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Food and Drug Administration
5630 Fishers Lane
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Rockville, Maryland 20852

August 10, 2006

RE: Docket Number 2006P-0071: Closure Medical Letter of August 9, 2006

The documents included in Attachment 1 of Closure Medical's letter to docket number 2006P-0071 dated August 9, 2006 are marked "confidential" on the bottom of each page. This was an administrative oversight. The documents provided in Attachment 1 are intended for public dissemination.

My apologies for the confusion.

Sincerely,

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ATTACHMENT 1

Discussions of 513(e) Petition for Reclassification of Tissue Adhesives for Soft Tissue Approximation, Anthony A. Parker, Ph. D., Principal Scientist, A.A. Parker Consulting and Product Development

Chemical and Polymer Manufacturing Discussions Pertinent to the FDA Petition for Reclassification of Cyanoacrylate Soft Tissue Adhesives, Joseph Marcinko, Ph. D., Principal Scientist and President, Polymer Synergies

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July 28, 2006

Discussions of 513e Petition for Reclassification of Tissue Adhesives for Soft Tissue Approximation

Submitted To:
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Introduction

As of May 2002, only two cyanoacrylate-based soft tissue adhesives have been approved for use by the FDA, both of which are regulated as Class III PMA devices, which means that they have been subjected to controlled clinical evaluations, to in-depth scientific reviews of product chemistry and manufacturing processes, and to pre-approval inspections of manufacturing facilities. Moreover, because of their classification as Class III PMA devices, all manufacturing changes in these products must be reported to the FDA.

From strictly a chemical mechanistic standpoint, the regulatory protection provided by the Class III classification is entirely appropriate and necessary to insure the reliability and efficacy of cyanoacrylate tissue adhesives. The chemistry of these adhesives, like that of other thermosetting addition-polymer systems, is tightly orchestrated by the presence or absence of minor compositional components, whose chemical structures and concentrations can inadvertently vary depending on the commercial source of each and every formulation ingredient. Hence, the shelf life and efficacy of these systems (i.e., the heat of reaction, green strength, cure rate, shear strength, tensile strength, peel strength, burst strength, etc.) can be easily affected by seemingly minor manufacturing changes (i.e., even a change in the commercial source of a raw material can sometimes lead to unpredictable consequences). Thus, it would be inappropriate to reclassify these systems as Class II devices, mainly because Class II 510k devices are minimally regulated after initial market clearance (i.e., there would be no obligation to report certain post-market manufacturing changes, such as a change in the commercial supplier of a raw material, even though such a change could affect both shelf-life and efficacy).

In general, any compositional change that affects the rate of polymerization and/or the rate of chain termination can have a dramatic impact on the physical properties of thermosetting formulations – both during the building of green strength, and after the cure reaction is complete. When a thermosetting formulation is initially designed, the formulator may add known concentrations and types of initiators and inhibitors to control the overall rate of polymerization, and the shelf-life of the product. The concentrations of these additives are usually tightly

controlled to achieve optimum product performance. In addition, the formulator will specify other key ingredients (i.e., monomers), several of which will already contain inhibitors that have been added by suppliers. The presence of these additional inhibitors (together with derivatives that have formed as a result of the supplier's processes) will also contribute to the overall observed rate of polymerization of the formulator's final formulation. Thus, any variance in the supplier's additives will have a direct impact on the efficacy of the final formula.

Compositional changes can happen by design, but more often than not, they occur when a formulator sources a key ingredient from a new supplier, or when he/she fails to know what attributes need to be specified from existing suppliers. For example, when sourced from different suppliers, a key monomer ingredient might contain different levels and types of trace additives (compounds that are purposely added such as inhibitors, stabilizers, etc.), trace impurities (i.e., contaminates whose presence may or may not be known, including cross-contaminates from prior manufacturing campaigns, from shipping, from storage, etc.), and chemically transformed trace additives (i.e., trace compounds such as inhibitors of known chemical composition that undergo chemical transformations during the lifespan of the monomer). Compositional variations of these types can affect the cure chemistry and hence the final physical properties of any addition-polymer system.

