



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

OCT 5 2015

Food and Drug Administration  
10903 New Hampshire Avenue  
Building #51  
Silver Spring, MD 20993

Laxmaiah Manchikanti, MD  
Chairman of the Board and Chief Executive Officer, and  
Ramsin Benyamin, MD, President  
American Society of Interventional Pain Physicians  
61 Lakeview Drive  
Paducah, KY 42001

Re: Docket No. FDA-2014-P-1343

Dear Drs. Manchikanti and Benyamin:

This letter responds to the citizen petition (Petition) you submitted to the Food and Drug Administration (FDA or Agency) on September 3, 2014, on behalf of the American Society of Interventional Pain Physicians (ASIPP). In the Petition, you ask, first, that FDA “amend” or “withdraw” the safety warning added to the labeling of injectable corticosteroid drug products related to the risk of rare but serious neurologic problems after epidural injection of these products for the treatment of pain (Petition at 1).<sup>1</sup> You ask that the Agency replace the current required warning with a warning limited to certain injection approaches, or techniques, and injection locations,<sup>2</sup> and that language be included that would state that “all procedures must be performed by well-trained providers in appropriate settings under fluoroscopy or other appropriate proven imaging modalities” (Petition at 1). Second, you ask that FDA not “adopt 17 recommendations developed by [the] Multi-Society Pain Workgroup (MPW)” (Petition at 1).

We have carefully considered the Petition. For the reasons set forth below, the Petition is denied in part and granted in part.

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<sup>1</sup> In the Petition, you describe your request variously as a request to “amend [the] April 23, 2014 Drug Safety Communication requiring” a new warning be added to injectable corticosteroid labeling and as a request to “withdraw the present Safety Warning that states the FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain . . .” (Petition at 1 (internal quotation marks omitted)). The Drug Safety Communication (DSC) announced the addition of the new warning that FDA required pursuant to its authority under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(4)). Thus, we are interpreting your request as a request for the Agency to require changes to the class warning that is described in the DSC, and not as a request to change the DSC itself.

<sup>2</sup> Specifically, you request that the warning state that injectable corticosteroids “can cause rare, but serious neurologic problems following cervical and thoracic transforaminal epidural injections and [are] associated with an increased risk with lumbar transforaminal epidural injections when performed without appropriate precautions” (Petition at 1).

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## I. Background

### A. Epidural Corticosteroid Injections for the Treatment of Pain

There are approved injectable corticosteroid drug products containing the following active ingredients: betamethasone, dexamethasone, hydrocortisone, methylprednisolone, and triamcinolone.<sup>3</sup> Injectable corticosteroids are approved to treat a variety of diseases and disorders, and the approved indications vary by approved drug product.<sup>4</sup> Similarly, the approved routes of administration vary by approved drug product and include intra-articular, soft tissue, intravenous, intramuscular, and/or intralesional administration.<sup>5</sup> Although epidural injection of corticosteroid drug products, also referred to as epidural steroid injections or ESIs, is a common procedure performed in the United States for the management of spinal pain,<sup>6</sup> the safety and effectiveness of injecting corticosteroids into the epidural space has not been established under section 505 of the FD&C Act, and injectable corticosteroid drug products are not approved for this use.<sup>7</sup>

<sup>3</sup> See FDA Briefing Document for the Anesthetic and Analgesic Drug Products Advisory Committee Meeting on Epidural Steroid Injections (ESI) and the Risk of Serious Neurologic Adverse Reactions, Food and Drug Administration, Center for Drug Evaluation and Research, November 24-25, 2014 (Advisory Committee Briefing Materials), at 12, available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm422691.htm>.

<sup>4</sup> See, e.g., labeling approved February 4, 2015, for Celestone Soluspan (betamethasone sodium phosphate and betamethasone acetate) Injectable Suspension, USP at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/014602s059lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/014602s059lbl.pdf); labeling approved July 3, 2014, for dexamethasone sodium phosphate injection, USP at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/040491s008lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/040491s008lbl.pdf); labeling approved July 3, 2014, for Solu-Cortef (hydrocortisone sodium succinate for injection, USP) at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/009866s104lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/009866s104lbl.pdf); labeling approved July 3, 2014, for Depo-Medrol (methylprednisolone acetate injectable suspension, USP) at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/011757s103lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/011757s103lbl.pdf); labeling approved July 3, 2014, for Solu-Medrol (methylprednisolone sodium succinate for injection, USP) at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/011856s123lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/011856s123lbl.pdf); labeling approved July 3, 2014, for Kenalog-10 Injection (triamcinolone acetonide injectable suspension, USP) at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/012041s042bledt.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/012041s042bledt.pdf); labeling approved July 3, 2014, for Kenalog-40 Injection (triamcinolone acetonide injectable suspension, USP) at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/014901s042bledt.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/014901s042bledt.pdf); labeling approved July 3, 2014, for Aristospan (triamcinolone hexacetonide injectable suspension, USP) at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/016466s046lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/016466s046lbl.pdf).

