Excipients, or inert ingredients, are those substances added to pharmacologically active compounds to facilitate dosage form production, enhance drug stability, and improve palatability for the patient. While their impact is often overlooked, these chemicals can cause adverse reactions apart from the active compound, including allergic reactions. Awareness of the potential for excipients to cause adverse effects has improved in the past decade, with increasing reports in the medical literature. However, the increasing availability of generic compounds and, in the case of oral products, incomplete product labeling make assessment of the risks associated with the inert ingredients difficult. This brief overview will describe the rationale for the addition of these ingredients and discuss some of the adverse reactions reported with their use.

Preservatives
Antimicrobials and antioxidants are added to pharmaceutical products to prolong shelf life and maintain sterility. Common antimicrobial agents include chlorbutol, benzyl alcohol, sodium benzoate, sorbic acid, phenol, thimerosal, parabens, and benzalkonium chloride. Antioxidants used in pharmaceutical products include butylated hydroxytoluene and hydroxyanisole, as well as propyl gallate and sulfites. While necessary to ensure the safety of pharmaceutical products, the addition of these agents has been associated with significant adverse effects in certain patient populations.

The link between benzyl alcohol and neonatal cardiovascular collapse, “the gasping baby syndrome,” is perhaps the most widely publicized adverse reaction related to the use of inert ingredients. This relationship was discovered in 1982 after a series of neonates died or developed a severe illness associated with gasping respirations, metabolic acidosis, and hematologic abnormalities. These cases were linked to the use of intravenous flush solutions and medications containing benzyl alcohol. As a result, both the FDA and the American Academy of Pediatrics now recommend that benzyl alcohol containing products should be avoided whenever possible in infants. In older patients, benzyl alcohol use has been associated with hypersensitivity reactions, including contact dermatitis, nausea, and angioedema.

Benzalkonium chloride has received considerable attention in the past several years, as a result of its use in many nasal sprays and metered dose inhalers. In some asthmatic patients, benzalkonium chloride can produce significant bronchoconstriction. In a study by Zhang and colleagues of 28 asthmatic patients, a significant decrease in pulmonary function tests was observed after benzalkonium chloride administration. The effect was greatest at 1 minute following exposure and lasted up to 60 minutes. The response was blocked by concomitant administration of cromolyn, suggesting an allergic mechanism. In non-asthmatic patients, the use of nasal sprays with benzalkonium chloride has been linked to increasing nasal congestion, and may, in part, explain the rebound congestion associated with prolonged use of these products. Many patients with asthma also experience hypersensitivity reactions when exposed to sulfites, a common antioxidant in inhaled medications.

Sweeteners and Flavorings
In a recent survey of medications for oral use, Kumar and colleagues found that more than 90% of the products they evaluated contained both sweeteners and flavorings. The wide-spread use of these excipients reflects society’s desire for medications which look and taste appealing. When prescribing medications for children, clinicians should keep in mind that taste perception changes with age. A preference for sweet taste is innate in humans and is most
pronounced in infants. Individual differences in
taste develop throughout life, influenced by early
feeding experiences and genetic factors. As a
result, products that are appealing to infants and
young children will not necessarily be accepted
by older children and young adults. This may be
of particular importance in teens who are unable
to swallow tablets and capsules. Liquids
containing large amounts of artificial sweeteners
can leave a noticeable bitter aftertaste and result
in decreased patient compliance.

Saccharin, sucrose, sorbitol, aspartame, and
fructose are the most commonly used sweeteners
in the United States. Often, two or more
sweeteners are combined in the preparation of
oral liquids. Lactose is used in the manufacturing
of tablet and capsule dosage forms as a diluent or
crype, rather than as a sweetener. Although most
patients tolerate these sugars without adverse
effects, some may experience hypersensitivity
reactions. The use of sorbitol and lactose may be
associated with diarrhea and abdominal pain, but
rarely is the quantity in pharmaceutical
preparations large enough to be responsible for
these effects. However, patients who are known
to be lactose-intolerant have been reported to
develop diarrhea even with the intake of small
quantities in tablet dosage forms.

The concentration of sweeteners in oral solutions
and suspensions averages 30-50% w/v of the
formulation. In some antibiotic and cough/cold
preparations, the sweetener content can be as
high as 80% w/v. Use of products containing
large quantities of sugar should be avoided in
children with diabetes, whenever possible. If
these products must be used, blood glucose
monitoring should be performed regularly to
tailor insulin therapy.

Long-term use of oral medications containing
large amounts of sweeteners has been linked to
excessive development of dental caries in children.
Sugars, especially sucrose, cause a
decrease in dental plaque pH, dissolving tooth
enamel and promoting dental cariogenesis. As a result, it is recommended that sugar-free
products be used whenever long-term therapy is
expected. If a product containing a sweetener
must be used, parents or care providers should
be instructed to have the child rinse his or her
mouth out with water following ingestion of each
dose. A wide variety of flavorings, both natural and
synthetic, are used in the production of
pharmaceutical products. Flavorings contain
numerous ingredients. As an example, one brand
of synthetic strawberry flavoring on the market
contains more than 30 different components.
While most manufacturers are moving towards
full disclosure on product labeling, flavorings
often remain unspecified as a “trade secret.” In
Kumar’s survey, 35% of products evaluated did
not provide information on flavorings. As a
result, it may be difficult to identify adverse
reactions or allergies to specific ingredients.
Reports of adverse effects associated with
flavorings are uncommon, but menthol, lemon
oil, and oil of peppermint have been associated
with hypersensitivity reactions.