There are many compositional and manufacturing variables that are known to influence the cure rate, the shelf-life, and the efficacy of cyanoacrylate tissue adhesives. However, the following discussions will focus on the potential deleterious effects of a specific type of manufacturing change – the sourcing of a nominally "identical" commercial monomer ingredient from an alternative supplier. This type of a manufacturing change would not necessarily have to be reported under Class II regulations (beyond the initial market clearance). However, this seemingly innocuous change could lead to uncontrolled variations in the compositions and levels of trace impurities, trace additives, and chemically transformed trace additives, all of which could have a significant impact on physical properties, cure rates, shelf-life, and efficacy.

The polymer applications literature is full of examples of curable thermosetting systems whose end-use properties can be easily influenced by minor compositional variations. A few examples include acrylates for coating and ophthalmic lens applications, as well as cyanaoacrylates for tissue adhesive applications. In each of these examples, a seemingly simple variation in a supplier's manufacturing procedures (a variation that may be unknown to the formulator, or a variation that may be unrecognized as important by all parties) can have a dramatic impact on the final physical properties of the formulator's finished product. The following discussions will make use of these examples to illustrate both the chemistry and the importance of variations that can arise as a result of manufacturer-to manufacturer differences in trace impurities, trace additives, and chemically transformed trace additives.

Trace impurities: the potential effects of cross-contamination

Samples of monomer from two different suppliers may sometimes appear to be nominally identical, but they may actually contain different types and levels of cross-contaminates. The nature of the cross-contaminates will be unique to each manufacturer, and their identities will

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depend on specific manufacturing procedures, and on the nature of the other monomer products that are produced at the manufacturer's facility. Therefore, if left unchecked, the substitution of one monomer source for another could lead to differences in cross-contaminates, which in turn could affect polymerization rates and physical properties in end-use formulations.

In one example, the rate of polymerization and the ultimate physical properties of a free-radically cured polyurethane acrylate coating were observed to vary when the coating composition was exposed to certain types of acrylic monomers [1]. Specifically, the exposure of the uncured coating formula (the formula was predominately comprised of aliphatic acrylic esters) to an aromatic acrylic ester was reported to decrease the rate of polymerization. The slower rate of polymerization was used to induce differential shrinkage along the z-axis of the coating, which in turn affected the specular reflection characteristics (gloss) of the finished product. Although this phenomenon was controlled for the benefit of achieving a desired property (i.e., controlled gloss was one object of the invention), it is clear that if left uncontrolled, the presence or absence of small amounts of such monomers could potentially have deleterious effects on the end-use properties.

In another example, the rate of polymerization and the ultimate physical properties of a free radically cured ophthalmic lens formulation (the formula was also predominately comprised of aliphatic acrylic esters) were controlled via the incorporation of aromatic acrylic monomers [2]. The inventors in this application recognized that the polymerization temperature was critical to the achievement of desirable end-use properties, and that the polymerization temperature was affected by the degree of exotherm, which scaled with the rate of the reaction. They found that they could slow the rate of polymerization by incorporating an aromatic acrylic monomer into their formulation. The monomers that were used in this patent were all obtained from the same supplier. As in the prior example, this phenomenon was controlled for the benefit of achieving a desired property. However, it is clear that if left uncontrolled, the presence or absence of small amounts of such monomers could potentially have deleterious effects on end-use properties.

If the inventors in these applications had no knowledge of the effects of aromatic monomers on their cure rates, the potential for product variability would have been high, particularly if cross contamination were to occur either in the supplier's location, or in the end-user's location. Cross-contamination can occur as a result of transfer procedures that are used when a manufacturer transfers materials (via pipes, hoses, pumps, etc.) from its inventory to a reactor, or from a reactor to storage vessels (i.e., totes, drums, truck, etc.). When a company manufactures multiple varieties of monomers (as some do), its reactors are often used to process multiple batches of different products. The length of a production campaign (the number of batches) for any one product will depend on commercial demand. If demand is high for a certain monomer, it may be economically justifiable to dedicate a reactor to that product. In such a case, the potential for cross contamination would be minimized. However, in many cases, a single reactor is often used to produce multiple products, in which case the potential for cross-contamination arises both before and after each production changeover.

In some cases, products are scheduled for sequential campaigns based on their mutual compatibility with one another. This is done to minimize the amount of lost production time that

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would be required for extensive clean-ups during changeovers. If the monomer is intended to be sold as a "general purpose" monomer, a certain degree of cross-contamination may be tolerated for the sake of economics. In many cases, the formulators (those who purchase the monomers) may unknowingly end up formulating their products with monomers that contain varying levels and types of cross-contaminates.

