevir (b) (4)¹ Risk Evaluation and Mitigation Strategy (REMS) in the new drug application (NDA) 201-917 submitted November 23, 2010. The proposed treatment, in combination with peg-interferon (Peg-IFN) and ribavirin (RBV) is for the indication of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or treated, including prior null responders, partial responders, and relapsers. The purpose of this review is to document our determination regarding the need for a REMS for telaprevir and, if a REMS is needed, to determine which elements would be required to mitigate the risks of the drug, if approved. The key risks associated with use of telaprevir in adults with genotype 1 CHC are severe rash and anemia.

The DAVP required the applicant to submit a proposed REMS for telaprevir with a Medication Guide and timetable for submission of assessments (September 28, 2010) based on the Agency's policy that any new Medication Guide needed to be part of a REMS. The applicant voluntarily added a communication plan with a Dear Healthcare Professional Letter to the proposed REMS elements. The DAVP acknowledged that the REMS with a Medication Guide was required based on the Agency's policy of REMS with a Medication Guide only, and was not required based on the DAVPs desire for a risk mitigation strategy for telaprevir, if approved. Based on the *Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* issued February 25, 2011, the Agency has the authority to remove (or not require) that every Medication Guide necessarily be part of a REMS depending on the risks involved. The DAVP explained that this *Draft Guidance for Industry* is part of the basis of the Agency not requiring a REMS for telaprevir with a Medication Guide. However, the DAVP will require that a Medication Guide be part of the labeling for telaprevir, if approved, in accordance with 21 Code of Federal Regulations (CFR) part 208.

The DAVP and DRISK concluded in a discussion (on March 24, 2011) that a REMS would not be required for telaprevir to ensure that the benefits of the drug outweigh the risks of severe rash and anemia associated with use of telaprevir based on analysis of clinical safety data in NDA 201-917. As stated above, a Medication Guide will be part of the labeling for telaprevir, if approved, in accordance with 21 CDR part 208.

Additional rationale for not requiring a REMS for telaprevir is the following:

1. The serious adverse events (severe rash and anemia) reported in the telaprevir Phase 2 and 3 clinical development program are consistent with the known serious risks associated with use of Peg-IFN and RBV.
2. The key prescribers for Peg-IFN and RBV, such as hepatologists, are the most likely prescribers for the proposed telaprevir formulation, in combination with Peg-IFN and RBV. The DAVP concludes that these specialists are familiar with the known risks of severe rash and anemia associated with use of Peg-IFN and RBV. The serious risks with telaprevir are the same as with Peg-IFN and RBV (as stated above).
3. In consideration of the above factors, the proposed labeling for telaprevir, including reference to the Peg-IFN and RBV labeling, should be adequate to mitigate the risks of severe rash and anemia with telaprevir, if approved.

¹ The Proprietary Name INCIVEK is under consideration by the Division of Medication Error, Prevention, and Analysis (DMEPA) as of March 31, 2011. The applicant originally proposed the Trade Name “(b) (4),”

- The proposed labeling (without a BOX WARNING) includes the WARNINGS AND PRECAUTIONS section with severe rash (Subsection 5.2), anemia (Subsection 5.3) with laboratory monitoring, specifically, hemoglobin monitoring (Subsections 5.6) to mitigate these two key serious risks with telaprevir. The rash management recommendations will be included in telaprevir labeling (if approved) with guidance from the Division of Dermatology and Dental Products (DDDP). The CONTRAINDICATIONS section includes the text, “Contraindications to peginterferon and ribavirin also apply to telaprevir combination treatment” and “Telaprevir must not be administered as monotherapy and must be prescribed in combination with both peg-interferon and ribavirin” to mitigate serious risks with telarpevir.
4. The Medication Guide will be removed from the required proposed REMS; however, the Medication Guide must be required to be part of the approved labeling in accordance with 21 CFR part 208 (if telaprevir is approved) to educate patients and their caregivers about the serious risks associated with use of telaprevir including severe rash and anemia. Comments from the Patient Labeling Reviewer in DRISK will be sent separately.

Post-marketing requirements and post-marketing commitments are under consideration by DAVP and OSE to better characterize the risks of severe rash and anemia, if telaprevir, in combination with Peg-IFN and RBV, is approved.

