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ISMP
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Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Food-drug allergies—inactive ingredients taking active roles

Problem: "Inactive" ingredients in medications are often assumed to be harmless, yet these substances, some of which may be food allergens, can pose a risk for certain patients. The most common type of allergic reaction that patients experience is an immunoglobulin E (IgE) mediated food allergy, which has increased in prevalence, resulting in the need to treat patients in hospitals for anaphylaxis due to food allergic reactions.[1] More than 170 different foods have been identified as allergens, some of which are found in medications, with the most common ones listed below.[2]

Top Eight Most Common Food Allergens

- Milk
- Wheat
- Shellfish
- Soy
- Eggs
- Fish
- Peanuts
- Tree nuts

Medications are formulated with inactive ingredients for a variety of reasons such as enhancing stability, absorption, appearance (e.g., dyes), or taste, but they can be a hidden source of food allergen exposure. This may occur by contact, ingestion, inhalation, or infusion of the product.[3] The Food Allergen Labeling and Consumer Protection Act of 2004 requires that a food product containing any one of the eight most common food allergens must have the allergen clearly listed on the label; however, this does not apply to drug products. Inactive ingredients in medications can sometimes be hidden in the drug's prescribing information, and there is no standardized language to convey the presence of allergens. Sometimes statements in the contraindication section of the prescribing information list specific allergens, and other times there may be a general statement such as, "This drug is contraindicated in those patients who have demonstrated or have a known hypersensitivity to (the drug) or any other constituents of the product." To complicate matters, manufacturers may use different inactive ingredients or may not disclose certain ingredients if it is considered "proprietary information." When a patient experiences a reaction of unclear origin (e.g., idiopathic anaphylaxis), it can be challenging for practitioners to identify a rare or hidden allergen.[3] If the true cause is not known, a practitioner may update the patient's chart to reflect an allergy to the medication, thus possibly limiting future use of all brands and all dosage formulations (e.g., tablet, suspension, injection). However, the reaction may have been the result of an inactive ingredient (e.g., egg) used by a particular manufacturer in their medication formulation; therefore, the medication produced by another manufacturer, or a different formulation may be safe to use.

Define and Document Allergies

Another challenge is that there may be a significant overestimation of food allergies. One study suggested at least 10.8% (greater than 26 million) of adults in the United States have a food allergy, whereas nearly 19% believe that they have one.[4] Not all patients or practitioners may understand the differences between an immunologic allergic reaction and an intolerance or sensitivity. With a true food allergy, even small amounts of the offending food can trigger a range of symptoms, which can be severe or life-threatening. In contrast, food intolerance is often limited to the digestive system and causes less serious symptoms.[5] Although not a true allergy, celiac

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Cyanokit—action needed! On February 6, 2025, BTG International (a SERB Pharmaceuticals company) issued a letter regarding a problem with their **CYANOKIT** (hydroxocobalamin) injection, which is indicated for the treatment of cyanide poisoning. The letter informs healthcare professionals that the manufacturing of Cyanokit has been suspended due to a quality defect involving potential microbial contamination, risking sterility and possibly causing systemic infection or sepsis in patients. This has resulted in a shortage of this critical antidote.

BTG International is working with the US Food and Drug Administration (FDA) to make impacted batches available during this period of shortage. All currently available batches of Cyanokit are included in the letter and are potentially affected by this quality defect. Although these batches met release

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IMPORTANT! Read and utilize the Acute Care Action Agenda

One of the most important ways to prevent medication errors is to learn about problems that have occurred in other organizations and to use that information to prevent similar problems at your practice site. To promote such a process, selected items from the **January – March 2025** issues of the ***ISMP Medication Safety Alert! Acute Care*** newsletters have been prepared for use by an interdisciplinary committee or with frontline staff to stimulate discussion and action to reduce the risk of medication errors. Each item includes a brief description of the medication safety problem, a few recommendations to reduce the risk of errors, and the issue number to locate additional information. The **Action Agenda** is available for download as an Excel file.

