ATTACHMENT 2

Suggestions with Respect to 513e Petition of Tissue Adhesives for Soft Tissue Approximation, William D. Spotnitz, M.D., Professor of Surgery and Director of The Surgical Therapeutic Advancement Center, University of Virginia Health System

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Closure Medical Corporation
5250 Greens Dairy Road
Raleigh, NC 27616

1) Reclassification Effects on Regulation of Cyanoacrylates

The use of tissue adhesives for skin closure is a relatively new clinical application which has been characterized by FDA clinical trials of two successfully approved products, Dermabond and Indermil. Thus, experience with these types of materials with respect to rigorously performed randomized clinical trials remains small. Allowing for reclassification of these types of devices from Class III to Class II will result in a lack of additional clinical carefully controlled studies providing knowledge with respect to the safe and effective use of these types of products.

The literature with respect to use of these materials for skin approximation still suggests controversies over the proper clinical settings and application methods of even the presently approved materials. Wound dehiscence remains a concern depending upon the methods of cyanoacrylate application. These controversies can only be resolved for the benefit of patients by continuing to maintain rigorous product standards and appropriate clinical trials. Class III regulation maintains these requirements and is desirable until a sufficient body of knowledge is accumulated to document the safe and effective use of cyanoacrylates in the new setting of wound closure.

2) Reclassification Effects on Regulation of Other Tissue Adhesives

The reclassification plan for tissue adhesives from Class III to Class II could cause significant deleterious effects for regulation of the entire field of tissue adhesives and not just for cyanaocrylates being employed for superficial skin closure. If these changes effect the regulation of all new tissue adhesives, it means that tissue adhesives developed for longer term internal use as opposed to skin closure with chemical formulas including and not including cyanoacrylate chemistry could now be considered Class II devices. This is concerning as all other FDA approved technologies for tissue adhesive use in addition to cyanoacrylates, specifically fibrin sealant, polyethylene glycol (PEG) polymers , and albumin cross-linked with glutaraldehyde required full PMA qualification. There have been safety issues with these types of materials that have not been evident until human testing was conducted in depth. These include rash, anaphylaxis, and death from aprotinin in Tisseel fibrin sealant, trends toward increased infection rates in Focalseal PEG polymer, and nerve injury associated with the use of Bioglue albumin

cross-linked with glutaraldehyde. Thus, to reduce the approval process from Class III to Class II for all tissue adhesives which are frequently used for internal application in addition to external bonding may be imprudent and premature. These materials should continue to undergo extensive human clinical trials in order to clearly define unanticipated dangers and best methods of use.

3) Value of Continued Rigorous Cyanoacrylate Clinical Evaluation

Because widespread clinical use of cyanoacrylates remains a new and recent area of surgical use, the accumulation of additional data for safe and effective employment remains important.

There are remaining clinical questions about the appropriate and most efficacious uses of these materials. The specific clinical settings as well as the methods of application are open to debate by even the most experienced clinicians. These controversies still need resolution and can be best addressed by the performance of additional rigorously controlled human clinical trials. Animal models are not capable of simulating all clinical settings in which these materials will be used.

The best methods of employing these agents in the human clinical setting also remains incompletely resolved. Pairing the cyanoacrylate with additional sutures depends on factors which need to be evaluated in humans. These factors include:

- Depth of the wound
- Age of the wound
- Age of the patient
- Thickness of the wound
- Skin strength and fragility
- Sub-dermal serous, lymphatic, or bloody fluid accumulations
- Soft tissue conditions including adipose content and edema

In addition, the use of cyanoacrylates in the setting of topical dermal application has also been associated with unpleasant sensations of burning or discomfort in a minority of patients. These effects can only continue to be evaluated and minimized using human clinical trials. Because a major advantage of these agents is avoidance of pain associated with dermal suture placement and removal, discomfort associated with cyanocrylate use is not an insignificant issue and still needs further evaluation.

4) Summary of Clinical Opinion

Thus, clinical concerns about reclassification of cyanoacrylates can be allocated to specific areas. First, it remains important to extend knowledge in the use of cyanoacrylates in the human setting which cannot be adequately simulated in animal models. Methods of safe wound approximation and wound closure can benefit patients from further definition. Second, the field of tissue adhesives is still a cutting edge new area which will benefit from rigorous controlled clinical trials for all new agents with or

without cyanoacrylate chemistry. This remains particularly important for those tissue adhesives planned for internal surgical use.

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