A detailed description of the proposed REMS for telaprevir (dated November 23, 2010) is in Section 3 of this review.

1 INTRODUCTION

Telaprevir (VX-950), a new molecular entity (NME), is in the therapeutic class of direct-acting antiviral agents, specifically, hepatitis C virus (HCV) non-structural protein 3 (NS3), NS3-4A protease inhibitors. As stated above, telaprevir is proposed for the treatment of adults with genotype 1 HCV. Telaprevir is proposed as a 350 mg Tablet, film-coated for oral use, to be taken as two tablets every 7 to 9 hours with food for 12 weeks followed by a response-guided regimen of either 12 weeks or 36 weeks of Peg-IFN/RBV depending on the viral response and prior response status. The proposed total daily dose is 6 tablets (2,250 mg).

The applicant reports that telaprevir, studied in adult patients with genotype 1 CHC for 12 weeks, in combination with Peg-IFN/RBV for 24 or 48 weeks, resulted in higher sustained virologic response (SVR) rates than treatment with 48 weeks of Peg-IFN/RBV treatment alone. According to the applicant, there have been no reports of unexpected adverse outcomes or withdrawal of investigational clinical studies with telaprevir in the United States (US) or other countries.

1.1 BACKGROUND AND REGULATORY HISTORY

Telaprevir is a reversible, selective, linear peptidomimetic inhibitor of NS3-4A serine protease that is required for replication of HCV. The applicant reports that telaprevir has an additive antiviral activity when combined with Peg-IFN and RBV. In study patients with genotype 1 CHC, telaprevir for 12 weeks, in combination with Peg-IFN/RBV for 24 or 48 weeks, efficacy demonstrated higher SVR rates than in patients treated with 48 weeks of Peg-IFN/RBV alone. Efficacy was also achieved in treatment-naïve patients and in patients who were prior treatment failures.

Hepatitis C

Based on the submission and current literature, the prevalence of HCV infection is estimated to be 130 to 170 million people or approximately 2% to 3% of the world population.² It is estimated that 55% to 85% of infections become chronic and chronic hepatitis C can lead to serious liver disease.³ Cirrhosis develops within 20 years in 4% to 20% of patients with chronic hepatitis C.⁴ Patients diagnosed with cirrhosis have an 18% to 29% risk of developing decompensated liver disease within 5 to 10 years, and a 10% to 30% risk of developing hepatocellular carcinoma.⁵

Regulatory History

In 2004, Vertex established the telaprevir clinical development program for use in the United States (US), Canada, and Mexico, and collaborated with Mitsubishi Tanabe Pharma Corporation for development in Southeast Asia, China, and Japan. In 2006, Vertex partnered with Johnson & Johnson companies (Janssen Pharmaceutica and Tibotec) to develop telaprevir for use in the rest of the world.

The regulatory history, listed by date of submission, that relates to the application for telaprevir is as follows:

- December 7, 2005: FDA granted telaprevir Fast Track designation.
- October 16, 2009: Applicant initiated a teleconference with FDA/DAVP. The DAVP indicated that a Medication Guide might be a potential REMS element.
- June 23, 2010: FDA granted telaprevir Rolling Submission designation under Investigation New Drug Application (IND) 71,832/Serial Number 45.
- September 28, 2010: Pre-NDA Meeting (including the DAVP, the Office of Clinical Pharmacology, and the Office of Surveillance and Epidemiology) informed Vertex that a Medication Guide would be a required element in the REMS for Telaprevir.

There is no approved Food and Drug Administration (FDA) formulation in the therapeutic class of HCV-direct acting antiviral agents. As of this review, telaprevir is not approved in any country and all known telaprevir recipients are in clinical investigation trials. A second hepatitis C ribonucleic acid (RNA) virus protease inhibitor, Boceprevir (NDA 202-258/Merck), is under review by FDA/DAVP and DRISK Patient Labeling, and appears to show improved cure rates (~70%) in patients with genotype 1 HCV when used with standard therapy

2 MATERIAL REVIEWED

2.1 DATA AND INFORMATION

The following materials, listed by document date, were reviewed from NDA 201-917 in regards to the proposed REMS for Telaprevir:

- November 23, 2010: Original submission with proposed REMS for telaprevir.

