Statement from McNeil Consumer Healthcare

At McNeil, our mission is to help people stay healthy and help take care of them when they are sick. All medicines have risks as well as benefits, and it is important to know that taking too much of any medicine can be harmful. Our hearts go out to those who have suffered from acetaminophen overdose, and to the families of those who have lost their lives as a result. We will continue to work hard to educate and warn consumers of the dangers of acetaminophen overdose, reminding them to read the labels on all medicines before taking them, to take medicines only as directed and to be aware that any medicine they take has risks.

Safety of TYLENOL®

When taken as directed, acetaminophen - the active ingredient in TYLENOL® - has one of the best safety profiles of any over-the-counter (OTC) medicine. When an overdose is taken, however, the risks include severe liver damage, which in some cases may even be fatal.[i] That's why it's so important for people to read and follow the label instructions for any medicine they are taking, including TYLENOL®. Consumers should be reassured that by following the instructions provided with OTC and prescription medicines containing acetaminophen, they can avoid acetaminophen overdose. Over the past five decades, acetaminophen has become one of the most studied and well-understood OTC medicines.[ii] In light of all they know about acetaminophen, the benefits and the risks, doctors recommend TYLENOL® more than any OTC brand of pain reliever.[iii]

The overall safety of acetaminophen must be considered in light of the risks of alternative pain relievers and the potential for unintended consequences of switching from one to another. Other types of OTC pain relievers including ibuprofen and naproxen sodium – which are known as non-steroidal anti-inflammatory drugs or NSAIDs – have important benefits, and also carry their own significant risks, even when taken as directed. Research has linked them to gastro-intestinal bleeding and kidney damage. For many consumers, including those with renal disease, stomach ulcers, cardiovascular disease, and many other common conditions, acetaminophen is the most appropriate option for safe and effective OTC pain relief because of these serious and potentially fatal risks associated with taking NSAIDs.[iv] Research suggests that even if a small percentage of patients shifted from acetaminophen to ibuprofen or other NSAIDs, it would increase the risk to public health, including more deaths and hospitalizations.[v]

Research & Openness about the Risks

The risks of acetaminophen overdose have been well documented in medical and public health literature, and known for decades. During that time, there has been discussion, and sometimes disagreement,

within the medical and public health community about which measures should be taken to attempt to reduce that risk. We have participated in that discussion, and have conducted and funded research to advance the medical community's understanding of acetaminophen and its risks and benefits, and of different measures to help avoid overdose. We believe that we have funded more studies on acetaminophen than any other public or private organization, and have helped make it one of the most studied OTC medicines in the world.

Our support for research includes a nationwide research program that led to the FDA approving an antidote for acetaminophen overdose in 1985. Utilization of this antidote has become the standard for treating acetaminophen overdose in hospitals and emergency rooms nationwide.[vi]

The published literature and McNeil's internal studies, which include over 150 efficacy and/or safety studies, have demonstrated acetaminophen's effectiveness in treating many types of pain: dental pain, headache, minor pain due to arthritis, pain due to menstrual cramps, and muscle aches and pains. Many of the studies we have conducted and supported have been peer-reviewed and shared openly with the scientific and medical communities through medical publications.[vii]

After decades of study and over half a century after acetaminophen was first made available to the public as an over-the-counter medicine, it remains a safe and critical OTC medicine when used as directed. Acetaminophen, the active ingredient in TYLENOL®, is recommended in guidelines developed by numerous medical organizations. In 2006, the FDA concluded unequivocally that:

> *"Acetaminophen and NSAIDs, when labeled appropriately and used as directed, are safe and effective OTC drug products that benefit tens of millions of consumers every year. FDA believes these products should continue to be accessible to consumers in the OTC setting.*[viii]

Pharmacovigilance

We have a deep respect for the Food and Drug Administration (FDA) and its role in establishing and enforcing regulations. We strive to report every adverse event involving TYLENOL® that we become aware of. In fact, although we are only required to report adverse events related to our products, we report adverse events related to all acetaminophen products, when the specific product is not known. ALL of our employees are required to be trained in adverse event reporting. Adverse event reporting is the responsibility of everyone in our company. Any time one of our employees hears of an adverse event, that person is required to report it within 24 hours to the company. All serious adverse events are reported to the FDA within 15 days.

When we or the FDA have observed any gaps in our adverse event reporting we have acted to correct them, and we continue to improve our systems. Computer databases have helped us further improve adverse event reporting by enabling us to search published journals faster and more efficiently for potential adverse events. In addition, we gather and analyze data from other groups, including the American Association of Poison Control Centers (AAPCC), that have a broad, nation-wide view of acetaminophen data across all manufacturers.

