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Vice President, Health, Safety, and Environment

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August 28, 2003

Via FEDEX—821729922913

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket 77N-094I:
Response to the Proposed Amendment of the Tentative Final Monograph for
Internal Analgesic, Anti-pyretic and Anti-rheumatic Drug Products to Include
Ibuprofen 200 mg Tablets for Over-The-Counter Human Use.**

Dear Sir/Madam:

Albemarle Corporation, a major domestic producer of bulk Ibuprofen, hereby submits the following comments in response to the proposed amendment of the Tentative Final Monograph (TFM) to include ibuprofen 200 mg tablets for Over-the-Counter (OTC) human use as a generally recognized safe and effective (GRASE) analgesic/antipyretic active ingredient. The proposed rule was published in the Federal Register (FR) on August 21, 2002 and the comment period has been extended until September 2, 2003.

Albemarle agrees with the FDA's conclusion that, historically, ibuprofen 200-mg tablets have been safe and effective. However, Albemarle believes this has been due in large part to the high degree of control and oversight that the FDA and the NDA/ANDA process have provided for this product. Albemarle questions whether this safety and effectiveness can be ensured with the proposed amendment of the TFM.

The proposed amendment of the TFM would eliminate much of the oversight and control which has historically been given to this product. It would allow lower quality and untested ibuprofen to be supplied to a significant proportion of the population. Under the proposed amendment, 200-mg tablets of ibuprofen could enter the US market with virtually no regulatory review of the bulk active manufacturing process or impurity profile, leading to the potential for exposure to dangerous impurities not previously found/qualified in ibuprofen drug products. One of the foremost of these dangerous impurities, as indicated in our October 2002 comment extension request, is LEAD.

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Lead Contamination in Ibuprofen Tablets

In our October 2002 petition letter requesting an extension of the TFM comment period, we informed the FDA that our preliminary analysis indicated some 200 mg ibuprofen tablets may contain measurable amounts of lead. To confirm this preliminary analysis, we made arrangements to purchase a variety of ibuprofen tablets in the US, Europe, and India. A total of nineteen tablet samples, with a minimum of 20 to 25 tablets of an identical lot per sample, were obtained and analyzed. The results of our analysis are shown in the following table:

LEAD (Pb) Determinations in Ibuprofen APIs and Tablets

Sample Source/ Country of Origin	Ibuprofen Content	Albemarle*	WCAS**	Albemarle	WCAS	WCAS based	
		ppm Pb (based on sample tablet weight)		ppm Pb (based on contained ibuprofen weight)		µg Pb/tablet	ug Pb/ 1200mg ibuprofen
	Bulk API						
Indian API Producer A	100%	2.7	3.06	2.7	3.06	NA	3.67
Indian API Producer A	100%	2.8	2.47	2.8	2.47	NA	2.96
Albemarle API	100%	ND	ND	ND	ND	NA	ND
Albemarle API	100%	ND	ND	ND	ND	NA	ND
Albemarle API	100%	ND	ND	ND	ND	NA	ND
US API Producer B	100%	ND	ND	ND	ND	NA	ND
US API Producer B	100%	ND	ND	ND	ND	NA	ND
US API Producer B	100%	ND	ND	ND	ND	NA	ND
	Preblend						
Indian Preblend A	63%	1.2	1.44	1.90	2.29	NA	2.75
Indian Preblend A	63%	1.1	1.19	1.75	1.89	NA	2.27
US Preblend	63%	ND	ND	ND	ND	NA	ND
	Tablet						
US Generic A	200 mg	0.22	0.181	0.38	0.31	0.062	0.37
US Generic B	200 mg	0.76	0.604	1.31	1.04	0.208	1.25
US Generic C	200 mg	ND	ND	ND	ND	ND	ND
US Name Brand A	200 mg	ND	ND	ND	ND	ND	ND
US Name Brand B	200 mg		0.014		0.03	0.007	0.04
US Generic D	200 mg		ND		ND	ND	ND
US Generic E	200 mg		ND		ND	ND	ND
Indian Company A	400 mg	0.05	0.044	0.12	0.11	0.043	0.13
Indian Company A	100 mg	0.06	0.036	0.22	0.13	0.013	0.16
Indian Company B	400 mg	7.4	5.91	10.34	8.26	3.30	9.91
Indian Company B	200 mg	5.6	4.04	7.81	5.64	1.13	6.77
Indian Company C	400 mg	5.4	4.03	6.87	5.13	2.05	6.16
Czech Rep. Company A	200 mg	0.25	0.458	0.39	0.72	0.144	0.86
Czech Rep. Company A	400 mg	7.3	6.83	11.57	10.83	4.33	13.00
UK Company A	200 mg	0.063	0.082	0.14	0.18	0.037	0.22
UK Company B	400 mg	ND	0.015	ND	0.03	0.013	0.04
UK Company A	200 mg	0.045	0.035	0.10	0.08	0.016	0.10
UK Company A	200 mg	0.04	ND	0.11	ND	ND	ND
UK Company C	400 mg	ND	ND	ND	ND	ND	ND

