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October 3, 2001

Via Hand Delivery

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

Re: Docket 77N-0094; Comments on Citizen Petition to Amend the Tentative Final Monograph For Internal Analgesic, Antipyretic and Antirheumatic Drug Products For Over-The-Counter Human Use - Addition of Ibuprofen 200 mg

Dear Sir or Madam:

On behalf of an interested client, Keller and Heckman LLP hereby submits comments on the Whitehall-Robins Healthcare ("Whitehall-Robins") Citizen Petition under 21 C.F.R. §§ 10.30 and 330.10, requesting that the Food and Drug Administration ("FDA") amend the Tentative Final Monograph ("TFM") for Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter ("OTC") Human Use to add ibuprofen as a single analgesic-antipyretic active ingredient in an oral dosage of 200 milligrams (mg). The Petition, dated November 25, 1997, asserts that OTC experience with ibuprofen, which was approved for non-prescription use in May 1984, fulfills the requirements of 21 C.F.R. § 330.10(4)(i) and (ii) regarding general recognition of safety and effectiveness. Further, the Petition claims that ibuprofen meets the additional provisions found in Section 201(p)(1) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") which require an eligible drug to be used "to a material extent" and "for a material time."

Keller and Heckman LLP submits these comments in response to FDA's May 2001 Semiannual Regulatory Agenda concerning the TFM for OTC internal analgesic drug products, in which the item "NPRM (Amendment) (Ibuprofen) 10/00/01," was listed.¹ It is believed that

¹ See Department of Health and Human Services Semiannual Regulatory Agenda, 66 *Fed. Reg.* 25387, 25407 (May 14, 2001). Although the Agenda was published in May 2001, this particular item apparently has not been the subject of any other public discussion and only recently came to our client's attention.

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FDA will grant the Petition and propose conditions under which ibuprofen may be considered generally recognized as safe and effective ("GRASE") for OTC use under the monograph.

In light of these anticipated actions, the Agency should consider the following comments in developing its response to the Whitehall-Robins Petition. First, prior to amending the TFM to add ibuprofen as an active ingredient in a dosage of 200 mg, FDA must take the necessary steps to ensure that the reduction of the Agency's control over the production of bulk ibuprofen does not result in a decrease in the quality of ibuprofen products available for OTC use.

Second, the ibuprofen that is described in the Petition has been supplied by two producers and is believed to be of higher quality than what is described by the United States Pharmacopoeia ("USP"). As a result, only this higher quality ibuprofen, which has been used in the ibuprofen market since it became available without a prescription in 1984, can be considered GRASE and used to a material extent for a material time. Since FDA is no doubt aware of the quality of OTC ibuprofen on the market,² it should carefully consider product quality factors in any proposal to amend the OTC monograph. This effort will guard against the possibility of subjecting consumers to potentially significant as-yet-unknown adverse health effects.

These steps are also necessary to prevent the development of two "classes" of ibuprofen: those still reviewed by FDA as part of higher strength products that will not be covered by the monograph (and thus still reviewed under an ANDA), and those used only for OTC monograph-compliant products. Unless FDA requires the same level of quality for both products, there can be no assurance that the public's health will be adequately protected.

I. Comments

A. FDA Must Implement Safeguards To Ensure That A Reduction In The Agency's Oversight Does Not Result In A Decrease In The Quality Of Ibuprofen Products Available OTC

Because of the current requirement that OTC ibuprofen drug products be the subject of an approved ANDA, FDA has a keen awareness of, and control over, the quality of the bulk ibuprofen used as the active pharmaceutical ingredient ("API") in OTC ibuprofen products. It is expected that manufacturing information about the ibuprofen is provided in various Drug Master Files ("DMFs")³ that are reviewed by the Agency in connection with the ANDA submissions.

² All currently marketed products are the subjects of a new drug application ("NDA") or abbreviated new drug application ("ANDA") reviewed and approved by the Agency.

³ FDA's DMF records indicate there are numerous active DMFs currently on file at the Agency covering the production of bulk ibuprofen.

This review provides assurance to the consuming public that any manufacturing changes to the API are fully evaluated for their potential impact on the substance.

Under an OTC monograph, however, this review is no longer provided. Importantly, the manufacturing process can have a significant effect on a product's quality. Process changes can introduce impurities that do not show up in a USP test designed to look only for the impurities that were known at the time the specifications were adopted. As a result, FDA's lack of control over the manufacturing of bulk ibuprofen would raise the potential that consumers may be exposed to impurities not previously found in ibuprofen drug products.