Doctor and Consumer Education

McNeil has been a leader in educating doctors and providing materials about overdose and misuse of medicines containing acetaminophen. We have supported continuing medical education, and have helped educate healthcare providers, when they're in training, about the risks and benefits of

acetaminophen. Since the early 1970s, we have provided information on the appropriate use of acetaminophen and over time included information related to acetaminophen overdose that is used in resources including the Physician Desk Reference. We provide the brochure, Guidelines for the Management of Acetaminophen Overdose, which is distributed and also housed on our Tylenol website dedicated to physicians, TYLENOL® Professional.com. This website allows doctors and other healthcare providers to access TYLENOL® information customized to fit their needs. For example, it houses overdose guidelines, clinical studies like the McNeil supported Framingham series on osteoarthritis, patient education handouts, and pediatric dosage charts.

To educate consumers about the risks of acetaminophen overdose, we created the Get Relief Responsibly initiative. A website, www.GetReliefResponsibly.com, offers consumers a wealth of information to help them use TYLENOL® safely. It includes a list of common OTC medicines that contain acetaminophen and emphasizes how important it is to read labels and avoid taking more than one medicine containing acetaminophen at the same time. We also have added a QR code, a two-dimensional barcode, on some product packaging that can be scanned with a Smartphone and which links to the educational website.[ix] Through our public awareness initiative and those of other stakeholders, like the FDA and the Consumer Healthcare Products Association, acetaminophen awareness messages have been seen over one billion times.[x]

Changes to Labels and Warnings

There are differences of opinion in the scientific and medical community about how best to communicate the risks and benefits of medicines. Perspectives about the information that should be included on medicine labels — and how that information should be presented — have evolved over time, as have labels.

After careful deliberation and discussion with the FDA, McNeil has made several label changes to TYLENOL® over the years – all for the purpose of eliminating potential confusion by consumers and protecting consumer safety. It is recognized by the FDA that labels will change over time along with new information. A label change does not mean that a prior label was inadequate, and in fact label changes are an indication that our medical understanding is evolving and that the pharmacovigilance system is working as intended.

Most recently, even though the existing maximum daily dose was safe, after consulting with the FDA, we voluntarily lowered the recommended maximum daily OTC dose of Extra Strength TYLENOL® to further expand the margin of safety between the recommended dose and potential overdose. The new dosing instructions reduce the maximum daily dose from 8 pills (4 grams) per day to 6 pills (3 grams) per day unless otherwise directed by a doctor.[xi] (This change was permitted within the products existing "OTC drug monograph," which can be found in section 300 of the *Code of Federal Regulations.*[xii]).

We have initiated discussions with the FDA and other makers of acetaminophen to adopt a common icon that would be prominently displayed on the label of all OTC and prescription medicines that contain acetaminophen.[xiii] And, because many prescription medicines contain acetaminophen, we have worked with pharmacies to improve prescription labeling to better communicate to consumers what's in their prescription medicine, like spelling out the word "acetaminophen" and putting a message directly on their purchase receipt.[xiv] Also, by the end of this year we will put a message on Extra Strength TYLENOL® bottle caps that tells consumers the product contains acetaminophen. We will continue to explore ways to educate healthcare professionals and our consumers about the safe use of TYLENOL and acetaminophen. We are proud of the work we have done to date and are committed to continue this work in the future.

[i] FDA Consumer Update, "Don't Double up on Acetaminophen", issued January 24, 2013
[ii] Response to Docket No. 1977N–0094L,FDA-Proposed Rule IAAA,McNeil Consumer Healthcare
[iii] IMS Health, IMS NDTI [2/2012-2/2013]
[iv] Docket No. FDA-2009-N-0138, Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory CommitteeMcNeil Consumer Healthcare September 30, 2009
[v] Docket No. FDA-2009-N-0138, Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee, McNeil Consumer Healthcare September 30, 2009
[vi] Guidelines for the Management of Acetaminophen Overdose, McNeil Consumer Healthcare (Bibliography)
[vii] Response to Docket No. 1977N–0094L,FDA-Proposed Rule IAAA,McNeil Consumer Healthcare
[viii] 2009 AdCom transcript and summary of minutes; 71 Fed Reg. 77314, 77315 (December 26, 2006)
[ix] Tylenol relies on mobile to educate consumers on responsible dosage", Mobile Marketer, January 31, 2012
[x] McNeil Consumer Healthcare Correspondence to the FDA, March 2013 (Docket Submission)
[xi] McNeil Consumer Healthcare Announces Plans for New Dosing Instructions for Tylenol Products," press release, July 28, 2011
[xii] Tentative Final Monograph for Internal Analgesic, AntiPyretic and AntiRheumatic Drug Products for Over-the-Counter Human Use (53 FR 46204)
[xiii] McNeil Consumer Healthcare Correspondence to the FDA, March 2013 (Docket Submission)
[xiv] National Council for Prescription Drug Programs, "NCPDP Recommendations for Improved Prescription Container Labels for Medications Containing Acetaminophen" Working Group Recommendations, July 2011

