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

PETITION FOR RECONSIDERATION
DOCKET NO. 2005P-0383/CP1 & SUP1; OXANDROLONE

The undersigned submits this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. 2005P-0383/CP1 & SUP1.

A. Decision Involved

On December 1, 2006, the Center for Drug Evaluation and Research ("CDER") denied the citizen petition, 2005P-0383/CP1 & SUP1, of our client Savient Pharmaceuticals, Inc. ("Savient"). This petition requested that Food and Drug Administration ("FDA" or "the Agency") refuse to approve any Abbreviated New Drug Applications ("ANDAs") for generic

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oral products containing oxandrolone until after the expiration of the geriatric labeling exclusivity granted to Oxandrin® drug products. At the same time, FDA granted approvals of ANDAs for generic oxandrolone 2.5mg tablet drug products for Sandoz Pharmaceutical Corporation ("Sandoz") and Upsher-Smith Laboratories ("Upsher-Smith"). These approvals contained labeling that is inconsistent with the reference Oxandrin® drug product, that is inadequate for the safe use of the drug in geriatric patients, and that is misleading by the novel geriatric label disclaimer. Further, FDA granted these drug products AB therapeutic equivalence ratings, permitting automatic generic substitution despite the labeling differences and safety concerns for the elderly.

B. Action Requested

We respectfully request that the Agency reconsider this unique decision. Savient requests that FDA find that no ANDA for a generic oxandrolone product can be approved until after the expiration of the geriatric labeling exclusivity on June 20, 2008. Alternatively, we request that the labeling for generic oxandrolone clearly distinguish it from Oxandrin® with a contraindication for use in the elderly, and that FDA take steps necessary to ensure generic oxandrolone cannot be used as a substitute for Oxandrin® in geriatric patients.

C. *Statement of Grounds*

Under its regulations, FDA must grant a petition for reconsideration if all of the following apply: (1) the petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered; (2) the petitioner's

position is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting reconsideration; and (4) reconsideration is not outweighed by public health or other public interests.[1] All of these conditions apply in the current situation.

FDA did not adequately consider the arguments within the citizen petition. As discussed further below, FDA did not fully consider how the lack of labeling information specific to the elderly for generic oxandrolone products would substantially increase the risks to geriatric patients. Furthermore, FDA did not adequately consider the ramifications of granting Savient exclusivity for studies it had conducted in the geriatric population and yet eviscerating the same exclusivity by allowing other products to substitute for Savient's Oxandrin® in the geriatric population. It reached an arbitrary and capricious decision that is inconsistent with its regulations and underlying policy.

Savient's position is not frivolous and is being pursued in good faith. Adverse events from drug products pose distinctly different risks to various subpopulations. It is vital that the labeling of drug products adequately disclose all the risks of use so that patients can make fully informed decisions about their health. If the risks cannot be clearly stated on a drug product's labeling, then the generic substitutability of a drug product should be restricted in at-risk subpopulations to protect them from drug products that fail to completely state the risks of the product.

There are sound public policy grounds to support reconsideration of Savient's Citizen Petition. The conundrum that FDA has created by approving the Sandoz and Upsher-Smith oxandrolone drug products with truncated and confused labeling creates a safety risk to elderly patients. As discussed in more detail below, through this action, FDA will significantly reduce

[1] 21 CFR § 10.33(d).

the incentives that Congress has established to encourage research into previously approved drugs if FDA allows generic drugs to be freely substitutable with those drugs that have already obtained labeling exclusivity. Further, the Agency will effectively undermine its regulations and policies designed to increase the information available for use of drugs in the geriatric population.

There are no public health or other public interests issues that outweigh granting Savient's request for reconsideration. In the short term, denying Savient's Citizen Petition will increase generic competition for oxandrolone. Nevertheless, this competition will expose significant number of geriatric patients to drug products that fail to completely disclose the risks. These risks to the elderly have the potential for long term harm to the patients themselves, as well as increased costs to the healthcare system associated with those increased risks. Furthermore, in the long term denying Savient's Citizen Petition will signal to manufacturers that FDA will not protect labeling exclusivity for research into the safety of geriatric drugs. Thus, there will be no incentive in obtaining three-year exclusivity, and research into the safe use of drugs in at-risk patients will decrease dramatically.

