Submitted for Ortho Molecular Products
By Patrick McGinley

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**General objections**

The proposed GMPs are, in fact, not GMPs at all. They do not stipulate practices consistent with quality assurance/control which are based on validated or verified procedures. Instead, they seem to rely solely on laboratory testing. It has long been an adage of industry quality programs that proper procedures, not testing, is how to build a quality product- these proposals deny the basic premise of effective and tested quality programs

We believe that the burden is removed from FDA in the auditing process of manufacturing facilities with these proposals FDA would no longer need to conduct thorough on site investigations of procedures but simply test product As FDA is aware, it is impossible to test for all potential sources of contamination and written procedures are vital to ensure quality products. It is our contention that unscrupulous manufacturers will devise methods to ensure proper laboratory results with inferior quality products. Laboratory testing should be used to validate or verify manufacturing procedures, not replace them.

**Specific comments**

**Written Procedures**

While you state that you would like comments on whether written procedures should be necessary, you state in 111 45 (a)(2), (b)(8)(i) that procedures must be validated. This presumes written procedures Of course written procedures must be required for all parts of the manufacturing process FDA auditing would be useless without the need for written procedures and investigations would be impossible to conduct. Day-to-day operation in the manufacturing process must be based on written procedures in order to ensure uniformity and consistency between various employees Again procedures/qualifications promote quality not testing.

**Other records should be required**

We believe that training records of responsible employees should be required in order to ensure that decision making employees have the requisite training and experience to adequately perform their duties Training will also ensure that procedures are understood and communicated to the staff that is required to fully understand and follow the procedures as part of the manufacturing process We believe documenting training will help validate employee's credentials and demonstrate they have the necessary experience and knowledge to do their job responsibly and correctly. Without training records the FDA will not know if employees engaging in manufacturing processes are trained to do their job and it would be hard to validate it without the documentation

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**Expiration dates**

Expiration dates should be required. Currently, expiration dates would not be required leading to a situation where no expiration date has the meaning of infinite label claim As your proposal only requires batch records to be kept for 3 years, this information would not be available for products without expiration date after 3 years time (as with infinite or no expiration date). Expiration date should be based on stability testing Batch records should be kept for 1 year past the expiration date instead of just 3 years

**GMP statement on label should not be allowed**

As the proposal mentioned, the use of "made in a GMP facility" language is fraught with potential misuse. We agree, and furthermore believe that it should not be permitted at all. The potential for confusion is overwhelming. Companies that are not GMP should eventually go out of business due to their inability to pass your audits and this issue would be void GMP is not a voluntary system and should not be marketed as one. There should be a prohibition on any comments related to GMP status on the label

**Batch records**

21 CFR 111 50 (c) (4) requires that all the equipment maintenance be included in the batch records. We feel this is not the right place for the storage of these files for it would not aid in showing history of maintenance/cleaning, which we feel is critical in following any type of maintenance program. Maintenance records on machines and instruments really belong in their own log which should be kept with the instrument and archived routinely. We do not feel these records should be archived with the batch records. However, the batch records should have a reference to which machine or instrument was used in the process by its serial number, make and model. Individual machine records should not be included in the batch records

**Cost of testing**

The FDA's estimated cost for laboratory testing seems to be incorrect from our perspective. Annually, we believe the testing requirements will cost significantly more for our organization and would be extremely burdensome to both us and our customers Our organization currently runs roughly 200 batches per month (or 2,400 batches per year) Our average batch has roughly 8 ingredients that would need to be tested for identity, purity, composition, quality, and strength. Looking at the average third party laboratory analysis cost we estimate that the average batch would cost us $3700 (based on analysis costs from Covance Laboratories: www.covance.com). Annually with 2,400 batches, the analysis cost would be $8.8 million. The analysis cost breakdown would be:

| Heavy Metal analysis: | |
|---|---|
| Arsenic- | $125 |
| Cadmium- | $49 |
| Lead- | $55 |

| | |
|---|---|
| Mercury- | $82 |
| Total- | $311 |

Pesticide Screening.