This risk is heightened by the complex manufacturing processes used to produce ibuprofen. Because of its complexity, the ibuprofen manufacturing process is more likely to result in the creation of byproducts and impurities than the manufacturing processes for other OTC monograph analgesic ingredients such as aspirin or acetaminophen.

Specifically, though ibuprofen is a relatively simple molecule compared to many prescription drugs, it is sufficiently complex that it can be made by a large number of different synthetic schemes. In fact, since the introduction of pharmaceutical products containing ibuprofen in the late 1960s and early 1970s, industrial and academic scientists have developed many potential production processes. Although nearly all of the current economically competitive industrial processes begin with isobutylbenzene (IBB), which itself has a very broad range of impurities depending on the purity of propylene used to react with toluene to form IBB, several different synthetic processes have been developed for ibuprofen manufacture which provide further opportunities for a wide variety of impurities to be present in the final ibuprofen product.⁴ In addition, each of these processes has different pivotal intermediates, meaning that the impurities likely to be present in the final ibuprofen product will vary widely depending on the process used.

Furthermore, since ibuprofen became available for use in OTC products, two manufacturers are believed to have supplied virtually all of the bulk ibuprofen used in OTC ibuprofen products sold in the United States. As a result, any impurities present in the OTC ibuprofen products have been limited to the tight starting material specifications and the well-controlled manufacturing processes practiced by the current manufacturers. However, if the OTC analgesic TFM is amended to include ibuprofen, as is currently proposed by the Whitehall-Robins Petition, ibuprofen produced by other potential routes, and by new manufacturers, would be available for use in OTC products, with little assurance that no "new" impurities would be present.

⁴ These processes are described in more detail in Exhibit 1 to these comments. All of the information in Exhibit 1 is derived from publicly-available sources.

In short, the highly complex processes used to manufacture the ibuprofen API present inherent risks for the development of impurities that will be present in the final ibuprofen products. FDA must consider appropriate safeguards to ensure that the finished products available if ibuprofen is added to the OTC analgesic TFM are of the same high quality as currently marketed ones.

B. The Whitehall-Robins Petition Does Not Address The Fact That The Majority Of The OTC Ibuprofen Available Since 1984 And Marketed Today Is Of Higher Purity Than What Is Described Under The USP

In its Petition, Whitehall-Robins notes that the type of ibuprofen under consideration is limited to "racemic ibuprofen, which since 1984 is the only form of ibuprofen marketed over the counter in the United States."⁵ As FDA is aware, the USP-NF monograph allows ibuprofen to contain a maximum chromatographic impurity level of 1.0%.⁶ In contrast, it is believed that all of the primary suppliers of the total ibuprofen market supply product that has between 0.2% and 0.4% impurities.⁷ These bulk ibuprofen sources have had consistent impurity profiles and known impurities throughout the time that ibuprofen has been available without a prescription.

Therefore, the vast majority of ibuprofen available on the market today and over the past 17 years has had, at the most, approximately 40% of the impurities allowed under the USP. Stated differently, the average *total* amount of impurities in currently-marketed ibuprofen equals the maximum allowable level of just *one* impurity under the USP.⁸ As a result, the ibuprofen that is the subject of the Whitehall-Robins Petition is of higher quality than, and therefore not truly the same as, the ibuprofen described in the USP.

C. This Previously-Marketed, Well-Controlled Ibuprofen Is The Only Material That Can Be Properly Characterized As GRASE

A drug becomes eligible for OTC monograph status when it is no longer considered a "new drug." The FDC Act defines a "new drug" as one that is not GRASE and that has not been

⁵ Whitehall-Robins Petition at 2.

⁶ See Ibuprofen, Official Monographs, USP 24, p.854. The USP standard allows not more than 0.3% of any individual impurity and total impurities not to exceed 1.0%.

⁷ As noted earlier, FDA has full access to information about ibuprofen quality through its review of DMFs, NDA, and ANDAs.

⁸ The USP standard allows not more than 0.3% of any individual impurity and total impurities not to exceed 1.0%.

used to a material extent or for a material time.⁹ Whitehall-Robins reports in its Petition that ibuprofen satisfies these conditions.