We do agree with the Agency's position that the Agency can permit "omission of geriatric labeling for a specific generic drug product if the omission would not render the generic drug less safe and effective than the listed drug for all remaining, non-protected conditions of use."[2]

While accepting this basic regulatory framework, we disagree with FDA's conclusions with regard to the specific situation with the omission of the protected geriatric labeling for Oxandrin®.

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[2] Citizen Petition Response from Steven K. Galson, M.D., M.P.H., Director, Center for Drug Evaluation and Research to Edward John Allera and Theodore Sullivan, Buchanan Ingersoll P.C., Dockent No. 2005P-0383/CP1 & SUP1 (Dec. 1, 2006) ("Petition Response") at 7.

For these reasons, discussed in further detail below, Savient requests that FDA reconsider its denial of Savient's citizen petition to confirm that no ANDA for a generic oxandrolone product can be approved until after the expiration of the geriatric labeling exclusivity. If FDA does not reverse its conclusion regarding the safety of generic oxandrolone drug products that contain less than full geriatric safety labeling, Savient requests that FDA take the necessary actions to ensure that drugs with incomplete warnings be restricted from substituting for Oxandrin®. Prevention of generic substitution could be accomplished either through requiring a specific contraindication that the drug is not for use in the elderly and is not substitutable for Oxandrin®; or by using the existing BX therapeutic equivalence code to prevent improper substitution.

I. FDA General Position on ANDA and Geriatric Labeling Regulations

Savient accepts FDA's analysis of the ANDA and geriatric labeling regulations as described in the Agency's petition response. That position is essentially that geriatric labeling found in a reference listed drug ("RLD") cannot be omitted from the labeling of a generic version of that RLD *if* the generic drug would be less safe without such labeling. Where such geriatric labeling is protected by Waxman-Hatch exclusivity, an ANDA referencing that RLD cannot be approved, since the protected labeling cannot be removed without rendering the generic drug product less safe than the referenced drug product.

FDA notes in its petition response that the geriatric labeling regulations at 21 C.F.R. § 201.80(f)(10) "require labeling for new drugs, whether approved under new drug applications (NDAs) or ANDAs, to include available geriatric use information"[3] The petition response further states that the ANDA labeling regulations require that generic drug labeling be the same as that for the RLD, except for differences permitted under the regulations. Among the

[3] Petition Response at 2.

permitted differences are those required "because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[4]

As a result of the regulation above, FDA determined that "[o]mission of protected geriatric labeling would, therefore, be permitted only if the product would remain as safe and effective as the reference list drug for all remaining, labeled uses, including in the geriatric population."[5] Elsewhere in the petition response, the Agency reinforces this position by stating that "[i]f the omission would render the generic drug product less safe or effective for any of the remaining conditions of use, in the geriatric population or otherwise, the omission will not be permitted."[6] If the omission of exclusivity protected labeling is not permitted, the ANDA for that drug cannot be approved.

Savient accepts FDA's interpretation of its regulations where FDA will only permit generic drugs from omitting exclusivity protected geriatric labeling where such omission does not render the generic drug less safe or effective.

II. FDA's Factual Analysis of the Omission of the Protected Oxandrin® Geriatric Labeling

The indications and geriatric information in the labeling that FDA has approved for the generic oxandrolone drug products are dramatically different from those in the RLD and specifically fail to reveal all material facts regarding use in the elderly.[7] As stated in the CItizen Petition, elderly patients constitute approximately one third of the patient population for

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[4] 21 CFR § 314.127(a)(7).
[5] Petition Response at 9.
[6] Id. at 7-8.
[7] See Chart A (attached) and labels.

Oxandrin®. The changes and omissions present serious potential safety issues for that vulnerable population.