ND=Non-detectable

NA=Not applicable

* Analyzed in-house by Zeeman Graphite Furnace Atomic Absorption Spectrophotometry. LOD is 0.03 ppm lead

** Analyzed by West Coast Analytical Services using ICPMS. LOD is 0.01 ppm lead.

As part of our analysis, the ibuprofen tablets were ashed and analyzed for lead using Zeeman Graphite Furnace Atomic Absorption Spectrophotometry with a limit of detection (LOD) of 0.03 ppm (proprietary method enclosed as Attachment I). However, in order to demonstrate that our testing and analytical method were unbiased, duplicate samples were also sent to a nationally recognized, independent testing laboratory, West Coast Analytical Service, Inc. ("WCAS"), Santa Fe Springs, CA, for lead determinations using an isotope dilution (ID) ICPMS method (LOD 0.01 ppm). The method (Attachment II) used by WCAS was specifically developed and validated to test for lead in nutritional supplements and antacids under California Proposition 65. Although this method was not specifically developed to detect lead in ibuprofen, the results reported by WCAS are very similar to the results generated by Albemarle.

Analytical data from both laboratories indicated that unusually high levels of lead were found in all five tablet samples from India and two from the Czech Republic. Lead levels detected in the UK samples were very low; comparable to or lower than the levels found in some US private store brands known to be formulated with Indian bulk ibuprofen. We can only believe that the stringent regulatory oversight exercised by the UK Medicine Control Agency (MCA) and the FDA have helped to keep higher lead contaminated ibuprofen from being shipped and used in the UK and the US. The highest lead level (7 ppm) was found in a sample purchased in the Czech Republic. This level is equivalent to about 11 ppm based on ibuprofen-contained weight. With the OTC 200 mg tablet samples purchased in the US, some private store brands were also found to contain lead, but in most instances, the levels were significantly lower than those found in the Indian or the Czech samples. Lead was not detected in any of the western-produced bulk ibuprofen samples, nor was lead detected in ibuprofen tablets formulated with western-sourced bulk ibuprofen. However, lead was detected in all four Indian bulk ibuprofen samples. Despite this limited sampling, it is reasonable to conclude the lead contaminant found in ibuprofen tablets is most likely coming from the imported ibuprofen API and not the excipients, since none of the US tablets known to be formulated with western-produced bulk ibuprofen were found to contain detectable levels of lead.

Lead Toxicity

The FDA has historically been concerned about lead toxicity, realizing that "some risk exists with any level of lead exposure."¹ Toxicity of lead is well known. Over the past 25 years, the FDA, CPSC and EPA have all made concerted efforts to minimize lead exposures to humans, both adults and children.

Lead affects practically all systems within the body. Lead accumulates in the body so that even small amounts can contribute to the overall level of lead in blood and to the subsequent risk of adverse health effects. The primary targets for the toxic effects of lead include the central and peripheral nervous systems and kidneys. Lead disrupts the functioning of almost every brain neurotransmitter by blocking calcium binding sites. Calcium is essential to nerve impulse transmission, heart activity and blood clotting. When these calcium sites are blocked by lead, cellular processes are adversely affected. A health risk summary of lead is enclosed as Attachment III.

¹ "Danger of Lead Still Linger", U.S. Food and Drug Administration, FDA Consumer, January-February 1998.