<sup>5</sup> Id.

<sup>6</sup> Advisory Committee Briefing Materials, at 10.

<sup>7</sup> See approved labeling for injectable corticosteroid drug products, *supra* note 4.

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## B. Evaluation of the Safety of ESIs

FDA has been evaluating the safety of ESIs since 2009 when it became aware of medical professionals' concerns about ESIs and the risk of serious neurologic adverse events.<sup>8</sup> FDA's initial safety review included a review of the FDA's Adverse Event Reporting System (AERS) and a review of "reports in the published literature associated with the five corticosteroid[s] . . . marketed for injection."<sup>9</sup> Based on the findings of this review, the Center for Drug Evaluation and Research (CDER) safety review team recommended that a class warning be added to injectable corticosteroid labeling describing the risk of serious neurologic adverse events with ESIs.<sup>10</sup> When this proposal was presented to FDA's Drug Safety Oversight Board (DSB) in September 2010, the DSB raised concerns about the potential unintended consequences of a class warning, including the fact that alternatives to ESIs include opioid therapy or surgery, each of which carries its own inherent risks.<sup>11</sup> The DSB also noted factors that add to the complexity of understanding the cause of the safety issue, including the injection approach and location of the injection.<sup>12</sup>

Because of the feedback from the DSB, and based on additional internal discussion in CDER, FDA referred the matter to the Safe Use Initiative (SUI) for further evaluation.<sup>13</sup> The SUI was created to facilitate public and private collaborations within the healthcare community, and its goal is to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector innovations with partners who are committed to safe medication use.<sup>14</sup> In the case of ESIs, the SUI facilitated the organization of a group of non-FDA expert physicians who had published scientific studies or scholarly works on the topic of ESIs (referred to herein as "the Working Group") whose goal was "to

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<sup>8</sup> Advisory Committee Briefing Materials, at 12.

<sup>9</sup> *Id.* The Adverse Event Reporting System (AERS) is a database that contains information about adverse event and medication error reports submitted to FDA. AERS was replaced on September 10, 2012, with the FDA Adverse Event Reporting System (FAERS).

<sup>10</sup> Advisory Committee Briefing Materials, at 12.

<sup>11</sup> *Id.* FDA's Drug Safety Oversight Board (DSB) is a panel of Federal partners that advises CDER on how to address important drug safety issues. It is composed of representatives from two FDA Centers and eight other Federal government departments/agencies: the Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, Department of Defense, Health Resources and Services Administration, Indian Health Service, National Institutes of Health, and Department of Veterans Affairs. See the DSB Web page at <http://www.fda.gov/aboutfda/centersoffices/officofmedicalproductsandtobacco/cder/ucm082129.htm>.

<sup>12</sup> Advisory Committee Briefing Materials, at 12.

<sup>13</sup> *Id.*

<sup>14</sup> *Id.* at 59. See the Safe Use Initiative Web page at <http://www.fda.gov/drugs/drugsafety/safeuseinitiative/default.htm>.

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understand the causes of the neurologic injuries associated with epidural steroid injections and devise strategies to minimize their risk."<sup>15</sup>

The Working Group independently developed a set of clinical considerations to minimize the risk of catastrophic neurological injury associated with epidural steroid injections.<sup>16</sup> The Working Group presented its initial set of clinical considerations at the 2013 American Society of Anesthesiologists (ASA) annual meeting.<sup>17</sup> Several months after that meeting, the Working Group asked for the input and assistance of the Multi-Society Pain Work Group (MPW), a different group of representatives of national medical organizations that had previously been convened by Medicare Administrative Contractors.<sup>18</sup> The members of the MPW, along with the existing members of the Working Group, revised and voted on a final set of clinical considerations, which were ultimately published in the journal *Anesthesiology* as "Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections: Consensus Opinions from a Multidisciplinary Working Group and National Organizations," in May, 2015.<sup>19</sup> The SUI facilitated the organization and meetings of the Working Group, but did not actively participate in the Working Group's deliberations or its decision-making process.<sup>20</sup> The clinical considerations developed by the Working Group are intended for the medical community. They are not recommendations for the FDA and, as such, are neither binding on FDA nor endorsed by the FDA.<sup>21</sup>