In cases where the formulator desires a specific rate of polymerization (i.e., for a coating or adhesive application), he or she may adjust the initiator or inhibitor levels accordingly to compensate not only for the reaction chemistry of the nominal monomer, but for the chemistry that is unknowingly imparted by the cross contaminate (i.e., a cross-contaminating monomer could have a reactivity ratio that slows the overall observed rate of polymerization, or it could serve as a chain transfer agent which changes the final molecular weight). Hence, unbeknownst to the formulator, he or she may end up adjusting the formula to compensate for the presence or absence of cross-contaminates, which may or may not be present in the next batch of monomer product that is procured by his or her company. Consequently, if no formulation changes are made to compensate for these differences (i.e., one might have to change the initiator level), then the resulting performance of the polymer system might be drastically altered.

Trace additives: components that are intentionally added to industrial grade monomers

Unlike cross contaminates, certain trace additives such as inhibitors and stabilizers are intentionally added by the manufacturer. These compounds are usually added both during the production of the monomer (pre-addition for in-process stability), and after the manufacturing process (post-addition for shelf stability).

"Inhibitors" such as quinones are typically added during the manufacture of acrylic ester monomers so as to prevent premature radical polymerization reactions between the acrylic moieties (acrylic esters are often formed via a thermally induced esterification reaction between an acrylic acid compound and an alcohol). During this process, the chemical composition of an inhibitor can actually be transformed via a series of side reactions either with oxygen, with acrylic moieties, or with other sources of free radicals that may be present (this will be discussed in the next section).

The chemical compositions and reactivities of transformed inhibitor species are usually not known, but they generally retain their ability to influence reaction rates. Given that different manufacturers will employ different conditions during the production of a monomer (i.e., different reaction temperatures, different reaction times, different atmospheric conditions, different head space volumes, etc.), the chemical nature of these transformed inhibitor species will inevitably vary from manufacturer to manufacturer – even when the nominal composition of each manufacturer's primary monomer is the same. Thus, a nominally identical monomer that is obtained from two different suppliers may produce finished formulations with completely different rates of polymerization. This difference would likely lead to unanticipated variations in the efficacy of a formulated product.

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Like the pre-addition inhibitors, post-addition inhibitors are also sometimes added to guard against similar types of unwanted side reactions. These compounds are usually added for the purpose of enhancing the shelf life of a monomer, or for controlling an end-user's induction period (if the end user has specified this). The chemical transformation of these additives will occur over longer periods of time, typically throughout the storage history of the monomer product. The chemical nature and concentrations of these transformed species will depend on the storage conditions (i.e., storage time, storage temperature, atmospheric exposure to oxygen, atmospheric exposure to moisture, chemical nature of the storage container, shipping conditions, etc.). Given that storage histories can vary from manufacturer to manufacturer, and from facility to facility, it follows that even a simple change in storage conditions can result in a finished formulation with altered cure characteristics.

Although it is possible in theory to specify the compositions and concentrations of post-addition inhibitors (assuming that one is skilled enough to know which additives need to be specified, and which analytical procedures would be required to insure that their concentrations fall within specified limits), it is usually difficult to specify the chemical nature of pre-addition inhibitors, primarily because this knowledge is often considered to be proprietary and specific to a given manufacturer's process. Moreover, it would be nearly impossible to specify the chemical compositions of transformed additives, mainly because the in-process chemical transformations will inevitably vary from manufacturer to manufacturer.

Of equal importance, the impact of a transformed trace-additive on cure chemistry may go completely unrecognized by both the monomer manufacturer and by the end user. Moreover, the implementation of analytical protocols for the detection of pre-addition and post-addition trace additives may not be sufficient to facilitate the detection of their chemically transformed counterparts, primarily because the identities and spectroscopic characteristics of these species are typically unknown and highly variable. To further complicate the matter, trace additives from a supplier's monomer may also be prone to undergo chemical transformations after they have been incorporated into a finished adhesive formulation. This could also alter the cure characteristics of the adhesive in potentially unpredictable ways. Thus, to reiterate, a nominally identical ingredient from two different commercial suppliers may actually contain different types and levels of trace additives and transformed trace-additives, any or all of which could influence the curing chemistry, and hence the shelf-life and efficacy of the entire formulation.