Dyes and Colorants
Dyes and other coloring agents are used both to
improve a medication’s appearance and to
provide a unique product identity. There are
currently more than 100 dyes and coloring agents
approved by the Food and Drug Administration
for use in pharmaceutical preparations. Most
oral liquid dosage formulations contain between
one and three different dyes.

Exposure to dyes and colorants in medications
has been associated with hypersensitivity
reactions in susceptible patients, including
anaphylaxis, bronchoconstriction, angioedema,
urticaria, abdominal pain and vomiting, and
contact dermatitis. Although not borne out in
controlled clinical trials, some parents and
clinicians have suggested a link between dyes
and hyperactivity and aggressive behavior in
children. Some of the dyes associated with hypersensitivity
reactions include azo dyes such as tartrazine
(FD&C Yellow 5), FD&C Yellow 6, FD&C Red
36, FD&C Red 17, and triphenylmethane dyes
(FD&C Blue 1 and 2 and Green 3). The first two
of these dyes (Yellow 5 and 6) have
demonstrated cross-reactivity with aspirin and
indomethacin. They should be avoided in
patients with known allergies to these
medications. Quinoline dyes (Yellow 10 and 11)
have been linked with contact sensitization.
Some xanthene dyes (FD&C Red 3 and Red 22)
are potent photosensitizers.

As reactions to dyes become more well described
in the medical literature, many manufacturers
have begun producing dye-free preparations. Sensitive patients should be instructed to look for these products when purchasing nonprescription medications. Most prescription products, such as the oral antibiotics, contain dyes. For these cases, health care providers must work with patients and their families to identify those dyes most likely to be related to the adverse reaction and to select products without the potential triggering agents.

Solvents
Medications which are not highly water soluble present a problem for pharmaceutical manufacturers. The product must be made soluble enough for oral, topical, or parenteral use, without significantly altering its stability. Propylene glycol and polyethylene glycol are used as solvents in many dosage formulations. Propylene glycol has been associated with a number of adverse effects, including cardiac arrhythmias, seizures, respiratory depression, severe hyperosmolality, lactic acidosis, and severe thrombophlebitis when administered by rapid intravenous injection. For this reason, medications such as phenobarbital, phenytoin, and diazepam must be administered slowly when given intravenously. Polyethylene glycol has recently been associated with nephrotoxicity in a patient exposed to large doses while receiving sedation with lorazepam.

Ethanol is commonly used as a solvent in the manufacturing of oral liquid dosage formulations. Two concerns exist with the use of ethanol in products designed for the pediatric market, acute intoxication with accidental overdose and chronic toxicity associated with routine use for chronic medical conditions.

In 1984, the American Academy of Pediatrics recommended limiting alcohol content to no more than 5% and restricting the volume of products containing alcohol to non-lethal quantities. In 1993, a committee representing the Food and Drug Administration and the Nonprescription Drug Manufacturers Association agreed to develop voluntary limits for the alcohol content of liquid dosage preparations. The committee concluded that all over-the-counter products designed for children less than six years of age should be alcohol-free. Products labeled for children 6-12 years of age should contain no more than 5% alcohol. Products for children over 12 years and adults should be limited to 10% alcohol content. In certain products requiring higher alcohol contents to achieve solubility, warning labels would instruct parents to contact a physician prior to giving these products to children.

In summary, the use of pharmaceutical excipients is necessary to produce the wide variety of medications available to patients. While most patients tolerate these inert ingredients without problems, it should be remembered that these compounds are capable of inducing adverse effects. The trend towards more prudent use of these chemicals by pharmaceutical manufacturers and the increasing availability of labeling information will help clinicians to select appropriate products for their patients.

References
Pharmacology Literature Review

Famotidine Use in Children
The authors of this brief review present a summary of the eight pharmacokinetic, pharmacodynamic, and safety studies of famotidine, an H$_2$-antagonist, in children. To date, three kinetics studies have been performed, demonstrating similar results. The average volume of distribution of famotidine in the children studied ranged from 0.3-0.7 L/kg and the average elimination half-life varied from 2.3 to 3.3 hours, similar to adult values. Based on the results of several pharmacodynamic studies, the authors suggest a famotidine starting dose of 0.5 mg/kg given every 8 to 12 hours for children with normal renal function. Doses should be reduced by 25% in children with moderate renal dysfunction and by 50% in patients with severe renal insufficiency. James LP, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in pediatric patients. Clin Pharmacokinet 1996;31:103-10.

Gender patterns revealed that boys were more likely than girls to receive psychotropic drugs at an early age (usually methylphenidate). This use then declines with advancing age. Usage in girls followed the opposite pattern, with higher rates of prescribing during teen-age years. The authors also found a direct relationship between parental psychotropic use and the use of these medications in their children. Although the retrospective nature of this study limits its application, it does provide useful basic demographic information on these medications in the pediatric population. Hong SH, Shepherd MD. Psychosocial and demographic predictors of pediatric psychotropic medication use. Am J Health-Syst Pharm 1996;53:1934-9.

Formulary Update

The Pharmacy and Therapeutics Committee took a summer recess and did not meet during August. Monthly sessions will resume in September.