Assuming Whitehall-Robins' assertions are correct, however, the conclusion that a product is no longer a "new drug" is very specific, and changes to that product can thrust it back into the "new drug" area. For example, in *United States v. Generix*,¹⁰ the Supreme Court found that a generic drug product should be considered a "new drug" until the entire product, not simply its active ingredients, no longer fell within the definition of a "new drug."¹¹ In *Generix*, the Court recognized that differences in excipients or inactive ingredients can potentially affect the safety and effectiveness of drug products.¹² By extension, other changes to a product that could affect its safety or effectiveness (e.g., manufacturing procedures) could lead to a "new drug" conclusion¹³

The OTC monograph process represents a departure from this strict "exact product" interpretation. The Agency has established by regulation the conditions under which OTC drug products will be deemed GRASE and "not misbranded."¹⁴ Although FDA originally proposed to have its expert Advisory Panels review inactive ingredients in OTC drug products,¹⁵ the Agency recognized that the OTC review was intended to cover only the safety and effectiveness of active

⁹ FDC Act § 201(p).

¹⁰ 460 U.S. 453 (1983).

¹¹ *Id.* at 461.

¹² *See id.* at 455. The Court pointed out that "[e]xcipients may affect the rate at which the active ingredient is delivered to a diseased organ. If delivery is too fast, the patient may be harmed just as if he received an overdose; if delivery is too slow, the treatment of the disease may be ineffective." *Id.*

¹³ *See also United States v. Undetermined Quantities of Bottles of an Article of Veterinary Drug*, 22 F.3d 235, 237 n.2 (10th Cir. 1994) (noting that based on the *Generix* decision, "[u]nder the Act, the term 'drug' does not refer merely to the active ingredient in a drug product, but to the entire product); James T. O'Reilly, FOOD AND DRUG ADMINISTRATION § 13.06 (West 1995) ("[t]his means that one cannot take the active ingredient of a drug that is GRASE, such as aspirin, and alter it through new dissolving agents, new coatings, etc., that had not been known before, while still calling the end product GRASE.").

¹⁴ *See* 21 C.F.R. § 330.1.

¹⁵ *See* FDA's general discussion in the preamble to the proposed rules establishing the OTC drug review. 37 *Fed. Reg.* 85, 88 (January 5, 1972).

ingredients¹⁶ and eliminated the proposal to review data on "inactive" ingredients.¹⁷ The only direction given to manufacturers with respect to the formulation of their products is a long-standing general requirement for all OTC drug products that they contain "only suitable inactive ingredients which are safe in the amounts administered"¹⁸ and which do not otherwise adversely affect the product.

The historical context for this position is unique. The Agency was faced with an estimated 100,000 to 500,000 OTC products on the market, many of which had been available for decades.¹⁹ FDA simply did not have the resources needed to proceed in a case-by-case manner against each individual product. FDA concluded that the public health would not be adequately protected by such an approach, and that "equitable enforcement of the law require[d] that the agency proceed against all manufacturers of similar preparations, since those not proceeded against would have an unfair competitive advantage."²⁰ Even with this expansive initial view, however, the Agency has recognized more recently that:

the "new drug" definition must be liberally construed in order to effectuate the policy of the act to protect the public health and safety (*United States v. Article of Drug * * * Bacto-Unidisk*, 394 U.S. 784, 798 (1969)). Conversely, the situations in which a drug product is not a "new drug" are to be narrowly defined (*Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795, 802 (2d Cir. 1980)).^[21]

The situation at the dawn of the OTC monograph process was vastly different from the circumstances outlined in the Whitehall-Robins Petition. In short, there is strong current support for the principle that in concluding that something is no longer a "new drug," the "same" product

¹⁶ "The OTC drug review is an active, not an inactive, ingredient review . . ." TFM for OTC Oral Health Care Drug Products, 56 *Fed. Reg.* 48302, 48305 (September 24, 1991) (FDA response to Comment 3).

¹⁷ 37 *Fed. Reg.* 9464, 9467 (May 11, 1972) (FDA response to comment 42);

¹⁸ 21 C.F.R. § 330.1(e).

¹⁹ 37 *Fed. Reg.* at 85 - 86.

²⁰ *Id.* at 86.