Lead exposure is an actual, rather than a potential, problem in humans. Lead usage has been highly regulated by all regulatory agencies in the US. Lead is no longer allowed in gasoline, house paints, and food/beverage containers. There are lead standards for drinking water and ceramic wares. Even the use of lead foil wraps on wine bottles was banned in 1996 by FDA due to lead residues left on the rims of wine bottles. In general, regulatory agencies have taken steps to eliminate all preventable exposures to lead to the most practical extent. As further evidence of FDA's overall efforts to reduce lead exposure from sources under its jurisdiction, FDA listed lead as poisonous and deleterious under 21 CFR 189 (Substances Prohibited from Use in Human Food) by banning the use of lead in solder from can seams. Attachment IV provides a summary of regulatory actions taken by different agencies to minimize potential lead exposures via either oral or inhalation routes of exposures. All of these suggest that FDA needs to turn its regulatory focus to drugs as a source of avoidable lead exposure.

In some cases, public exposure to lead is unavoidable. For instance, in the case of water sourced from public water distribution systems, the EPA recognizes a drinking water standard of 15 ppb allowable maximum concentration level (MCL) for lead. This reflects the reality that lead has historically been used in public water distribution infrastructures and some leaching of lead into drinking water is inevitable. However, in 1994, FDA, recognizing EPA's maximum concentration level goal (MCLG) for lead as being 0 ppb and lead leaching from public water distribution system and residential plumbing is not a factor in bottled water, adopted an allowable limit of 5 ppb in bottled drinking water (59 FR 26933). This action is consistent with the FDA's goal of reducing consumers' exposure to lead to the extent practicable.

The presence of lead in 200 mg ibuprofen tablets is not unavoidable (i.e., lead is not a necessary by-product of ibuprofen production). This is demonstrated by the fact that ibuprofen products are available with no detectable lead levels (LOD <0.01 ppm). The FDA has a duty to protect the public against this avoidable risk from lead.

The proposed 200 mg tablets label has no restriction for consumption by pregnant women or women of childbearing age other than a warning to consult a physician. Pregnant women are at risk to lead exposures since lead is found to readily cross the placenta to the fetus. Even low maternal blood lead levels are associated with low birth weights and pre-term delivery. Blood lead levels in excess of 30 ug/dl have been shown to cause spontaneous abortion. Women of childbearing age are also at risk since lead is accumulated in bones and is readily released into the circulatory system during pregnancy. Thus, a woman of childbearing age may unknowingly risk the health to her fetus due to lead accumulated long before pregnancy occurs.

Although provisional tolerable total intake levels (PTTIL) were established by FDA for children at 6 ug/day and 75 ug/day for adults in 1993, to our knowledge, neither FDA nor EPA has established a TDI (tolerable daily intake) or a RfD (reference dose) for lead due to concerns of adverse effects from low level lead exposures and the uncertainty in establishing a safety factor. Recent studies have found that low-level lead exposure is not only associated with IQ reductions, but also with learning disabilities, attention deficit disorder and aggressive behavior (Lanphear et. al. Attachment V). In women, at blood lead levels well below the current US occupational exposure limit guidelines (40 ug/dl), lead is associated with changes in both systolic and diastolic blood pressure (Nash et al., Attachment VI). This relationship is most pronounced

in postmenopausal women at a time when they are most prone to aches and pain (and therefore, presumably, have a need for NSAIDs such as ibuprofen).

Based on these widely accepted research findings, it is generally agreed in scientific literature that a "no effect level" for lead has yet to be identified. EPA has now officially adopted the position that there is no threshold dose below which lead does not cause neurological damage in infants and young children. Since the original 1993 PTTILs were determined based on the lowest levels of lead exposures associated with adverse effects at the time, and adverse effects are now known to be associated at even lower lead levels than those used in the 1993 determination, it is reasonable to conclude that the established PTTILs no longer offer the margin of safety previously determined.

Contamination of OTC 200 mg ibuprofen tablets with lead could be an even more significant health concern than the well publicized lead contamination in calcium supplements. Calcium is known to block lead absorption, as both metals are absorbed at the same intestinal site (Attachment VII). Since the amount of calcium intake far exceeds the lead contaminant in the calcium supplement, lead absorption is essentially blocked when the two are taken at the same time. However, in the case of lead contamination in ibuprofen, the beneficial blocking agent, calcium, is absent. As a result lead should be more readily absorbed across the intestinal wall, increasing the total lead burden.

Albemarle's data indicates lead contaminants are present in ibuprofen tablets ranging from non-detectable to as high as 7 ppm per tablet. At the 7 ppm level, a person could be exposed to 13 ug/day based on the recommended OTC maximum dose of 1200 mg/day; accounting for 50% of the 25 ug/day provisional tolerance total intake level (PTTIL) recommended for pregnant women and 17% for adults. This exposure level is the same order of magnitude as the lead intake from the US daily diet. Therefore, US consumers would be at risk to double their daily dietary intake of lead as a result of the consumption of lead contaminated ibuprofen.