Inhibitor reaction chemistry

As noted in the prior section, inhibitors are added to acrylic and vinyl monomers to prevent premature polymerization reactions during manufacture and storage [3]. Many inhibitors perform this function by reacting with oxygen and carbon-centered radicals to form stable free radical intermediates (their stability is attributed to resonance stabilization, and to steric hindrance from bulky aromatic substituents – depending on structure) [3,4]. In turn, these intermediates are not capable of initiating free radical polymerizations by themselves. However, inhibitors can influence the course of polymerization reactions, particularly at the onset where they can react with initiators and with growing chain ends to inhibit chain growth.

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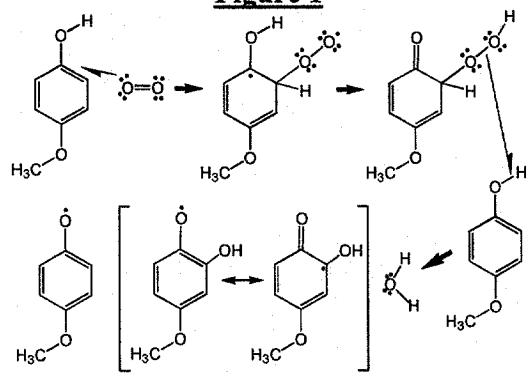
Independent of whether inhibitors are knowingly used (by design), or unknowingly used (by default), their presence or absence can influence the physical properties of resultant polymers. Depending on the nature of the polymerization reaction (i.e., the type and level of initiator, the presence or absence of oxygen, the source of initiation, etc.), the presence or absence of inhibitors can affect molecular weight distributions, cross-link densities, shrinkage, gloss, color, strength, modulus, impact resistance, and even adhesion.

Inhibitors for acrylic monomers are typically chosen from a broad class of hydroxyaromatic compounds [3], including compounds like hydroquinone (HQ), 4-methoxyphenol (MEHQ), butylated hydroxytoluene (BHT), di-tertbutylhydroquinone, tertbutylhydroquinone, and the like. In the presence of oxidizing agents (i.e., oxygen, carbon-centered and oxygen-centered free radicals, certain metal ions, etc.), these compounds can be reversibly oxidized to yield quinones [3,4,5,6,7].

Figure 1 illustrates a potential reaction pathway involving 2 equivalents of MEHQ and atmospheric oxygen to yield two types of resonance stabilized, radical intermediates.

Figure 1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hydroxyaromatic radical and a fairly stable hydroperoxide [3]. Note that in the later case, the hydroxyaromatic radical can go on to react in other ways, including: 1) through coupling reactions with monomeric, dimeric, oligomeric or polymeric radicals to yield ethers (via reaction with the oxygen centered radical); 2) through coupling reactions with other similar radicals to yield quinones (via reaction with the aromatic ring); or 3) through methyl hydrogen abstraction and disproportionation with growing radical chains [3].

Quinones can also interact with hydroquinones to form stable charge-transfer complexes [7]. Thus, it is sometimes important to control the molar ratio of the two species. In addition, quinones and hydroquinones can participate in redox reactions with certain metals. Thus, the chemical nature of a metal transfer container is also an important consideration when dealing with certain types of monomers.

From these discussions, it should be apparent that the transformation products of inhibitors are affected by a variety of process and storage-related variables. It is therefore expected that the composition of a nominally identical monomer from two different commercial suppliers may actually contain different types and levels of trace additives and transformed trace-additives. These differences can potentially impact the curing chemistry, the shelf-life, and the efficacy of comparative formulations that contains them.

The Potential Effects of Trace Additives (and Transformed Trace Additives) on Cyanoacrylate Chemistry

Like other types of acrylic based curing systems, the end-use performance characteristics of cyanoacrylate soft tissue adhesives are potentially vulnerable to minor variations in composition [9]. As noted earlier, a simple supplier substitution for a key monomer ingredient could result in an unanticipated change in the polymerization rate (i.e., due to differences in the types and concentrations of cross contaminates, trace additives, and chemically transformed trace additives).