APPENDIX: ***Chronology of Actions Taken to Advance Safe Use of Acetaminophen***

- Adult TYLENOL® Regular Strength Tablets launch as OTC (1961).
- Barry Rumack of the Rocky Mountain Poison and Drug Center published a paper this year in *Pediatrics* warning of the danger of overdose with acetaminophen if not used as directed. McNeil funded the research as well as the creation of the Rumack-Matthews nomogram for acetaminophen poisoning. (1975)
- Adult Extra Strength TYLENOL® Tablets launch and TYLENOL® becomes the #1 brand of OTC analgesics in the US (1976)
- Began developing an understanding of how N-acetylcysteine (NAC) was an effective treatment for acetaminophen overdose. (1978)
- Provided funding to support Rocky Mountain Poison and Drug Center's services related to helping healthcare providers manage acetaminophen overdose. (1979-present)
- Provided acetaminophen overdose management guidelines, including fundamental information published in the Physician's Desk Reference (1979-present) and more detailed information in the Guidelines for the Management of Acute Acetaminophen Overdose. (2000-present)
- Dr. Anthony Temple published "Pediatric Dosing of Acetaminophen" in Pediatric Pharmacology with research funded by McNeil Consumer Healthcare. McNeil with Dr. Temple developed acetaminophen-dosing schedules based on age and weight, to supplement the labeling instructions as published in the 1977 Proposed Rule. These schedules were made available to healthcare professionals through the Physicians' Desk Reference (PDR) and through professional materials. (1983)
- The FDA approves N-acetylcysteine (NAC) as an antidote for acetaminophen overdose on the basis of the Rocky Mountain Poison and Drug Center Research (1985).
- Replaced capsules with tamper-resistant caplet formulation in response to product tampering. (1986)
- Voluntarily added statements telling consumers to Use One Acetaminophen Product at a time to the warnings section of acetaminophen labeling in addition to voluntarily adding the warning about liver damage risk from alcohol use in combination with TYLENOL, four years in advance of the FDA's requirement that acetaminophen labels carry the warning. (1994)
- Initiated an education program about Children's TYLENOL® products, focusing on the use of the proper dosage device. (1997)
- Implemented an easier-to-read format on TYLENOL labeling in advance of the Drug Facts final rule. (1998)
- McNeil Consumer Healthcare files a Citizen Petition with the FDA to expand dosing directions for acetaminophen to include dosing for children under two years of age. (1999)

- Introduced SAFE-TY-LOCK™ system for Infants' TYLENOL® Suspension Drops to promote proper administration of infants' concentrated acetaminophen drops. (1999)

- McNeil launched its "Know Your Medicine" campaign to complement another major campaign developed by the National Council on Patient Information and Education (NCPIE, described below). This initiative sought to encourage proper dosing and awareness of OTC analgesic products (2002)

- Distribution of over 11 million "Know Your Medicine" consumer education brochures, in English and Spanish, in retail stores, by direct mail, at pharmacy counters, and doctors' offices. (2002)

- FDA issued its final regulation on labeling for OTC pain relievers and fever reducers, including acetaminophen. Most of these warnings were implemented voluntarily by McNeil, prior to FDA's final rule. (2009)

- McNeil assembles advisory board and begins Icon Development and Research Program with preliminary presentation at the Institute of Medicine. (2009)

- McNeil launches an educational initiative, "Get Relief Responsibly" which is supported by a website, www.getreliefresponsibly.com, a **QR code on some of our product boxes** that can be scanned with a smart phone and links the consumer back to www.getreliefresponsibly.com, online advertising, patient handouts for physicians to utilize with patients, and a media relations effort. (2011)

- OTC industry announces voluntary transition to one concentration of single-ingredient pediatric liquid acetaminophen medicines. (2011)

- Coordinated with FDA to reduce maximum recommended daily dose of OTC Extra Strength TYLENOL from 4,000 mg to 3,000 mg daily, unless directed by a doctor, to further expand the margin of safety between the recommended dose and any potential overdose. (2011)