The patch-work labeling that FDA has approved for the generic oxandrolone drug products is false and misleading for use in elderly patients, and the potential safety problems are compounded by FDA's decision to grant AB therapeutic equivalence ratings for these drugs. FDA's actions violate the statutory and regulatory prohibition on drug labeling that is false or misleading in any particular. Only a requirement that the generic oxandrolone label contain the exclusivity protected geriatric information, or carry a specific statement that the drug is not intended for use in the elderly (or for administrative convenience assignment of a BX therapeutic equivalence rating) ensures that the labeling is safe for the labeled indications.

As noted in the previous section, FDA will not permit the omission of protected geriatric labeling from generic drug labeling where such an omission would render the generic drug less safe or effective. In making the determination of whether any such omission would be permitted, FDA stated in the petition response that "[t]he Agency has, therefore, concluded that the permissibility of omitting protected geriatric user information from the ANDA labeling should be considered on a drug product-specific basis and will depend upon whether the particular omission complies with § 314.127(a)(7)"[8] It is in this drug-product specific factual analysis that Savient disagrees with FDA's petition response.

In the petition response, FDA states that for oxandrolone "all the safety and effectiveness issues addresses in the new geriatric use information are of concern within the general adult population and, as a consequence, are adequately addressed elsewhere in the label."[9] The response further states that:

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[8] Petition Response at 10.
[9] Id. at 13.

> we have concluded that, if the new geriatric labeling were omitted, generic oxandrolone products would remain safe and effective for all remaining, nonprotected conditions of use. This is based on the determination that the labeling for generic oxandrolone would still contain adequate information to permit appropriate use and to minimize risks in all adults, including the geriatric population, with regard to each of the safety considerations also identified in the new geriatric labeling: edema, liver toxicity, and dosing.[10]

As discussed in particular below, FDA has incorrectly characterized sections of the non-protected labeling dealing with edema, liver toxicity, and dosing, as an adequate substitute for the exclusivity protected and clinical study supported geriatric information. It has ignored the critical difference in elimination half-life of the drug in the elderly.

A. General Drug Safety

As a general matter, Savient disagrees with FDA's determination that the regulatory requirement for removal of exclusivity protected language has been met for oxandrolone. FDA's statement that the safety and effectiveness issues are "adequately addressed elsewhere in the label" and that the "labeling for generic oxandrolone would still contain adequate information ... with regard to each of the safety considerations" is not the appropriate standard. The appropriate legal standard as established by rule is that the difference between the RLD labeling and the generic labeling cannot "render the proposed drug less safe or effective than the listed drug for all remaining, non-protected conditions of use."[11] Adequate safety is not in this case equivalent to the regulatory requirements that the generic not be less safe than the RLD. As discussed below for each specific instance, the "old" (i.e. prior to the addition of the exclusive geriatric information) label does not provide the same level of information or safety as does the current Oxandrin® label. Thus, while the old label may have been adequate to demonstrate that the drug

[10] Id. at 14.
[11] 21 CFR § 314.127(a)(7).

was safe and effective for use, the new label includes information that makes use of the drug safer than it was before.

Failure to include the protected geriatric information therefore renders drugs with the old labeling materially false and misleading for that particular patient population. As such, if the generic oxandrolone drug products are to retain this truncated labeling, they should be specifically contraindicated for use in the elderly and not directly substitutable for Oxandrin®.

Drug approval involves a cost-benefit analysis. FDA has long acknowledged that all pharmaceuticals have some inherent risk to their use. Where a drug's risks are outweighed by the treatment benefit, the drug can be deemed safe and effective. The "old" non-protected Oxandrin® label was sufficient for the safe and effective use of the drug, since, under that labeling, the risk associated with use of the drug were outweighed by the benefit. The new labeling was approved, containing new clinical studies data regarding geriatric use, which changes the analysis. This new approval was sought under the FDA policy encouraging development of geriatric data for pharmaceuticals. Once the new label was approved, it represented the contemporary standard for safety and effectiveness for oxandrolone drug products. That the old labeling may have been "adequate" for the safe and effective use of the drug prior to the approval of the new labeling is immaterial. The new labeling, including the exclusivity protected geriatric information, is safer than the labeling without such information. The regulatory standard is clear. Therefore, omission of that geriatric information would result in a drug that is less safe than the RLD.