While the Working Group's activities were ongoing, and in light of continuing concern about the neurologic risks of ESIs, FDA issued safety labeling change (SLC) notification letters to the sponsors of injectable corticosteroid drug product applications on April 23, 2014. The SLC notification letters informed sponsors of the risks associated with ESIs and instructed them to submit supplements adding the following warning to the corticosteroid labeling:

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<sup>15</sup> Advisory Committee Briefing Materials, at 59.

<sup>16</sup> *Id.* The Working Group initially referred to the clinical considerations as "recommendations," as you do in your Petition, but that was later changed to reflect the fact that the clinical considerations are based on expert opinion and not a more formal evidentiary basis. Transcript for the November 24, 2014, Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (Advisory Committee Day 1 Transcript), at 206-208, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM434384.pdf>.

<sup>17</sup> Advisory Committee Briefing Materials, at 59.

<sup>18</sup> Advisory Committee Briefing Materials, at 59-60.

<sup>19</sup> Rathmell, JP, et al., May 2015, Safeguards to Prevent Neurologic Complications After Epidural Steroid Injections: Consensus Opinions From a Multidisciplinary Working Group and National Organizations, *Anesthesiology*, 122:974-984.

<sup>20</sup> Advisory Committee Briefing Materials, at 59.

<sup>21</sup> Safe Use Initiative Website at <http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm434387.htm#esi>.

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#### WARNING

##### **Serious Neurologic Adverse Reactions With Epidural Administration**

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids (see **WARNINGS: Neurologic**). Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.<sup>22</sup>

FDA issued a Drug Safety Communication (DSC) the same day the SLC notification letters were sent.<sup>23</sup> The DSC advised health care providers and the public of the risks of serious neurologic adverse events associated with ESIs.<sup>24</sup> It also informed the public that FDA was requiring the addition of a warning to the drug labels of injectable corticosteroids to describe these risks.<sup>25</sup> In the DSC, FDA indicated that it intended to convene an advisory committee meeting in late 2014 to discuss the benefits and risks of ESIs and determine whether further actions were needed.<sup>26</sup> The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met on November 24-25, 2014, to discuss ESIs and the risk of serious neurologic adverse reactions.<sup>27</sup>

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<sup>22</sup> Section 505(o)(4) of the FD&C Act authorizes FDA to require “certain drug and biological product application holders to make safety-related labeling changes based on new safety information that becomes available after approval of the drug or biological product.” Guidance for industry *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act*, at 1. FDA invoked this authority to require the addition of the warning to the labeling of all injectable corticosteroid products. After receiving the SLC notification letters, the corticosteroid application holders submitted revised labeling to the Agency, and the changes were approved on July 3, 2014.

<sup>23</sup> See “Epidural Corticosteroid Injection: Drug Safety Communication — Risk of Rare But Serious Neurologic Problems” (Apr. 23, 2014), available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm394530.htm>.

<sup>24</sup> *Id.*

<sup>25</sup> *Id.*

<sup>26</sup> *Id.*

<sup>27</sup> Materials related to the Advisory Committee meeting are available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm390304.htm>. Dr. Manchikanti participated in the Open Public Hearing portion of the Advisory Committee meeting both on behalf of Dr. David Bryce (Treasurer of ASIPP) and as Chairman of the Board of ASIPP. Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting, November 24-25, 2014, Food and Drug Administration, Center for Drug Evaluation and Research, at 3, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM429414.pdf>.