As with other types of acrylates, the cure characteristics of cyanoacrylates are susceptible to variations in ingredients that affect free radical reaction chemistry. However, in addition, the cure chemistry of cyanoacrylates is also susceptible to variations in ingredients that affect anionic polymerizations (cyanoacrylates will cure by both free radical and anionic polymerization mechanisms).

As noted by Azevedo [10], cyanoacrylates are purposely formulated with two principal groups of stabilizers: those that prevent free radical polymerization, and those that inhibit anionic polymerization. According to Wojciak [11], several protic and/or Lewis acids are useful as anionic polymerization inhibitors. Wojciak also noted that certain impurities (the nature of the impurities was not specified) should be avoided since they can catalyze the hydrolysis of cyanoacrylate esters to yield carboxylic acids, which in turn can inhibit polymerization and impact the physical properties of the cured adhesive. Like Azevedo, Wojciak also noted that cyanoacrylates are also formulated with free radical scavengers of the phenolic type such as quinone, hydroquinone, t-butyl catechol, p-methoxy-phenol, and others. Importantly, the

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preferred inhibitor of Wojciak was hydroquinone at a level of about 0.02% to about 1.0% by weight.

It is interesting to note that both inventors, although skilled in the art, have made a distinction between compounds that are capable of imparting free radical stabilizing functions, and those that are capable of imparting anionic stabilizing functions. This distinction implies that those skilled in the art of formulating cyanoacrylate adhesives may not necessarily realize that certain free radical stabilizers can also function as protic acids. In fact, hydroxyaromatic compounds of the type specified by Wojciak (hydroquinone is his case) are actually weak acids [7]. Furthermore, the pKa's (and hence reactivity) of these types of compounds will vary depending upon the nature of the chemical transformations that the compounds undergo when they are incorporated into the monomers (i.e., the reactivity of a hydroxyaromatic compound can be altered by aromatic substitution).

Thus, aside from the potential variability that is possible via free-radical reaction pathways (as was discussed in prior sections), the polymerization rates of cyanoacrylates adhesives, by virtue of their ability to polymerize anionically, are susceptible to variations in the types and concentrations of protic acids that are incorporated into the adhesive formulation. Ironically, certain free radical inhibitors can also serve as protic acids, and as such, they have the potential to perform additional chemistry in cyanoacrylate systems (the acidities of these compounds will scale with their anionic inhibition potentials). Furthermore, it follows that the relative acidities of these compounds will depend on their chemical structures (i.e., both the structures of trace additives, as well as the structures of their transformed counterparts).

The following hypothetical example illustrates how the unregulated presence of these structures can have an unanticipated impact on end-use performance. Let's assume that Company A's monomer was stored in a warehouse for six months before it was procured by a formulator. Furthermore, during the six-month storage period, a fraction of the hydroquinone inhibitor molecules have reacted with atmospheric oxygen to yield quinones. By the time the formulator receives the monomer it will contain some ratio of the two species – call it x. Next, the formulator prepares his adhesive formula with Company A's monomer and seeks FDA approval. Once it is approved as a Class II device, the formulator sells a large amount of adhesive and he now needs to produce a new batch. Company A no longer makes the monomer, so the formulator procures the same monomer from Company B. Company B uses the same procedures and the same inhibitors as Company A (this is not likely, but we'll assume it is true for this example). The formulator needs to make adhesive quickly, so he requests immediate shipment. Company B ships the product within 2 days of its manufacture. Consequently, and unbeknownst to either party, there is a much higher level of hydroquinone in this monomer than in the monomer from Company B – not because more was added, but because less has been oxidized to yield quinone. Remember, a higher level of hydroquinone will equate to a change in the protic acid concentration, because hydroquinone is itself a weak protic acid. The formulator now makes the adhesive, packages it, and ships it to distributors. He does not report this change to the FDA, because according to Class II regulations, there has been no reportable change. Next, a customer purchases a quantity of the new batch, and then discovers that the adhesive does not work – it does not cure quickly enough, it has poor green strength, and it cracks before

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it sets. This was not a problem when they first tried this formulator's adhesive a few months earlier…

Conclusions

The physical properties of cyanoacrylate polymers as well as other polymers that cure through addition polymerization mechanisms (i.e., free radical, radical-cation, and anionic polymerization mechanisms) are generally susceptible to seemingly minor, yet inordinately complex, compositional variations that can arise (either by design or by chance) from even the simplest of manufacturing changes (i.e., from a change in the source of a raw material, or from a change in a manufacturing process procedure, etc.). For example, a simple change in the supplier of a key monomer ingredient can lead to a cascade of unforeseen chemical compositional changes, any one of which could impact the rate of polymerization, the shelf-life, and the end-use properties (efficacy) of thermosetting addition polymer systems.