The safety issue is exacerbated by the approved indications for the Sandoz and Upsher-Smith oxandrolone products. These products are indicated as "adjunctive therapy to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief

of the bone pain frequently accompanying osteoporosis." The trauma and infection indications found in Oxadrin® were omitted from the labeling of these drugs. The generic indications represent uses for oxandrolone that are heavily or primarily geriatric indications. As a result, these generic oxandrolone products are primarily intended to treat the elderly population, and the omission of the exclusivity protected geriatric information represents a critical safety issue.

B. Edema

With regard to the specific safety issues addressed by the protected geriatric information, Savient disagrees with FDA that the information in the "old" label provides the same level of safety as the protected label. The geriatric information for Oxandrin® provides specific data from multiple clinical trials that is not present elsewhere in the label.

The geriatric information states that "the elderly, particularly in women, had a greater sensitivity to fluid retention." According to FDA's petition response, statements in the warnings and the adverse reactions section of the label are an adequate substitute for this specific information. Those sections, in their relevant parts, state:

> WARNINGS
> Edema with or without congestive hear failure may be a serious complication in patients with pre-existing cardiac-renal or hepatic disease...
>
> ADVERSE REACTIONS - Fluid and Electrolytes Edema, retention of serum electrolytes

These references to edema are not equivalent to the specific information contained in the protected geriatric label. That label notes that the elderly, and in particular elderly women, are at an increased risk of edema. The petition response states that:

> The edema adverse reaction is a well-established side effect of all anabolic steroids, including oxandrolone. As in the general adult population, geriatric patients with underlying cardiac, renal, and hepatic disease would be at greatest risk of a serious clinical complication from edema. Because the oxandrolone labeling would retain the ... warning and adverse information related to edema and adult patients, the absence of a specific geriatric use statement that edema

> occurred more frequently in the elderly patients in certain clinical studies will not render generic products less safe or effective than Oxandrin in the geriatric population.[12]

FDA's conclusion in this regard is clearly erroneous. Specific warnings with regard to increased edema risks in the elderly, and in particular elderly women, is not found expressly or impliedly in the warning and adverse events sections FDA quotes. The specific risk information for these patient groups provides physicians with information that is not empirically obvious and not implied elsewhere in the old labeling. The "adequate notice" of edema risks generally is not a sufficient substitute for population specific, clinically based, risk information. Further, FDA's stance is contrary to the policy underlying FDA's geriatric labeling regulations. In the preamble to the 1997 geriatric labeling final rule, FDA stated:

> The final rule recognizes the special concerns associated with the geriatric use of prescription drugs and acknowledges the need to communicate important information so that drugs can be used safely and effectively in older patients. ... The medical community has become increasingly aware that prescription drugs can produce effects in elderly patients that are significantly different from those produced in younger patients. ... FDA has encouraged sponsors to include more elderly subjects, especially those over 75 years of age, in clinical studies.[13]

In that final rule, FDA expressly acknowledged that specific clinical data regarding use in the elderly is important, since drug effects may be different in that population. That indeed was the case with Oxandrin® use in the elderly, and the studies demonstrating different effects in the elderly was the basis for FDA's approval of the geriatric labeling. It is not reasonable for FDA to now take the position that the specific warnings on particular effects of the drug in the elderly have no value to the safe use of the drug.

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[12] Petition Response at 14.
[13] 62 Fed. Reg. 45,313 (Aug. 27, 1997).

The protected geriatric label noted that the increase in edema was found at the higher 10mg dose level, and this finding was a basis for the 5mg dosing recommendation. Contrary to FDA's assertion in the petition response, the safety implications of the lower dosing level is not evident from the non-protected labeling. Without the specific protected geriatric labeling, a physician may not have sufficient guidance on the recommended and safer dose for the elderly generally, and elderly women specifically.