²¹ Additional Criteria and Procedures for Classifying Over-the-Counter Drugs as Generally Recognized as Safe and Effective and Not Misbranded, 64 *Fed. Reg.* 71062, 71070 (Dec. 20, 1999) (to be codified at 21 C.F.R. pt. 330).

must continue to be marketed to take advantage of the exclusion in the law. Subtle changes can shift a product back into "new drug" territory.²² As detailed above, currently-marketed ibuprofen API differs from the USP in level of actual impurities (and may differ in manufacturing processes as well). Only the product that is currently used in the ibuprofen market has undergone thorough testing and has been the subject of significant scientific studies regarding safety and effectiveness. Ibuprofen that pushes the upper limit of the USP standard (up to 1.0% impurities, perhaps including two impurities at up to 0.3% each that have never been present in the ibuprofen for which significant experience exists) has not been assessed to determine GRASE status, nor has it been used to a material extent and for a material time.

D. FDA Should Consider Product Quality Factors In Any Proposal To Amend TFM

In a recent proposed rulemaking, FDA outlined certain criteria and procedures that would need to be met before an active ingredient may become eligible for consideration in the OTC drug monograph system.²³ Although the proposed rule deals with evaluating foreign marketing experience, the discussion is nonetheless instructive because the principles apply equally to domestic products.

Proposed 21 C.F.R. § 330.14(i) provides, in relevant part, that before marketing of a drug product may begin, any active ingredient included in a final OTC drug monograph must be recognized in an official USP-NF drug monograph, setting forth its standards of identity, strength, *quality*, and *purity*.²⁴ To this effect, FDA suggests that, in establishing GRASE status of a drug product, "[t]he official USP-NF monograph should be consistent with the active ingredient(s) or botanical drug substance(s) . . ."²⁵ FDA's goal in proposing this compendial monograph requirement is to "ensure that all OTC drug products contain ingredients that are equivalent to the active ingredients or botanical drug substances included in an OTC drug monograph."²⁶ This is supported by FDA's statement that since April 3, 1989²⁷ it has been

²² See 21 C.F.R. § 310.3(h) (giving examples of, in same case minor, changes that can result in a product being a "new drug").

²³ See 64 *Fed. Reg.* 71062 (to be codified at 21 C.F.R. Part 330).

²⁴ See *id.* at 71065 (emphasis added).

²⁵ *Id.*

²⁶ *Id.* FDA explains further that "[i]nclusion in an official compendium of an ingredient's standards of identity, strength, quality, and purity would help ensure that OTC drugs are safe and effective for their intended uses." *Id.*

²⁷ See TFM for OTC Pediculicide Drug Products, 54 *Fed. Reg.* 13480, 13486 (Apr. 3, 1989).

Agency policy that each ingredient included in a final OTC drug monograph must also have a compendial monograph that "sets forth the identity, strength, *quality*, and *purity* of the drug substance and drug products made from the drug substance and would include, for example, specifications relating to stability, sterility, particle size, crystalline form, and analytical methods."²⁸

The proposed regulations also provide for a revision to 21 C.F.R. § 330.10(a)(2) to require an applicant for OTC monograph status to submit to FDA information certifying that the active ingredient in the drug product is the same as the active ingredient as described by the official or proposed compendial USP.²⁹ Specifically, this would provide FDA with information to determine whether the active ingredient is, in fact, GRASE and meets the requirements of being used to a material extent and for a material time. The proposed regulations would require the applicant to explain the differences between its active ingredient and those of the USP monograph if any differences exist.³⁰

Apart from this proposed rule, the Agency has similarly emphasized careful consideration of the official USP-NF monograph when examining active ingredients that are included in OTC monographs. For example, in response to comments on the TFM for oral antiseptic products, FDA highlighted the importance of standardizing and characterizing active ingredients for quality and purity when including them in official compendia.³¹ Further, coordination with the USP regarding standards for quality and purity is encouraged by FDA.³²

²⁸ 64 *Fed. Reg.* at 71074 (emphasis added).

²⁹ *Id.* at 71067

³⁰ Differences between the drug product and the USP monograph will help FDA determine (1) appropriate warning statements, and (2) general recognition of safety and effectiveness. *Id.*

³¹ TFM for Oral Antiseptic Drug Products, 59 *Fed. Reg.* 6084, 6120 (Feb. 9, 1994). FDA stated the following:

For an active ingredient to be included in an OTC drug final monograph, in addition to information demonstrating safety and effectiveness, it is necessary to have publicly available sufficient chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products.