Each supplier of a nominally identical product will have its own unique set of manufacturing procedures, raw material sources, additives, storage conditions, and shipping conditions. In turn, each of these factors has the potential to influence the chemical structures and concentrations of minor compositional components, including trace additives (i.e., inhibitors, stabilizers, etc.), trace impurities (i.e., contaminates from prior manufacturing campaigns, from shipping, from storage, etc.), and transformed trace additives. The concentrations and chemical identities of these minor components will inevitably vary from manufacturer to manufacturer, even when the primary components are nominally the same. Moreover, even if a formulator were able to specify the tolerable limits and structures of specific trace additives, it is unlikely that he/she would ever have control over the compositions of chemically transformed additives, mainly because the nature of these species will be specific to both the monomer's process history, and to the manufacturer's synthetic procedures, which are usually proprietary.

In addition, for the case of cyanoacrylate tissue adhesives, no quantifiable link has been established between cure rates, physical properties, and clinical performance. No standardized methods are currently available to measure biomechanical strength in ways that correlate directly to clinical performance. No standard methods exist for directly measuring tissue adherence, durability, thermal skin reaction, or the affect of the adhesive film on underlying microbial growth. The methods listed in the FDA guidance document for cyanoacrylate skin adhesives (such as those for conducting overlap shear strength, flat-wise tensile strength, peel strength, and burst strength) all measure mechanical strength in ways that are not directly indicative of clinical performance. Thus, it follows that the windows of tolerance for cure rate and degree cure (both of which affect mechanical properties) have not been standardized and linked to clinical performance. Consequently, the tolerance for compositional variations of the types discussed in this report (i.e., variations that affect cure rates) also remains unknown. Hence, it follows that the types of manufacturing changes that have been discussed in this report as well as all analogous manufacturing changes should continue to be scrutinized via Class III regulations, because reclassification to Class II would potentially lead to unacceptable variations in product efficacy.

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In some end-use applications, the windows of tolerance for physical property and cure rate variations may be relatively high. In such cases, variations that are induced by minor manufacturing changes may be insignificant. However, in many applications (i.e., cyanoacrylate adhesives for soft tissue applications), the windows of tolerance for cure rate and physical property variations are either small or unknown. In these cases, it is critical to scrutinize all manufacturing changes before they are implemented.

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This report is submitted in confidence to Closure Medical Corporation by

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Chemical and Polymer Manufacturing Discussions Pertinent to the FDA Petition for Reclassification of Cyanoacrylate Soft Tissue Adhesives

Submitted To:

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Introduction:
The following discussion relates to issues associated with the manufacturing of cyanoacrylate based, soft tissue adhesives and the petition to the FDA to reclassify these materials by from Class III to Class II devices. Technical concerns about manufacturing controls and impurities are presented with respect to their influence on the polymerization of cyanoacrylate polymers, their physical properties, durability, degradation, and potential toxilogical concerns. Comparisons are made to polymethyl methacrylate (PMMA) bone cements, which have recently been reclassified from Class III to Class II devices.

The Importance of Manufacturing Controls:
The importance of "strict" manufacturing controls in the preparation of cyanoacrylate Class III medical adhesives are necessary in part because of the inherent issues with the manufacturing of polymers in general. Specifically, a polymer is not a single product when manufactured; rather it is a family or distribution of heterogeneous products. The structurally different variations arising may include branching differences, segment or oligomer ordering differences, molecular weight and polydispersity differences, and polymer chain packing differences arising from the variations in the molecular architecture. These variations can also lead to differences in physical properties, differences in durability, differences in stability, and differences in the degradation of these materials.