C. Liver Toxicity

As with the edema warning, the protected geriatric information regarding increases in hepatic transaminases (related to liver toxicity) cannot be omitted from the label without making use of the drug less safe. The clinical trials that supported the protected information showed an increase in liver toxicity for the elderly in general, and for elderly women in particular when those patients were treated with the 10mg dose, as opposed to the 5mg dose. Again, FDA states that there is an adequate substitute for this information elsewhere in the unprotected portions of the label. In particular, FDA states:

> Hepatotoxicity (liver toxicity) is a serious side-effect of anabolic steroids, which the labeling of Oxandrin has long addressed. In addition to the new geriatric labeling regarding elevated transaminases, the label for oxandrolone currently contains several statements concerning liver toxicity that are not protected. A *Boxed Warning* describes the occurrence of peliosis hepatis and liver cell tumors. In addition, the PRECAUTIONS section states the following: "Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.[14]

This labeling warning is not sufficient to provide the same level of safety for the elderly as is provided with the protected geriatric information. As with the edema warning, the general warning that liver toxicity may be an issue does nothing to alert physicians of the particular risk to the elderly, and elderly women in particular. Further the non-protected labeling does not warn

[14] Petition Response at 14 - 15.

against the increased risk associated with a higher dose, which (as discussed below) does not increase treatment effectiveness.

FDA's suggestion that liver function testing is a sufficient alterative to the protected geriatric information is not reasonable. Elevations of liver function tests (specifically transaminases) may indicate that come decreased has already resulted from the use of the drug. The proactive warning contained in the exclusivity protected information is superior to the recommendation for liver testing alone that is found in the unprotected labeling. Additionally, FDA's dismissal of the importance of geriatric labeling it approved is again contrary to the rationale behind its own geriatric labeling regulations.

D. Dosing

The protected geriatric labeling has a dose recommendation of 5mg twice a day for elderly patients. FDA states that this dosing level is obvious for elderly patients, and that a generic oxandrolone drug product without the protected geriatric information would be just as safe as Oxandrin®. FDA's assertion is not reasonable. The specific protected labeling for the 5mg dosing is based on the results of clinical trials. Data generated in those trials demonstrated that there is a significantly different elimination half-life for the drug between elderly and non-elderly patients. The specific data regarding elimination is of value to physicians treating geriatric patients, and is not empirically obvious or implied elsewhere in the label.
Those trials showed that 1) there were less adverse events in the elderly at the 5mg dose level, and of equal or greater importance, 2) there is no significant increase in drug effectiveness in the elderly for the 10mg dosing compared to the 5mg dosing. The 5mg dosing recommendation is based on the combination of these two pieces of information, both of which are new, and not obvious. Absent the protected label, a physician would have no way of knowing that there is no

therapeutic advantage to the 10mg dose and that there is an increased risks of adverse events associated with a higher dose. Thus, the physician may prescribe this less safe higher dosage level (with increased edema and liver function risks) with the false hope of obtaining greater therapeutic results. Therefore, generic oxandrolone is not as safe without the protected geriatric information.

E. Granting of Exclusivity

In 2005, FDA approved Savient's labeling supplement for the new geriatric dosing information. This supplement, supported by clinical trials, was granted three years of Waxman-Hatch labeling exclusivity. FDA's geriatric labeling regulations require that:

> If evidence from clinical studies ... indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection of the labeling shall contain a brief description of the observed differences or specific monitoring or dosing requirements and, as appropriate, shall refer to more discussions in the "Contraindications," "Warnings," "Dosage and Administration," or other sections of the labeling.

In accordance with these regulations, Savient submitted the labeling supplement with the appropriate geriatric information. FDA approved these changes, and the only rational interpretation of FDA's approval and subsequent granting of exclusivity for the change was that the new information represented new and important safety and efficacy information for use of the drug in the elderly. It is illogical for FDA to now take the position that such a change was in essence meaningless, since it has now taken the position in its petition response that a generic oxandrolone that does not contain this protected geriatric labeling is equally safe to Oxandrin®, which does have this new information.