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## II. Discussion

### A. Amending the Class Warning for Injectable Corticosteroids

In the Petition, you claim that the new class warning for injectable corticosteroid products related to the risk of serious neurologic adverse events that is described in the April 23, 2014, DSC is “both under inclusive and over inclusive” because it fails to include a distinction between different ESI approaches and injection locations (Petition at 2, 3).<sup>28</sup> You say that “[c]ervical, thoracic, and lumbar interlaminar and caudal epidural injections do not cause the rare serious neurological problems associated with transforaminal epidural injections,” and that the “distinction between these two epidural techniques regarding the rare serious neurological consequences needs to be emphasized so that the interlaminar and caudal epidurals are not included in the Safety Warning” (Petition at 2).<sup>29</sup>

In support of your position, you state that there are “no reports for lumbar and caudal epidural injections” (Petition at 3).<sup>30</sup> You claim that, in requiring the addition of the class warning that does not distinguish among ESI approaches or locations, FDA inappropriately “applied the grossly limited evidence from cervical transforaminal epidurals to all other techniques of epidural injections” (Petition at 2).<sup>31</sup>

We do not agree with your assertion that interlaminar and caudal epidural injections do not cause serious neurologic adverse events or with your assertion that there are “no reports” for

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<sup>28</sup> Epidural corticosteroid injections can be administered in the cervical, thoracic, or lumbosacral regions of the spine, depending on the pain being treated. See Advisory Committee Briefing Materials, at 85. There also are several different approaches used for administering ESIs, including interlaminar, transforaminal, and caudal. *Id.* at 17. Since you do not explain how the warning is under inclusive and provide no support for the assertion, it is not addressed in this response.

<sup>29</sup> You also say that the warning should be revised to provide that “all procedures must be performed by well-trained providers in appropriate settings under fluoroscopy or other appropriate proven imaging modalities” (Petition at 1) and appear to claim that FDA’s regulatory action was inappropriate because the Agency failed to take into consideration “alternate techniques to classic traditional teachings to improve safety” (Petition at 2). However, you provide no data to demonstrate that the alternate techniques actually result in a reduction in the risk for serious neurologic adverse events.

<sup>30</sup> You also say that there is “high quality” evidence supporting the use of epidural corticosteroid injections, except for cervical and thoracic transforaminal injections, to manage spinal pain when indicated and medically necessary (Petition at 3). As stated previously, the safety and effectiveness of corticosteroids for epidural injection has not been established under section 505 of the FD&C Act, and corticosteroids are not approved for this use. In any case, as discussed in this Section of the response, there is evidence adequate to support the class safety warning that encompasses all ESI approaches and locations.

<sup>31</sup> We disagree with your assertions that FDA has “not reviewed all of the relevant literature,” and that the literature that was reviewed was “improperly assessed leading to inappropriate conclusions” (Petition at 2). As discussed in this Section, there is evidence from FAERS and in the literature adequate to support the class safety warning that encompasses all ESI approaches and locations. In addition, aside from disagreeing with our conclusions, you have not articulated any specific deficiencies with regard to how our review was conducted that substantiates your assertion that the literature was “improperly assessed.”

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lumbar or caudal epidural injections. FDA has identified case reports of serious neurologic adverse events associated with all ESI approaches and all injection sites.

Using FAERS, FDA identified 131 cases of serious neurologic adverse events associated with the use of ESI.<sup>32</sup> Of these cases, 15 reported the transforaminal approach, 6 reported the interlaminar approach, and 2 reported the caudal approach; the approach used was not identified in the remaining 108 cases. Although the majority of cases that reported the interlaminar and caudal approach were associated with transient or reversible events, there were cases of catastrophic neurologic events with these approaches as well, including quadriplegia and bowel and bladder dysfunction. Cases were also reported with each injection site (cervical, thoracic, and lumbar).<sup>33</sup>

The medical literature also contains reports of serious neurologic events associated with ESIs other than cervical and thoracic transforaminal ESIs. Included in these reports are Cohen-Adad et al. describing a case of left hemiparesis and sensory loss persisting for at least 28 months after a cervical interlaminar injection,<sup>34</sup> and Thefenne et al. describing a case of paraplegia with some recovery, though with persistent urinary and sensory disorders, lasting at least four months after a lumbar interlaminar injection.<sup>35</sup>

Another relevant study evaluated malpractice claims arising from cervical pain treatments collected from the American Society of Anesthesiologists' (ASA) closed claims database between 2005 and 2008.<sup>36</sup> Of the 64 claims associated with cervical procedures, 43 were epidural procedures (67%), and steroids were injected in 41 of the 43. The two most common procedure-related events for all cervical pain treatments were direct needle trauma to a nerve or the spinal cord (31%) and cord infarction/stroke after intra-arterial injection (14%). Thirty-one of the cervical epidural procedures were associated with spinal cord injury, and of those, 20 were injected by the interlaminar approach, 10 were injected by the transforaminal approach, and in one case the approach was unknown. The authors observed that, "[a]lthough direct needle trauma to the spinal cord occurred with the transforaminal approach, direct

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<sup>32</sup> These cases include reports from November 1, 1997, through April 23, 2014, identified through a narrative text search, as well as cases coded in the database to the event "arachnoiditis."