3 RESULTS OF REVIEW

² Lavanchy D. The global burden of hepatitis C. *Liver Int.* 2009;29(s1):74-81.

³ Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology.* 2002; 336:S21-9.

⁴ Brass V, Moradpour D, Blum HE. Molecular virology of hepatitis C virus (HCV): 2006 update. *Int J Med Sci.* 2006;3(2):29-34.

⁵ World Health Organization. Department of measurement and health information. December 2004.

3.1 OVERVIEW OF THE CLINICAL PROGRAM

Eight (8) clinical studies were conducted to evaluate efficacy and safety of treatment with a telaprevir-based regimen in patients with genotype 1 CHC: five studies in treatment-naïve patients (Phase 3 Studies 108 and 111, and Phase 2 Studies 104, 104EU, and C208) and 3 studies in prior treatment-failure patients (Phase 3, Study C216 and Phase 2 Studies 106 and 107). There were 3,594 patients (2,362 treatment-naïve and 1,232 treatment-failure) treated in these 8 studies, of whom 2,830 received at least 1 dose of telaprevir. Demographics and baseline characteristics were similar among patients enrolled in the Phase 3 studies.

Efficacy: In all efficacy studies, the main efficacy endpoint was the SVR, defined as HCV RNA undetectable 24 weeks after the end of therapy. The telaprevir containing regimens achieved significantly higher SVR rates in both treatment naïve and treatment-failure populations compared to standard treatment with Peg-IFN/RBV (PR). More than half (58% in Study 108, 65% in Study 111) of treatment-naïve patients on T12wk/PR achieved extended rapid viral response (eRVR, defined as undetectable HCV RNA at Weeks 4 and 12) and were eligible for 24 weeks of telaprevir compared to 48 weeks for standard treatment. The benefit of triple therapy (telaprevir-containing regimen over standard Peg-IFN/RBV was the higher SVR rate in all the study populations and supported a 6-month shorter treatment duration for treatment-naïve patients and prior relapsers who achieved eRVR.

Safety: These clinical safety data are in adults with genotype 1 CHC who received telaprevir at the proposed dose (750 mg q8h) for 12 weeks in combination with Peg-IFN/RBV for a total treatment duration of 24 or 48 weeks. In pooling 8 controlled and uncontrolled Phase 2 and 3 studies, data were available for 2,085 patients in the T12wk/PR group and for 2,830 patients who received at least 1 dose of telaprevir in different treatment regimens.

3.2 SAFETY CONCERNS

As explained by the applicant and concurred with by DAVP and DRISK, the safety profile of telaprevir is well characterized in the telaprevir clinical development program. The reported adverse events (AE) demonstrate a consistent pattern and frequency in both treatment-naïve patients and prior treatment-failure patients. The most frequent AEs during the T12wk/placebo (PBO) treatment phase (> 20% of patients in the T12wk/PR group) were fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, and pyrexia. In T12wk/PR treated-patients, pruritus (47%) was the most frequently observed common AE compared with 25% in PBO-treated patients (exposed to PR), followed by nausea (40%) compared with 29% in PBO-treated patients, and rash (33%) compared with 17% in PBO-treated patients.

Deaths

Eleven (11) deaths were reported and in 7 of these 11 deaths, the patients received telaprevir. Among the 7 telaprevir-exposed deaths, two (2) were considered possibly related to telaprevir: one 60-year old male (40 year old, > 30 pack per day smoking history) experienced a malignant lung neoplasm and one 62-year old male experienced a pulmonary embolism 12 days after his last dose of telaprevir.

3.2.1 ADVERSE EVENTS OF SPECIAL INTEREST

The AEs of special interest with use of telaprevir are **serious rash** and **anemia**. The most frequently reported serious adverse events (SAE) in the T12wk/PR treated patients were anemia (2%) and rash (0.7%). The most frequent ($\geq 1\%$ in T12/PR-treated patients) AEs leading to

permanent discontinuation of T12wk/PR were anemia (3% in the T12wk/PR group versus 0.4% in the PBO/PR group), rash (3% versus 0.1%), and pruritus (1% versus 0.1%), respectively. The most frequently reported AEs \geq Grade 3 severity (incidence of \geq 2.0% in the T12wk/PR group) were anemia (5% in the T12wk/PR group versus 0.8% in the PBO/PR group), neutropenia (4% versus 4%), leukopenia (2% versus 1%), and rash (2% versus 0.1%), respectively.