In general, the lead level detected in US 200 mg tablet samples is much lower than the level detected in samples obtained in less regulated countries. Domestically produced bulk ibuprofen is free of lead at the limit of detection (0.01 ppm). We believe the current FDA regulatory oversight most likely has succeeded in keeping the higher lead containing tablets off the market in the United States due to the NDA/ANDA approval process currently in place for the OTC 200 mg ibuprofen tablets.

A Case History of Lead Poisoning – An Example

Under the CDC's Adult Blood Lead Epidemiology and Surveillance program (ABLES), participating states mandate laboratories to report elevated blood lead levels (BLLs) to that state's health department. The ABLES' definition of an elevated BLL is greater than or equal to

²Egan, S.K., et. al. (2002) US Food & Drug Administration's Total Diet Study: Intake of Nutritional and Toxic Elements, 1991-96. Food Additive and Contaminants, vol. 19(2), pages 103-125.

25 ug/dL. Its program has a follow-up procedure to identify sources of lead exposure and to prevent future exposures.

On February 19, 1997, a Cambodian family was screened at a free lead-screening event sponsored by a community center in Connecticut. The father and children all had BLLs less than 10 ug/dL, but the mother had a BLL of 44 ug/dL. While in this case the woman was asymptomatic, high lead levels have been shown to cause anemia, nervous system dysfunction, kidney problems, hypertension, decreased fertility, and increased miscarriages. Upon investigation, the woman was found to have taken an Asian remedy ("Koo Sar" pills) for menstrual cramps for 7 days each month. The pills from two bottles at her home were found to contain lead ranging from 1.2 ppm to 3.5 ppm (Attachment VIII). Two subsequent samples purchased by the California Dept. of Health Services in different shops in San Francisco confirmed the presence of lead at 2.7 ppm (0.9 ug/pill) and 4.3 pm (1.5 ug/pill) respectively. It is interesting to note that the levels of lead present in these Koo Sar pills are comparable to, and in some cases less than, the lead levels that were detected in the ibuprofen tablets purchased in India and the Czech Republic.

If FDA allows the TFM to include 200 mg ibuprofen tablets, it is reasonable to predict that US consumers will be increasingly exposed to imported ibuprofen containing levels of lead similar to those detected in the ibuprofen tablet samples purchased in India and the Czech Republic. This could result in lead poisoning and high blood lead levels similar to that found in the Cambodian woman, potentially leading to a catastrophic public health problem in the US.

Consumer Protection Against Lead in Ibuprofen

Under the proposed amendment to the TFM, 200-mg tablets and the bulk ibuprofen utilized in such tablets would only have to meet USP test specifications. The USP monograph for bulk ibuprofen contains an insensitive and highly subjective color test for controlling heavy metals (such as, but not specifically addressing, lead). The specification for heavy metals in bulk ibuprofen is 20 ppm maximum meaning that, according to the specification, bulk ibuprofen containing much higher levels of lead than that previously discussed could still meet the current USP specifications. The current USP monograph test specifications do nothing to protect the public from incremental lead exposure.

In light of the fact essentially lead-free ibuprofen is readily available, and incremental lead exposure is avoidable (i.e., lead is not a necessary impurity from ibuprofen production), FDA should take all steps necessary to ensure public safety and assess the ramifications of our findings before relinquishing control over the quality of OTC 200 mg ibuprofen tablets. We also call on the FDA to address this important and avoidable public health issue before the proposed amendment is further considered. With the availability of reliable analytical detection of lead, the FDA should act proactively to ensure public safety by monitoring lead content in all existing OTC drug products.

Lead is But One Example of Potential Changes to Impurity Profile

Lead is but one example of the underlying issues with the proposed amendment to the TFM. As the comments from Keller and Heckman LLP presented to the FDA in October 2001 (Attachment IX) would indicate, the OTC monograph would, in the absence of FDA oversight, create the opportunity for new, untested, and significantly different quality ibuprofen to be supplied to the US public. The synthesis of ibuprofen is much more complex than that of other NSAID products listed in the TFM. This complexity, as well as the large number of possible routes available for ibuprofen production, has the potential to lead to significantly different (and potentially dangerous) impurity profiles for bulk ibuprofen. The assessment of safety for the 200-mg tablets provided in the proposed amendment to the TFM does not address such impurities, even through an important part of the FDA's current NDA/ANDA review process focuses on impurity identification, toxicity, and control.