<sup>33</sup> For a discussion of the cases reported in the FAERS database, see Advisory Committee Briefing Materials, at 74-119.

<sup>34</sup> Cohen-Adad, J, et al., Nov. 2012, Cervical Spinal Cord Injection of Epidural Corticosteroids: Comprehensive Longitudinal Study Including Multiparametric Magnetic Resonance Imaging, *Pain*, 153(11):2292-2299.

<sup>35</sup> Thefenne, L, et al., Nov. 2010, A Rare Case of Paraplegia Complicating Lumbar Epidural Infiltration, *Ann Phys and Rehabil Med*, 53(9): 575-583.

<sup>36</sup> Rathmell, JP, et al., Apr. 2011, Injury and Liability Associated with Cervical Procedures for Chronic Pain, *Anesthesiology*, 114(4): 918-926. As described in the article, the ASA's Closed Claims Project is a structured evaluation of adverse anesthetic outcomes obtained from the closed claims files of 35 U.S. professional liability insurance companies. In response to an increase in chronic pain claims since the 1990s, a revised Institutional Review Board-approved form, designed specifically to collect detailed information on chronic pain claims, was used to review closed malpractice claims for chronic pain management, collected from 2005 onward.

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needle trauma was far more common during a cervical interlaminar injection.”<sup>37</sup> Although this study is limited to ESIs performed in the cervical region, it provides clear evidence that serious neurologic harm is not limited to ESIs administered by the transforaminal approach, but rather some injuries (i.e., direct needle trauma to the spinal cord) occurred with the interlaminar approach.

Thus, contrary to the assertion in your Petition, serious neurologic adverse events have been reported with ESIs administered by the caudal and interlaminar, in addition to the transforaminal approach, and with injections in the lumbar spine, in addition to the cervical and thoracic regions. The totality of the available information provides evidence adequate to support the class safety warning that encompasses all ESI approaches and locations. We therefore deny your request to revise the class warning to limit it to cervical and thoracic transforaminal ESIs.

#### **B. Recommendations of the Safe Use Initiative**

In your Petition you ask FDA “not to adopt 17 recommendations developed by [the] Multi-Society Pain Workgroup (MPW)” (Petition at 1). You say that FDA provided the class safety warning “without the input of members working on the Safe Use Initiative. In addition, to promote one persons [sic] philosophy and ideas the 17 recommendations were moved from the Safe Use Initiative to the MPW which was formed by individuals to promote certain philosophy and benefit from them” (Petition at 2).

You are correct that FDA did not seek “the input of members working on the Safe Use Initiative” prior to issuing the new class warning. As discussed above in section I.B, the goal of the Working Group was to try to understand the causes of the neurologic injuries associated with ESIs and devise strategies to mitigate the risk. The members of the Working Group led the discussions and independently evaluated ways to minimize the risk of catastrophic neurologic injury associated with ESIs. After the initial set of clinical considerations had been drafted, the Working Group sought the input and assistance of the MPW. Ultimately, the Working Group published a list of 17 “clinical considerations” aimed at improving the safety of ESIs.<sup>38</sup> The clinical considerations are intended for the medical community. They are not recommendations for the FDA and, as such, are neither binding on FDA nor endorsed by the FDA.<sup>39</sup>

Although we do not agree with the unsupported characterizations of the Working Group, its activities, or its relationship to the MPW as asserted in your Petition, because FDA did not “adopt” or endorse the clinical considerations developed and published by the Working Group, your Petition is granted to the extent it asks us not to adopt those clinical considerations.

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<sup>37</sup> Id. at 923.

<sup>38</sup> Rathmell, JP, et al., *supra* note 19.

<sup>39</sup> Safe Use Initiative Web Page at <http://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/ucm434387.htm#esi>.

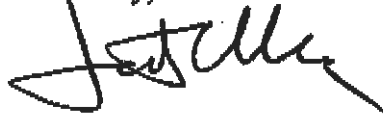


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**III. Conclusion**

For the reasons set forth above, the Petition is denied in part and granted in part.

Sincerely,



Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research