3.2.1.1 SKIN REACTIONS

As explained by the applicant, cutaneous drug reactions occur frequently during treatment with Peg-IFN/RBV with incidences ranging from 13% to 23%.⁶ The frequency and severity of adverse skin events increased with co-administration of telaprevir and Peg-IFN/RBV. As explained by DAVP, the rash management plan evolved during the Phase 3 clinical trials based on the increased observed risk of serious rash with telaprevir in the Phase 2 clinical trials. Based on increased adverse skin reactions reported in the Phase 2 studies with telaprevir, the applicant and DAVP collaborated to develop a Rash Management Plan for the Phase 3 clinical trials to recommend early withdrawing of a component of the triple-therapy (or stopping triple therapy) for signs of a possible drug-related skin reaction. The Rash Management Plan employed in the Phase 3 studies appeared to be effective as fewer patients in the T12wk/PR-treated group discontinued all study drugs (telaprevir, Peg-IFN, and RBV) due to rash Special Search Categories (SSC) events in Phase 3 studies (1%) compared with Phase 2 studies (6%).

Understanding of the frequency and severity of skin AEs improved and the ability to manage rashes early increased. Both of these factors contributed to decreased discontinuations of all study drugs in Phase 3 studies compared with the earlier studies and, consequently, lead to higher SVR rates. Note that telaprevir/PBO was discontinued for any Grade 3 rash while PR treatment (without telaprevir) could be continued at the clinical investigator's discretion.

In the T12wk/PR (750 mg q8h) treatment group (1,346 patients), there were 23 (2%) SAEs for rash compared with zero in PBO/PR (764 patients). There were 65 events (5%) of at least Grade 3 in the T12wk/PR-treatment group compared with three events (0.4%) in the PBO/PR-treatment group.

Dermatology Expert Panel

The applicant convened a Dermatology Expert Panel (DEP) to evaluate rash events possibly associated with telaprevir and to characterize the rash cases. The DEP was reported to conclude, based on review of rash cases with photographs and biopsies that with the exception of greater severity and extent, that the appearance and histopathology of the rash associated with telaprevir/PR was indistinguishable from a rash associated with Peg-IFN/RBV. However, the telaprevir rash differed from commonly seen drug rashes, for example, an antibiotic drug-related rash, clinically and histologically. The telaprevir-associated rashes appeared to be of greater severity, may occur at any time during telaprevir treatment, and resolved over weeks after discontinuation of telaprevir.

Based on a review of 221 rash cases, the DEP reported 11 cases of suspected drug reaction with eosinophilia with systemic symptoms (DRESS) and three (3) cases of suspected Stevens-Johnson syndrome (SJS). One SJS case was observed in the pooled PBO-controlled Phase 2 and Phase 3 studies 11 weeks after the last dose of telaprevir and may or may not be causally related to

⁶ Mistry N, Sharpero J, Crawford RI. A review of adverse cutaneous drug reactions resulting from the use of interferon and ribavirin. *Can J Gastroenterol*. 2009;23(10):677-83.

telaprevir. The two (2) other SJS cases occurred in studies performed by Mitsubishi (Japan). All cases, except for one case of suspected DRESS, resolved by the last follow-up. In addition, one case of suspected acute generalized exanthematous pustulosis (AGEP) was identified by the DEP.

3.2.1.2 ANEMIA

It is well known that interferon-related bone marrow suppression limits red blood cell (RBC) production and results in decreased hemoglobin (Hgb) levels. Therefore, anemia is a well-known AE with use of Peg-IFN and RBV. Telaprevir demonstrated an additive risk for anemia with the triple-drug therapy regimen. Patients treated with telaprevir/PR had a higher frequency of anemia, higher frequency of Grade 3 anemia, and higher frequency of anemia-related discontinuations compared with PR-treated patients. After patients discontinued telaprevir/PR treatment and were only treated with PR, the applicant reports that patients Hgb levels rose to a level comparable with patients receiving PR alone.