We believe that the FDA should specifically address the comments in Attachment IX. We also believe the FDA should demonstrate to the US public how the FDA will ensure, with reduced FDA oversight, that the same quality ibuprofen which has been supplied safely and effectively for the past 25 years will continue to be supplied to the American public under the proposed amendment to the TFM.

Conversely, the current NDA/ANDA process provides for a detailed review of the manufacturing process, including the chemistry utilized, in order to fully investigate all potential impurities in the product that may pose human health risks. This review process includes a pre-approval inspection of the bulk product manufacturing site. In the case of ibuprofen, a pre-approval inspection could possibly result in the discovery of conditions that could lead to the introduction of lead into ibuprofen. For instance, the desire to control costs might lead a foreign manufacturer to use lead-lined equipment instead of the glass-lined standard found in the US. Lead has the potential to leach from this lead lining and contaminate the bulk ibuprofen product. Pre-approval inspections, which are not required under the proposed amendment to the TFM, might lead to the discovery of such conditions.

Furthermore, the NDA/ANDA chemistry review process may often lead an FDA reviewer to request additional information on impurities, including toxicology studies. Unlike the production of aspirin, acetaminophen and salicylates, the synthesis of ibuprofen is a multi-step, extremely complex process which can result in impurities and impurity levels that are not known to occur in the production of the other NSAIDs. This issue was extensively discussed in Attachment IX, along with a schematic diagram of the numerous known routes of ibuprofen synthesis. Both aspirin and acetaminophen can be produced by means of a single step reaction from salicylic acid or p-nitrophenol respectively, whereas ibuprofen synthesis typically takes a minimum of a 5-step reaction process. Some potential routes to ibuprofen synthesis involve α , β -unsaturated ketone intermediates and impurities which have known concerns as potential mutagens. A chemistry review during the NDA/ANDA process would flag these concerns to the FDA investigator.

Frequently, as a result of the NDA/ANDA chemistry review, FDA may require bulk drug specifications over and above those required by the USP monograph. During FDA's numerous

reviews of our own DMFs, FDA has raised questions and concerns on a number of impurities, thereby resulting in additional and more stringent specifications being placed on our bulk ibuprofen than are required by USP. These additional requirements have been partly a result of FDA's initiative to tighten specifications and reduce impurities to match demonstrated process capabilities. The NDA/ANDA process has resulted in Albemarle's bulk ibuprofen, through added capital investment and operating procedures, to be of much higher quality than that required under USP.

Under the lower USP quality standards and reduced FDA oversight associated with the proposed amendment to the TFM, new suppliers will have an unfair and inappropriate advantage over historically highly regulated western API producers in supplying bulk ibuprofen to the 200-mg tablet market. We wish to stress the potential risk from the presence of new impurities or changes in impurity profiles in ibuprofen versus other NSAIDs that are produced in simple one-step and less impurity-prone processes. Ibuprofen is one of the most consumed drug products on the market today, and the OTC market makes up as much as 80% of the total ibuprofen sold to the public. As such, FDA needs to address the concerns that were raised in Attachment IX in light of the new FDA safety initiatives to public health.

We have serious doubts about the level of regulatory scrutiny that will be applied to OTC tablets if the TFM is finalized to include ibuprofen. It is also difficult for the regulated industry to understand FDA's current regulatory approach in developing two "classes" of ibuprofen: one for prescription products with a stringent, tighter specification subject to FDA approval; and one for OTC monograph products with little or no FDA oversight other than being USP monograph compliant. Such uneven regulatory oversight would further promote the importation of lower quality foreign drug products/API into the US OTC market. According to the FDA ORA statistics presented at the 27th International cGMP Conference, Athens, GA in March 2003, 90% of the international inspections were triggered by "pre-approval" requests. In fiscal year 2002, only 281 or 11% of the 2585 total FDA inspections were conducted at foreign facilities despite the fact that 80% of the API used in the US is reported to be imported. In an October 3, 2000 FDA testimony before the Committee on Commerce, Dr. Jane E. Henney testified that there were 242 foreign API manufacturers that appear to have exported API into the US in 1999, but their establishment facilities had not been inspected by the Agency. FDA statistics also showed foreign manufacturers were found to have significant GMP problems relative to domestic facilities and yet, due to limited resources, routine cGMP inspections are rarely scheduled. Unless foreign inspections are increased to a comparable inspection rate encountered by domestic facilities, the public will continue to be at risk from lower quality drugs. Without such inspections, there can be no assurances that public health safety will be protected (such as in the case of lead contamination in ibuprofen tablets).