³² In response to comments to a TFM for Oral Antiseptic Products, the Agency took the following position:

In the final monograph for OTC sunscreen drug products, FDA stated that it would include in the final monograph "only those active ingredients that are the subject of an official USP compendial monograph that sets forth its standards of identity, strength, quality, and purity."³³ Similarly, as part of the developments of a proposed monograph for OTC antigingivitis and antiplaque products, FDA is expected to recommend that "a full description of the ingredient including its physical and chemical characteristics and stability be provided, and that manufacturers contact and work with the U.S.P. to develop monographs for ingredients that are not currently included in that compendium."³⁴

In sum, it is clear that FDA frequently utilizes the USP monograph system for purposes of setting standards and providing a frame of reference for OTC drug products. Overall, FDA regards compliance with the USP-NF system to be extremely significant. Because of this, FDA should not shift ibuprofen to OTC monograph status without confirming that the ibuprofen USP monograph will provide suitable assurance of continuity of product quality.

E. If FDA Does Not Address The Issue Of Quality Differences Between Currently-Marketed And USP-Ibuprofen Before Granting Ibuprofen OTC Monograph Status, The Agency Will Create Two "Classes" Of Ibuprofen With Potential Adverse Health Consequences

As described in the Petition, over 90 billion 200 mg tablets of ibuprofen were sold through 1996 since it became dispensable without a prescription. The current OTC market for 200 mg ibuprofen is estimated to be over 20 billion tablets per year. If FDA permits the marketing of ibuprofen meeting the upper limits of the USP specifications, millions of consumers may be exposed to an ibuprofen drug product that is different in quality from what they have become accustomed to. To avoid this problem, FDA should impose a higher standard of ibuprofen product quality than is found in the USP if it decides to amend the TFM.

The Agency believes that it would be appropriate for parties interested in upgrading nonmonograph ingredients to monograph status to develop with the United States Pharmacopoeial Convention appropriate standards for the quality and purity of any of these ingredients that are not already included in official compendia. Should appropriate standards fail to be established, ingredients otherwise eligible for monograph status will not be included in the final monograph. [59 *Fed. Reg.* at 6120.]

³³ Final Monograph for OTC Sunscreen Drug Products, 64 *Fed. Reg.* 27666, 27670 (May 21, 1999).

³⁴ See Draft Report of the Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Committee (released for public comment in November 1998), at 55.

There are numerous ibuprofen-containing drug products that would not be affected by a switch to monograph status. A check of the Agency's electronic "Orange Book"³⁵ revealed over 40 prescription drug products with ibuprofen strengths in excess of 200 mg. These products would clearly not be covered by the inclusion of 200 mg ibuprofen in an OTC monograph, and would still need to meet all of the conditions of their approved NDAs and ANDAs. More significantly, the bulk ibuprofen manufacturers would still need to comply with the product specifications already established. As a result, companies currently supplying bulk product for the prescription ibuprofen market would be likely to continue producing ibuprofen to the high quality specifications and with the well-established manufacturing procedures that have been used for long periods of time.

In contrast, establishing 200 mg ibuprofen as an OTC monograph product opens a potential market for new bulk suppliers interested in supplying the pharmaceutical industry without otherwise subjecting themselves to the rigorous scrutiny of an FDA pre-approval inspection. In this sense, two "classes" of ibuprofen would be created: one generated by suppliers to the prescription industry (which meets long-established high product quality characteristics) and one produced by suppliers exclusively to the 200 mg oral dosage OTC monograph market,³⁶ which suppliers may introduce new product quality issues through the absence of FDA oversight.

II. Conclusion

FDA should consider the future implications and potentially significant health effects that could result from allowing a lower quality drug product to be added to a monograph after a well-controlled, higher quality product has supplied the majority of the market for a number of years. In essence, it is important for FDA to allow only the *same* drug to move from "new drug" to OTC monograph status.

The issues in these comments may already be under consideration at FDA. To the extent they are not, they should be addressed as part of any proposal to amend the TFM. FDA must implement appropriate safeguards to ensure that reducing FDA's oversight of ibuprofen-

³⁵ Available at <http://www.fda.gov/cder/ob/default.htm> (site visited on October 1, 2001) (search conducted for prescription drugs with "ibuprofen" as the active ingredient).

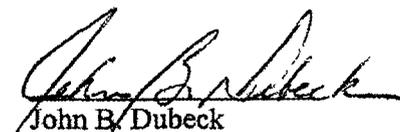
³⁶ Some OTC products would still require FDA approval of an ANDA. The Petition specifically notes that it "is not requesting that the monograph conditions allow labeling for usage by children under 12 years of age." Whitehall-Robins Petition, at 2, footnote 2. Thus, an OTC product such as Whitehall-Robins' Children's Advil® Oral Suspension presumably would not fall within the monograph and would still need to comply with all the requirements of its approved ANDA, including the bulk ibuprofen specifications.