III. Proposed Remedy

FDA has failed to consider all relevant factors in its decision to approve the ANDAs for generic oxandrolone with labels that contain the confusing geriatric information disclaimer, and with omissions that make the label less safe than the label for Oxandrin®. FDA has come under criticism for failing to consider all the safety considerations in approving new drug applications in its emphasis on rapid drug approvals. The rush to approve ANDAs with inconsistent patch-work labels illustrates the same failure to consider numerous relevant factors. Among factors not considered or given sufficient weight in the current generic oxandrolone approval are the following: the impact of the generic labeling that omits material facts about use in the elderly; the impact of the novel disclaimer; the impact of these approvals on FDA's laudable public health policy in encouraging the generation of additional data on drug use in the elderly; and the potential liability of the pioneer drug manufacturer (Savient) for the problems created by misuse of the generic drugs (with their inadequate geriatric labeling) in the elderly.

For all the reasons stated above, FDA must reconsider its previous decision to deny Savient's Citizen Petition. Any generic oxandrolone drug labeling that excludes that protected geriatric information is inherently less safe than the labeling for Oxandrin®. In reconsidering its previous decision, FDA should not approve any ANDAs for drug products that cannot include Savient's protected generic dosing information for geriatric patients.

Although we believe that Savient is entitled to this legal and equitable remedy, we acknowledge that FDA may be reluctant to block approval for all ANDAs based upon this exclusivity due to the political demands for generic drug product approvals. Savient understands that the political pressure for granting approval to generic drugs is extraordinary, and that FDA is hesitant to take any steps to delay any such approvals. Nevertheless, FDA cannot permit drug products with false and misleading labeling on the market. The failure to include all relevant

information on geriatric use renders the generic oxandrolone products misbranded under the Federal Food Drug and Cosmetic Act.

Therefore, recognizing that this is a matter of first impression with the Agency, Savient respectfully requests that FDA make a determination that generic oxandrolone products are contraindicated for use in the elderly in the absence of the specific language covered by market exclusivity. As discussed in this petition, oxandrolone drug products that do not have Savient's exclusivity protected geriatric information are safe than Oxandrin® in elderly patients. Under FDA regulations, approval of such drugs is not permitted.[15] The use of such generic drugs would represent an increased risk in the vulnerable elderly population. It is incumbent on FDA to take steps to mitigate such a risk. One such solution would be to approve the generic oxandrolone products with a specific contraindication that the drug is not approved for use in elderly patients. In order for such a labeling to be effective, truthful, and accurate, the generic oxandrolone drug products would require a therapeutic equivalence code that prevented their automatic substitution by pharmacists. Such a code could be a new code, or in the alternative and for administrative convenience, FDA could assign generic oxandrolone BX status to indicate that generic oxandrolone is therapeutically inequivalent to Oxadrin®. This step is necessary in order to restrict others from involuntarily substituting generic oxandrolone products that contain inadequate disclosure of the risks for Oxandrin®.

Only this approach considers all the relevant factors, and promotes the proper interaction of all FDA public health policies and regulations. Failure to take even these basic steps to ensure the safety and health of the public would certainly qualify as arbitrary and capricious action if reviewed by the Federal Courts, even if reviewed under the deference typically accorded agency actions.

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[15] 21 CFR § 314.127(a)(7)

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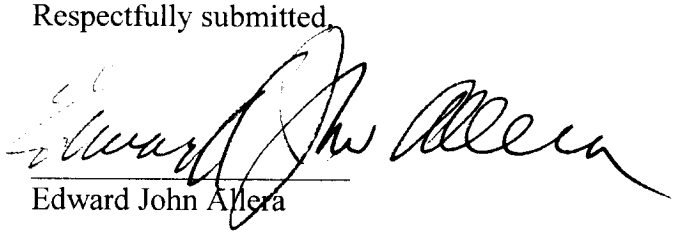
Based on the forgoing, Savient respectfully requests that FDA reverse the decision of CDER.

Respectfully submitted,



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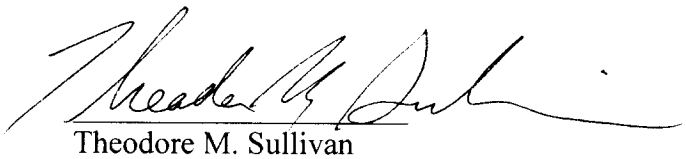

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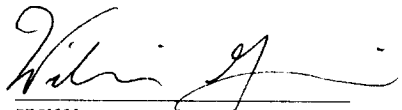

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