GRASE for a Material Time and to a Material Extent is not Satisfied

FDA has asserted in the proposed amendment that 200 mg ibuprofen tablets (i) have been marketed since 1984, (ii) meet the statutory requirement under section 201 (p) of the Act of marketing "to a material extent" and "for a material time," (iii) are GRASE and (iv) are no longer considered "new drugs." The proposed amendment therefore deduces that quality OTC 200 mg ibuprofen tablets can be manufactured under USP standards only and without FDA oversight

through the NDA/ANDA process. Using lead as an example, Albemarle strongly disagrees with this assertion and deduction.

The 200 mg ibuprofen tablets were first approved for OTC human use in 1984 and have been on the market for well over 19 years. During this time, ibuprofen has been used extensively by consumers for relief of minor aches, pain and fever reduction. In most of the 19 years during which 200 mg ibuprofen tablets have been available in the US OTC market, the tablets were predominantly produced with bulk ibuprofen manufactured by two western producers, namely Albemarle in the US and Boots Healthcare in the UK. The latter divested its ibuprofen API business to BASF in 1997 and, recently, BASF consolidated bulk ibuprofen production in Bishop, TX. Thus, for much of the 200 mg ibuprofen OTC product life cycle in the US, the bulk ibuprofen used in the 200 mg tablets was western-sourced and produced under cGMP, meeting the high quality standard required by both the FDA and the MCA. It is apparent that only tablets made from this western-sourced high quality ibuprofen may be considered GRASE and used "to a material extent" and "for a material time".

Since the filing of the citizen petition in 1997, however, domestically produced ibuprofen has been increasingly replaced by imported bulk ibuprofen in the formulation of ibuprofen tablets. We believe the assertion in the original petition that 200 mg ibuprofen tablets are GRASE "to a material extent" and "for a material time" is no longer applicable. The criterion of GRASE was originally based only on 200 mg ibuprofen tablets made with high quality western bulk ibuprofen produced in the US and UK. Thus, what was deemed GRASE may no longer be deemed GRASE if the quality of the 200 mg ibuprofen is not substantially similar to the tablets that were in commerce "for a material time" and "to a material extent." The detection of lead in formulated tablets and the potential adverse effects for as-yet-unknown changes in ibuprofen impurity profiles could pose a significant negative impact to the health of the US consumers, since the non-western sourced ibuprofen has not been on the market "for a material time" and used "to a material extent".

We believe that additional toxicological assessments should be made before the principal of "for a material time" and "to a material extent" is applied to the proposed TFM amendment. In the meantime, to protect the general public, FDA should continue the current OTC NDA/ANDA review process until the criteria of "to a material extent" and "for a material time" are met. We believe this would be in line with the current FDA initiatives to apply a risk-based approach to maintain public health safety.

The Future with 200 mg Tablet Ibuprofen Monograph

It could be reasonably expected that once the TFM is finalized, and OTC ibuprofen is no longer subject to ANDA approvals by the FDA, foreign produced ibuprofen tablets (as well as tablets made with foreign-sourced bulk ibuprofen) will dominate the US 200 mg ibuprofen market. This is due, in part, to the lower costs foreign manufacturers encounter because of the lesser regulatory (FDA, EPA, OSHA) requirements applicable to foreign manufacturers. The potential of incremental lead intake from these imported ibuprofen/ibuprofen tablets by adults who are on a daily regimen to relieve chronic pain may pose a serious safety concern not previously addressed by the FDA. Although we do not have statistical survey data to support

this observation at present, it is a common and well-known practice for physicians to frequently advise their patients to purchase OTC tablets in lieu of Rx tablets despite the labeling differences between OTC and prescription. This is due to the substantial cost savings to the patients who do not have prescription reimbursement. Private label ibuprofen tablets may be purchased as low as 1¢/200 mg OTC tablet vs. an average of 20¢/800 mg Rx tablet. By taking four 200 mg OTC tablets instead of one 800 mg tablet at one time, a Medicare patient can reduce his/her ibuprofen cost by 80% per day. The elderly account for a significant population who are in need of chronic pain relief due to rheumatoid arthritis. For these patients, their risk of exposure would be 2 1/2 times the OTC dosage recommended for minor pain or fever. Furthermore, the duration of exposure would be chronic compared to the 10-day maximum recommended for the OTC label.