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containing drug products does not result in diminishing the quality of OTC ibuprofen products available to consumers.

Respectfully submitted,


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Enclosure – Exhibit 1

cc (via facsimile) (w/enclosure):

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Director
FDA Division of OTC Drug Products

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IBUPROFEN PRODUCTION

While ibuprofen is a relatively simple molecule, there is still sufficient structural complexity to ensure that a large number of different synthetic schemes are possible. Since the introduction of pharmaceutical products containing ibuprofen in the late 1960's and early 1970's, many potential production processes have been developed by industrial and academic scientists.

Essentially all OTC ibuprofen market in the United States has been supplied by two manufacturers since the product switched to OTC. Therefore, the impurities present in the OTC ibuprofen products have so far been limited to the tight starting material specification and the well controlled manufacturing process practiced by the current manufacturers. If the OTC Analgesic Monograph is amended as proposed to include ibuprofen, ibuprofen produced from other potential routes would be available in OTC products with up to 1% of different new impurities under the current USP ibuprofen specification. The safety of these potential new impurities in OTC products has not been assessed nor do they have a long term consumption history by consumers.

Nearly all of the economically competitive industrial processes begin with isobutylbenzene (IBB), which is manufactured by at least two major chemical companies in the United States and perhaps more abroad. Commercial IBB has a very broad range of impurities depending on the purity of propylene used to react with toluene to form IBB, the starting material of ibuprofen. Typical propylene grade contains ethylene, isopropylene and butene as impurities. These olefins react equally well with toluene resulting in the corresponding alkyl benzene impurities in IBB. These impurities can then undergo further reactions in the ibuprofen process to form additional impurities that are analogs to ibuprofen.

In addition to varying concentrations of alkylbenzene in the most common raw material, the large number of different synthetic processes that have been developed for ibuprofen manufacture provide other opportunities for a wide variety of impurities to be present in the final ibuprofen product. Seven routes are diagrammed in the attached illustration. Each of these processes is, or has been, used to produce commercial quantities of ibuprofen, or has been developed through the pilot plant stage and thus is capable of producing commercial quantities of product.

The pivotal intermediates for each of these processes are shown in boxes. Note that nearly all of the illustrated processes have different pivotal intermediates. This means that the impurities likely to be present in the final ibuprofen product will vary widely depending on the process used. A brief description of each process follows:

Route A is a commercial manufacturing process developed by the Boots Pure Drug Company in England (U.S. Patent 3,385,886). The route is a six-step process that begins with isobutylbenzene. The pivotal intermediate in this route contains a cyanide

functionality that must be completely hydrolyzed to yield ibuprofen. Conversion of this intermediate to the final product must be conducted with extreme care to avoid any contamination of product ibuprofen.

Route B was developed by the Council of Scientific & Industrial Research in India (European Patent 336031). Following acylation of isobutylbenzene with propionyl chloride, the resulting 4-*i*-butylpropiophenone is chlorinated to yield the pivotal intermediate, 2-chloro-4-*i*-butylpropiophenone. Rearrangement of this compound yields the methyl ester of ibuprofen. Hydrolysis of this material yields crude ibuprofen that is then purified for sale.

Route C was developed and implemented by the BHC Company (U. S. Patents 4,981,995 and 5,068,448). This route begins with isobutylbenzene and uses highly toxic and corrosive hydrogen fluoride to produce 4-*i*-butylacetophenone, which is subsequently reduced to 1-(4-*i*-butylphenyl)-ethanol, the pivotal intermediate. Reaction of this material with carbon monoxide produces crude ibuprofen, which is then purified for sale.

Route D was developed by the Nippon Company (European Patent Specification 0170147). This route begins by reacting isobutylbenzene with acetaldehyde to form 1,1-di-(4-*i*-butylphenyl)ethane, which is then thermally cracked to the pivotal intermediate, 4-*i*-butylstyrene. This material is reacted with carbon monoxide to produce ibuprofen ester, which is then hydrolyzed to form crude ibuprofen.