In the T12wk/PR study phase, anemia was the most frequently reported preferred term (PT), 29% in T12wk/PR-treated patients compared with 12% in PBO/PR-treated patients, and in any telaprevir/PR-treated group (7%). Blood transfusions were administered to 2% and 0.1% of patients, T12wk/PR- and PBO/PR-treatment groups, respectively, during the T12wk/PR phase. Erythropoiesis-stimulating agents (ESA) were administered to 1% and 0.8% of patients, T12wk/PR and PBO/PR-treatment groups, respectively. These events, even in PBO/PR patients underscore the risk of anemia with this class of drug.

4 APPLICANT'S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY FOR TELAPREVIR

The applicant submitted a proposed REMS for telaprevir (dated November 23, 2010) with a Medication Guide, a communication plan and a timetable for submission of assessments to address the serious risks of severe skin reaction and anemia, proposed for the treatment of genotype 1 CHC, if approved. Note that the proposed proprietary name has not been approved by the Agency. The proposed REMS (submitted November 23, 2010) includes the originally proposed proprietary name of (b)(4). Described below are the proposed goals and brief summaries of each proposed element in the proposed REMS for telaprevir:

4.1 GOALS

(b)(4)

4.2 MEDICATION GUIDE

In accordance with 21 CFR 208.24, a Medication Guide will be included in each (b)(4) prescription as described below:

- (b)(4) is supplied as 375-mg Tablet, Film-Coated for Oral Use, in a 28-day (unit-of use) packer containing four weekly boxes of seven blisters each (six tablets per blister).

- (b)(4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

4.3 COMMUNICATION PLAN

[Redacted]

(b) (4)

4.4 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

[Redacted]

(b) (4)

5 DISCUSSION

Hepatitis C is a life-threatening disease with significant morbidity and mortality as stated in the Background Section of this review. Telaprevir, in combination with Peg-IFN and RBV, achieved efficacy with significantly higher SVR rates across Phase 3/2 studies and achieved a 6-month shorter treatment duration for treatment-naïve patients and prior relapsers who achieved extended rapid virologic response (eRVR). The majority of treatment naïve and prior relapsers were treated effectively with 24 weeks therapy, half the treatment duration required for standard Peg-IFN/RBV with 70% or higher cure rates.

Though triple-drug therapy efficacy represents a major advance in treatment of genotype 1 CHC (the hardest to treat for the viral infection), this regimen makes the treatment of CHC more complex including the increased incidence and severity of the serious risks, severe rashes and anemia. The safety profile of Peg-IFN and RBV have well characterized clinical toxicity (anemia, severe skin reactions, pregnancy risks, and drug interactions) and contraindication in patients with congenital or acquired QT prolongation or a family history of QT prolongation or sudden death.

The DAVP and DRISK concur that the serious risks associated with the use of telarpevir, severe rash and anemia, are familiar to and recognizable by prescribers (such as hepatologists), manageable with regular laboratory monitoring, and appear to be reversible based on the clinical safety data in this NDA application. The most severe cutaneous skin reactions (SCAR), a drug rash with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS) occurred in less than 1% of patients in the telaprevir clinical development program. The Rash Management Plan intervention (developed based on the Phase 2 clinical trials and employed in the Phase 3 clinical trials) demonstrated a decrease in the percentage of patients with severe rash exposed to telaprevir (see Section 3.2 Safety Concerns in this review).

The DAVP concluded that specialty prescribers most likely to prescribe Peg-IFN and RBV are hepatologists who are familiar with the known risks of severe rash and anemia. The reported risks of severe rash and anemia in the telaprevir clinical development program are the same risks associated with use of Peg-IFN and RBV. However, the risks associated with telaprevir (in combination with Peg-IFN and RBV) appear to be increased, though the number of severe rash events remained small (see the Safety Concerns in Section 3.2 of this review).