The distribution of products can arise, in part, from the "purity" of the starting monomers, the type and ratio of initiator to monomer, the processing or manufacturing of the monomers and initiators, the handling of the monomers and initiators resulting in the transfer of impurities, storage of the monomers and initiators, and the addition of additives for the stability of those monomers. Numerous, chemical and structural variations can be obtained in the polymerization of cyanoacrylate monomers caused by the presence of impurities and trace additives (either known of unknown) of different types and concentrations. These variations arise because physicochemical differences can affect solubility, rates of reactivity, and stereoselectivity or chemical susceptibility of the reactants.

In addition to the reactant chemistry purity, the reaction conditions can affect the chemical microstructure of the distribution of products obtained in a polymerization. For example, it is well known that many polymers that polymerize via a free radical mechanism are affected by reaction temperature (like methyl methacrylate (MMA) used in bone cements). Temperature differences will not only affect the rate of polymerization of methyl methacrylate, but also the molecular weight averages and polydispersities of the resultant polymer acrylates produced. Strict control of reaction conditions is also necessary since the rate of polymerization can affect the amount of residual monomer in the final product. Temperature can also affect the stabilizers or inhibitors added to "protect" or enhance shelf life of these materials. In the case of cyanoacrylate tissue adhesives, temperature is very important because cyanoacrylates polymerize via free radical and anionic cure mechanisms. Therefore, the resultant distribution of products, as a function of temperature, is even more complicated than that obtained for MMA.

The concern over residual monomer is illustrated in studies discussed by Pohler and others in which the adsorption of residual monomer into the circulation during veterinary applications of PMMA bone adhesives have been implicated in causing a precipitous fall in blood pressure, and occasional fatalities.[1,2] When these type polymers are used in denture applications, dissolved monomer in combination with traumatization of the oral mucosa caused by ill fitting dentures has been implicated in the growth of tumors in humans.[3] As such, the control of MMA polymerization conditions is very important for controlling the rate and degree of polymerization and for controlling the amount of residual monomer. Analogously, it should be apparent that these same issues are of concern when it comes to the manufacturing and control of cyanoacrylate soft tissue adhesives.

"Residual monomer" is the amount of monomer that remains unreacted due to incomplete conversion during the curing of the adhesive. Cervantes, et al. showed that the amount of residual monomer in acrylic bone cements could be in the range of 1.0 % to 4.8 % depending on the acidity or basicity of the co-monomers used. [4] It follows that changes in the acid/base chemistry (caused by impurities and minor component additives) will have a similar affect. In fact, Vezin and Florence reported such a finding for poly (n-alkyl-cyanoacrylates). [5] It was reported that very small quantities of impurities in monomers tended to considerably reduce the final molecular weights of the resultant cyanoacrylate polymers. It was further reported that the rate of degradation of residual monomer to yield formaldehyde depends on pH.

Cervantes further showed that the presence of residual monomer could also affect the physical properties of functionalized methacrylate bone cements. The rational behind these findings is that it is known that free monomer can act as a plasticizer in bone cements.[6] For cyanoacrylate adhesives this is a concern because the adhesive and

physical properties are known to be dependent on molecular weight, as well as the n-alkyl chain length.

The specification and control of monomers, copolymers, and initiators, along with any minor component additives in a formulation is important for another reason. It is known that sterilization methods for polymeric biomaterials can cause decreases in polymer molecular weight.[7,8] As was mentioned earlier, the presence of trace impurities could dramatically affect polymerization rates and molecular architecture. It is important to recognize that impurities and minor stabilizing additives could also be affected by sterilization. This could further contribute to the complexity of the reaction product distribution and the resultant physical properties, durability, degradation, and potential toxicological properties of the resultant polymers.

Another potential area for the introduction of impurities is from cross contamination via the purification process of the monomer. Monomer purification is performed to remove inhibitors or retarders that are present to suppress the polymerization of the monomer during storage. Removal of inhibitors is usually performed by distillation or passing the monomer through a chromatographic column which separates the inhibitor from the monomer. The potential for cross contamination can occur if different sources of monomer are used which use different inhibitor and trace amounts of stabilizing chemicals. The relative solubility and affinity of the inhibitor in the column or in the distillate may be different leaving unknown quantities of these materials in the monomer. As we have discussed this could affect the reaction chemistry. Since there is no obligation to report a change in commercial supplier if cyanoacrylate tissue adhesives are reclassified as a Class II product, a manufacturer could chooses a new source of monomer that is nominally the same as the original pre-market submission. In doing so the manufacturer may unknowingly introduce chemical changes that impact reaction kinetics, physical properties, and the efficacy of the product.