| | |
|---|---|
| 375 compounds- | $380 |

USP Microbiology

| | |
|---|---|
| Total aerobic plate count- | $42 |
| Salmonella- | $54 |
| Staphylococcus aureua- | $54 |
| Yeast and mold- | $42 |
| E coli | $54 |
| Pseudomonas aeruginosa- | $54 |
| Preparatory cost- | $15 |
| Total- | $315 |

| | |
|---|---|
| Weight Variation test. | $50 |
| FTIR spectral analysis | $250 |
| 8 Ingredients potency analysis | $300/ingredient → $2400 |

**Grand Total: ~$3700/finished good batch**

We would also incur an additional $1600 for each raw material received into the facility. This would be for heavy metal analysis, pesticide screen, microbiology analysis, FTIR identity, and a purity/potency analysis (typically HPLC). We turn our inventory roughly 6 times per year and we have roughly 500 raw materials. Therefore, we would have an additional cost of $4.8 million per year

The grand total cost for our organization would be roughly **$13.6 million dollars annually, not $60,000** as the commentary states. We feel that this additional cost would be extremely burdensome to our business, as well as any small business. We also feel that all this analysis does not necessarily increase the quality or the safety of the product We feel some testing may be necessary on each batch to verify that validated procedures were followed in the manufacturing process. However, testing in combination with validations or verifications of the methods/procedures, vendor certifications/audits would be a more reasonable approach to assuring safety and quality instead of a full round of analysis, especially since you can not test for every single contaminate possible It is also possible to have validated procedures that would test for one or two ingredients in a finished product, consisting of 10-15 ingredients that could be used to confirm the identity, purity, strength, potency, composition, and quality of the finished product without testing for everything. Again this is procedural based instead of testing based.

In seems that the way the posed regulations are stated that a company could have really no procedures in place and just use the testing as the means to approve or reject finished products This seems to be contractive of the intent of the GMPs.

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Under the proposed regulations, raw material vendors would be required to follow the same regulations as manufactures. They would need to have and follow GMP procedures. They would have to have supporting documentation for all batches and all analysis performed. They would also be held to the same GMP standards as we the manufacturer would be Therefore it does not make sense that if a vendor was to be certified, audited, and approved by us to have GMP procedures in place, then why would we not be able to use their analysis results as confirmation that the raw material had the correct identity, purity, strength, potency, composition, and quality. I would think this would be totally acceptable if during the audit a vender's analysis documentation and procedures were to be confirmed against outside testing We do agree that some analysis may be required on each lot received to confirm some of the Certificate of Analysis results- such as identity. However, full analysis would not seem to increase the quality or the safety of the raw materials received. Under these proposed regulations it would also seem that if a Certificate of Analysis could not be used then a vendor supplied expiration date or storage conditions would not mean anything and that each manufacturing would need to do their own stability testing on all their raw materials. We feel this goes against the general premise of GMPs, which are procedurally based and driven

Under 21 CFR 211 84 (d) (2) drug manufactures may use a Certificate of Analysis as long as they confirm the reliability of the supplier's analysis results and they perform one test to confirm the identity of the material. This seems to be more reasonable then the proposed testing requirements that 21 CFR 111 proposes and this is what we propose that you change the regulations to

**5 log reduction sanitation scheme**

It appears that FDA may have adopted the AOAC and/or EPA standards for the evaluation of sanitation methods. What standards are acceptable are unfortunately not made clear in the definition of *"sanitize"* in the proposed regulations The ambiguous wording leaves room for the interpretation that FDA actually expects a 5 log reduction of representative disease microorganisms, regardless of the condition of the equipment prior to sanitizing Clearly the 5 log reduction standard as adopted by the AOAC is intended to demonstrate the efficacy of a given disinfectant method, starting from a clearly established microbial population. Using the incomplete definition in the proposed regulations, "sanitize" can be interpreted as an unattainable level of sterility, or as a meaningless reduction in contamination from a level that is "astoundingly dirty" to a level that is 99 999 percent less dirty (leaving it only "very dirty"). This definition needs clarification If it is the intention of FDA to adopt the AOAC methods for validation of sanitation methods, that intent should be specified.