The proposed telaprevir labeling also includes recommendations for skin monitoring (Subsection 5.2) based on the Rash Management Plan interventions employed in Phase 3 clinical trials. For management of the rash, the DAVP will work with the DDDP to include the Rash Management Plan in the proposed labeling for telaprevir, if approved. The proposed telaprevir labeling includes recommendations for hemoglobin monitoring (Subsection 5.3 and 5.6) prior to and during telaprevir combination treatment. For management of anemia, prescribers are directed to the Prescribing Information for RBV for dose reduction guidelines. Most patients in the clinical studies were administered antihistamines and topical corticosteroids and experienced improvement of the rash after telaprevir dosing was completed or discontinued.

The consult from the Division of Dermatology and Dental Products (DDDP) included the following recommendations: 1) the REMS for telaprevir should include a Medication Guide, a communication plan, and timetable for submission of assessments, and 2) the Agency should consider establishing a post-marketing requirement (if telaprevir is approved) to better characterize the rash with triple-drug therapy versus monotherapy.

The DAVP and OSE/DRISK concur that the most likely prescribers of telaprevir (if approved) are hepatologists who currently prescribe Peg-IFN/RBV, and that these prescribers are familiar

with the key risks of severe rash and anemia, such that a REMS for telaprevir is not necessary to ensure that the benefits outweigh the risks. The DAVP and DRISK concur that the Medication Guide is not required as part of the REMS but must be required as part of the approved labeling in accordance with 21 CFR part 208 to inform patients about the serious risks associated with use of triple-drug therapy, telaprevir, for genotype 1 CHC. Under the *Draft Guidance for Industry* (see the Executive Summary) and the factors stated above, the DAVP and DRISK do not recommend requiring a REMS for telaprevir. The DAVP plans to require postmarketing study to monitor skin reactions and anemia with telaprevir, if approved.

6 CONCLUSION

The Office of Surveillance and Epidemiology, the Division of Risk Management, completed review of the clinical safety for telaprevir in patients with genotype 1 CHC (NDA 201-917, submitted November 23, 2010) and the required proposed REMS for (b) (4). The DRISK concluded that the key serious adverse events of severe rash and anemia can be adequately managed at this time with labeling including a required Medication Guide, if telaprevir is approved.

Based on discussion between the DAVP and DRISK (March 24, 2011), both Divisions concurred that the required proposed REMS for (b) (4) (per DAVP) is no longer a necessary requirement by the Agency based on the following:

- 1) The clinical safety data in this NDA 201-917 submission and the consistency of the reported safety signals in this application with the well-known risks with Peg-IFN and RBV therapy.
- 2) The prescribers (mainly hepatologists) for Peg-IFN and RBV will be the most likely prescribers for the proposed formulation of telaprevir, in combination with Peg-IFN and RBV. The expertise of these prescribers with anti-viral therapy and their familiarity with the risks of severe rash and anemia with use of Peg-IFN and RBV formed the basis for the DAVP and DRISK conclusion to not require a REMS for telaprevir with a Medication Guide.
- 3) Based on the *Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* issued February 25, 2011, the Agency will not require a REMS with a Medication Guide only for telaprevir. The Medication Guide will be a required part of the labeling for telaprevir, if approved, in accordance with 21 CFR part 208.
- 4) Post-marketing requirements are under consideration for telaprevir, if approved, by DAVP to better characterize the severe rash and the anemia observed in the controlled clinical trials with telaprevir.

Though the DAVP required the applicant to submit a proposed REMS for telaprevir, after review of the clinical safety data (including the 120-Day Safety Update), the DAVP and OSE/DRISK concluded that a REMS for telaprevir is not required to adequately mitigate the serious risks of severe rash and anemia with telaprevir, if approved.

7 RECOMMENDATIONS

The Office of Surveillance and Epidemiology, the Division of Risk Management, recommends that the proposed REMS for telaprevir no longer be required by the Agency based on the rationale stated in the Executive Summary and Conclusion section of this review. The OSE/DRISK determined that a Medication Guide is required in the approved labeling for telaprevir (if approved) to support patient information about the serious risks of severe rash and anemia associated with use of telaprevir.

- A Retraction Letter from the Agency to the applicant must be issued in regard to retracting the requirement for the proposed REMS for telaprevir with goals and the elements of a Medication Guide and a timetable for submission of assessments.

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

/s/

CAROLYN L YANCEY

04/25/2011

REMS for Telaprevir Not Required Review

MARY E WILLY

04/25/2011

For Claudia Karwoski

I concur