Often bulk polymerizations are conducted without removing the inhibitor. This is done by increasing the amount of initiator to compensate for the inhibitors present. This is also an area of manufacturing concern because the ratio of monomer to initiator and the type of initiator can greatly affect the properties of a polymer like methyl methacrylate, as was shown by Scorah, et al. for bone cements.[9] Inhibitors are known to change with time, temperature, and environment upon storage. It is reasonable to expect that different suppliers and adhesive manufacturers will store and handle their monomers in different ways. Thus, the chemical nature of the inhibitor and the resultant polymers produced could be different. As we discussed, the differences may include different rates of polymerization, molecular weights, and the resulting molecular architecture. For cyanoacrylate tissue adhesives, this is a greater concern because the polymerization mechanism is free radical and anionic. Thus, the degree of chemical complexity and potential variability could be much greater.

Chemical Impurities from Handling and Manufacturing:
Chemical impurities can be introduced from handling or transport of monomers. They can also be introduced by chemical residues within the reaction vessel. Transfer impurities from batch-to-batch manufacturing of polymeric materials has always been of great concern to manufacturers. Each manufacturer has a product base. Some products may have dedicated reactors and some may not. In addition, production demands contribute to the utilization of reactors and reactors that once were dedicated to a specific product will be utilized for other products should the demand arise. Because only minimal amounts of impurities are necessary to create a chemical variation, it is important that impurities transferred from non-dedicated reactors be minimized. In addition, batch size is also an important factor in minimizing transfer impurities. Capacity of the reactor, head space in the reaction vessel, and agitation efficiency can contribute to impurity levels. These factors will vary with manufacturer and so if a change in supplier of raw material were enacted, variation in the type and concentration of such impurities would be inherent even though nominally the product is classified as the same. As has been discussed in the preceding paragraphs, these differences in trace impurities can have a dramatic effect on the polymer produced, its properties, and its degradation. In light of the petition to reclassify cyanoacrylate soft tissue adhesives to Class II, changes in the supplier of a commercial material would not need to be reported even though such an action could have a dramatic effect on the chemistry and efficacy of the adhesive.

To further our discussion of the sources of manufacturing impurities, reaction vessel make-up (metal or glass) and routes of synthesis can also have an affect on the polymer product distribution. In the manufacturing process raw materials are typically pumped into and out of reactors via transfer lines. Metals in the form of atoms or oxides can be adsorbed and desorbed via physical or chemical means and act as a source of impurity. Trace metal impurities can greatly influence the rate and nature of a chemical reaction. Manufacturing differences between suppliers of similar chemicals is a common source of product variability. The best way to reduce the unknown impact of this variability on cyanoacrylate tissue adhesives is by retaining he Class III designation.

Conclusions:

The petition to reclassify cyanoacrylate soft tissue adhesives from Class III to Class II materials warrants careful consideration by the FDA. In the preceding paragraphs a number of discussions were presented concerning the importance of manufacturing controls, sources of impurities, and the need to minimize and understand the influence of these impurities. A comparison of the research data and concerns associated with PMMA bone cements was made and related to the concerns the FDA needs to

considered in the manufacturing of cyanoacrylate tissue adhesives and their reclassification.

It is known to those skilled in the art that controlling impurities present in monomers and in adhesive formulations is very important. The potential of impurities and reaction conditions to affect polymerization and the resultant polymers physical, adhesive, and degradation properties should not be underestimated. This type of understanding is often the foundation for intellectual property and trade secrets. It should also be the reason the Class III designation is retained for cyanoacrylate tissue adhesives.

It is interesting to me that the FDA has allowed reclassification of PMMA bone cements to Class II, considering the factors discussed within this document. It is my opinion that the reclassification of PMMA bone cements was a mistake. It should be apparent from the discussions presented that reclassification of cyanoacrylate tissue adhesives from Class III to Class II would be a "bold," unjustifiable action, considering the degree of chemical complexity in the manufacturing of these materials and the potential for negative impact on physical, adhesive, degradation, and toxicological properties.

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