Route E was developed by the Dow Chemical Company (U.S. Patent 4,186,270). This route involves reaction of isobutylbenzene with formaldehyde and hydrogen chloride to form 4-*i*-butylbenzylchloride. This material is then converted to the corresponding cyanide-containing derivative, 4-*i*-butylphenylacetonitrile, by reaction with sodium cyanide. Alkylation with methyl chloride gives the cyanide-containing compound 2-(4-*i*-butylphenyl)propionitrile as the pivotal intermediate. This is then converted to ibuprofen by hydrolysis of the cyanide functionality to the methyl ester followed by acidification to ibuprofen.

Route F was developed in China by the Wuhan Institute of Chemical Technology (Huaxi Yoxue Zazhi, (1995), 10(3), 129-31). Acylation of isobutylbenzene with propionyl chloride gives *i*-butylpropiophenone. Halogenation of this material with copper bromide gives 2-bromo-4-*i*-butylpropiophenone. Ketalization of 2-bromo-4-*i*-butylpropiophenone with ethylene glycol gives the pivotal intermediate 2-(1-bromoethyl)-2-(4-*i*-butylphenyl)-1,3-dioxolane. This compound is rearranged to ibuprofen methyl ester, which is then hydrolyzed directly to ibuprofen.

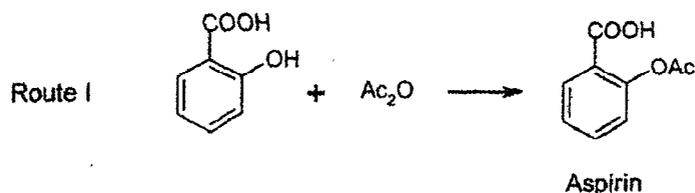
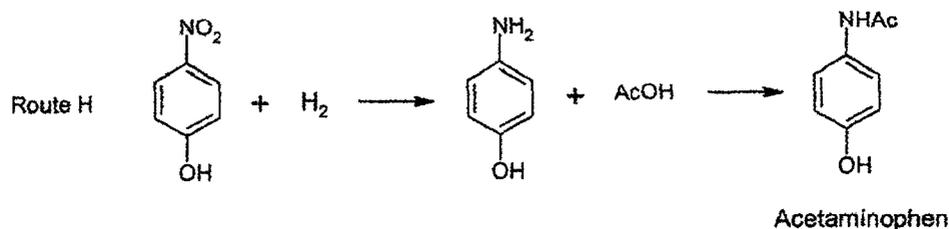
Route G was developed by the Upjohn Company (U.S. Patent 3,975,431). Acetylation of isobutylbenzene yields 4-*i*-butylacetophenone, which is then converted to 3-methyl-3-(*p*-*i*-butylphenyl)glycidonitrile by reaction with chloroacetonitrile. Hydrolysis of the glycidonitrile gives 2-hydroxy-3-methyl-3-(4-*i*-butylphenyl)-3-chloropropionitrile. This material is then acetylated and dehydrochlorinated to yield the pivotal intermediate 2-acetoxy-3-(4-*i*-butylphenyl)acrylonitrile. Hydrolysis of the

contained cyanide group in the presence of alcohol produces ibuprofen ester, which is then further hydrolyzed to yield ibuprofen.

To further compound the impurity issue, ibuprofen can also be made from starting material other than isobutylbenzene. In these cases, additional potential new impurities not previously known or tested would be present as well.

Following the ibuprofen processes is an illustration of the processes used to manufacture acetaminophen and aspirin. It is obvious that these processes are significantly simpler than those used for ibuprofen. In addition, these processes are common to all the major manufacturers of acetaminophen and aspirin so that the chances of unexpected impurities arising from different routes are very much reduced.

Acetaminophen and Aspirin Manufacturing Routes



Route H produces acetaminophen by catalytic reduction of 4-nitrophenol with hydrogen followed by acetylation of 4-aminophenol with acetic acid or acetic anhydride to form acetaminophen.

Route I produces aspirin by simple acetylation of salicylic acid

References

- Route A - U.S. Patent 3,385,886
- Route B - European Patent 336031
- Route C - U.S. Patents 4,981,995 & 5,068,448
- Route D - European Patent Specification 0170147
- Route E - U.S. Patent 4,186,270
- Route F - *Huaxi Yaoxue Zazhi*, 10(3), 129-31, (1995)
- Route G - U.S. Patent 3,975,431
- Acetaminophen Route – European Patent 622354
- Aspirin Route – U.S. Patent 3,373,187