In a recent OTC painkiller survey sponsored by National Consumers League (NCL) and conducted by the Harris Interactive® in December 2002 (Attachment X), 84% of the 4,263 adults surveyed said they had taken an OTC pain reliever such as ibuprofen and naproxen within the past year. Of those who had taken an OTC painkiller, 44% admitted to exceeding the recommended dose. According to NCL, the results have a statistical precision of plus or minus 1.5 percentage points. Based on the survey results, it is clear that a significant portion of the adult U.S. population consumes OTC analgesics for pain relief, and too often, the average consumer just wants the pain to go away and may not be reading the label or may ignore the recommended label dosage. In light of the incremental lead exposures and the potential unknown impurity toxicity, it is important for the Agency to recognize the significance of this consumer survey in the safety assessment for the proposed OTC tentative final monograph.

No Consumer Benefits in the Ibuprofen OTC Monograph

In the Federal Register's summary of the proposed rule, FDA provides an analysis of the impacts of the proposed amendment to the TFM. Implicit in the FDA's analysis is that giving monograph status to OTC ibuprofen tablets will reduce the cost of these products to the consumer. However, our unscientific market research indicates that OTC ibuprofen prices are already comparable to the price of other OTC NSAIDs on the retail market. Both generic ibuprofen and acetaminophen may be purchased at about \$8.00/500 tablets, while the branded versions of both products are priced at \$12.00/250 tablets. We believe that the price of OTC ibuprofen tablets will continue to be driven by the cost of competing NSAIDs, and will not be affected by any cost savings due to a reduced regulatory burden. Therefore, any savings generated from this proposed rule should not be expected to be passed on to the consumer but will simply be pocketed by retailers and tabletters due to pricing strategy versus other NSAIDs. Thus, the consumer will be unknowingly accepting more risk with no economic saving.

Conclusion

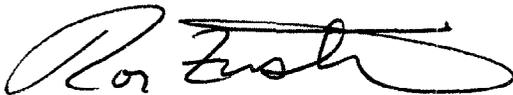
In conclusion, we recommend before the FDA takes any regulatory action on the TFM, the Agency should take time to sample, analyze and evaluate the extent of lead contamination in ibuprofen tablets for both prescription and OTC products that are currently regulated and approved by the FDA. FDA should also estimate the potential increase in lead exposure to US consumers from imported bulk ibuprofen based on measured levels of lead in the bulk drug

substance and determine the potential risk to US consumer from that exposure. The analysis will allow the Agency to determine whether lead contamination is already an issue in the US and, if not, to provide a regulatory benchmark for future lead content in both Rx and OTC ibuprofen tablets. In addition, to ensure public health safety, the Agency should make a detailed quality assessment of imported ibuprofen API to ensure that impurity profiles are substantially similar and there are no toxicological concerns from any new unspecified/unqualified impurities. Furthermore, FDA should implement appropriate safeguards to insure the quality of all OTC ibuprofen tablets, both domestically-produced and imported. OTC tablets must be required to meet the same quality standards as those that are approved via the NDA/ANDA process. Finally, if the goal is to lower the total blood lead level in both children and adults, then FDA should, with the cooperation of USP, tighten the lead specifications in all USP monographs so that consistent with FDA's stated goals, the amount of lead ingested by US consumers from FDA regulated products is minimized (especially when products containing lead at levels at least one hundred fold below those found in certain samples of foreign made products are available).

We also request that before FDA takes any regulatory action on the TFM, the Agency define how it plans to prevent lower quality ibuprofen from being allowed into the US consumer market. The issue of lead may only be the beginning of more serious human health risks in the future as FDA allows more imported drug products to come into the US with little regulatory oversight.

We appreciate the opportunity to submit comment on the subject proposed rule. If you have any questions, please feel free to contact me at 225-388-7135 or my staff, Louise Wen at 225-388-7650.

Sincerely,
Albemarle Corporation



Ron Zumstein, Ph.D.
Vice President, Health, Safety and Environment