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disease is an autoimmune condition, and the ingestion of gluten initiates a complex inflammatory reaction that can make people with celiac disease very sick. Some patients experience symptoms after ingesting a food that is not related to an allergy, intolerance, or celiac disease. These are referred to as food sensitivities, where exposure to specific foods may create an immune reaction that generates a multitude of symptoms (e.g., joint pain, stomach pain, fatigue, rashes, and brain fog). The symptoms are not life-threatening, but they can be disruptive. Gluten is one of the best-known triggers of food sensitivities.[6] Patients may also have a preference to avoid a particular food due to a variety of reasons (e.g., psychological, aversion, religious, or cultural).

If a practitioner documents that a patient has an allergy to milk in the electronic health record (EHR), when in fact the patient has an intolerance (e.g., lactose intolerance) or preference to avoid dairy, this could impact which medications are prescribed for the patient. Inaccurately categorizing an intolerance or preference as an allergy could also lead to practitioners receiving unactionable or nuisance alerts.

Clinical Decision Support (CDS) Configuration

Documentation of reactions to medications, foods, and other potential healthcare exposures occurs in the EHR allergy field to inform future prescribing and prevent adverse events by triggering allergy alerts as part of CDS. There are often different fields in the EHR for practitioners to use when describing an allergy (e.g., allergen, reaction, reaction type, date noted, severity, criticality).[6] Documentation of allergens can be in a structured, coded data format (e.g., drop-down lists, checkboxes, flowsheets) that will trigger alerts, or in an unstructured free-text format that will not trigger alerts.[7] Food and other inactive ingredients in medications may not be configured within the EHR, so practitioners may need to free-text this information, bypassing CDS. In addition, alerts may only be triggered for active ingredients in drug products in the EHR, leaving a gap in CDS for inactive ingredient allergies. This has led to some organizations creating customized configurations for select inactive ingredients.[8] However, since inactive ingredients may vary by manufacturer and may be modified over time, this can be challenging for organizations to maintain actionable alerts.

Error Reports

*A nurse administered a **SMOFLIPID** (lipid emulsion, fish oil and plant based) infusion to a patient. Shortly after the emulsion began infusing, the patient experienced symptoms of an allergic reaction. The nurse stopped the infusion, and the symptoms subsided. Afterward, the nurse identified that the patient had a shellfish allergy, but it was not documented in the allergy field in the EHR. The prescribing information states that SMOFlipid is contraindicated in patients with known hypersensitivity to fish, eggs, soybeans, peanuts, or any of the active or inactive ingredients in SMOFlipid, but does not mention shellfish. The pharmacist contacted the manufacturer, Fresenius Kabi, to determine the source of fish oil in the product. They were told, "The fish source is from the open sea and therefore the fish type could include different types of fish (such as, but not limited to, anchovies, sardines, smelt, tuna, herring, and Jack Mackerel) and can also include shellfish. The USP definition for fish oil allows a very broad variety of fish families that may be used to obtain fish oil. The manufacturing process for the fish oil is proprietary. SMOFlipid's crude fish oil is tested for dioxins and PCB (polychlorinated biphenyl). The fish oil for SMOFlipid is fully refined, deodorized, and purified." The nurse updated the patient's allergy list to include SMOFlipid and shellfish.*

*A patient with a documented (in the EHR) history of an anaphylactic reaction to dairy and milk products was prescribed a probiotic, **FLORANEX** chewable (L. acidophilus and L. bulgaricus). After administration, the patient experienced a respiratory event after an episode of emesis. While the medical team was investigating potential causes of the patient's symptoms, the pharmacist reviewed the Floranex inactive ingredients listed on the product label and discovered that it contained milk. The EHR did not alert the prescriber or the pharmacist when the order was*

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specifications, sterility and endotoxin content cannot be ensured.

According to the letter, practitioners should weigh the potential benefit of using Cyanokit against the potential risk of infection. Patients who receive Cyanokit need to be closely monitored for signs of systemic infection or sepsis. If systemic infection or sepsis is suspected (e.g., fever, persistent hypotension indicative of shock), initiate blood cultures and start empiric antibiotic therapy, adjusting treatment based on pathogen identification and susceptibility results. Practitioners should administer these Cyanokit batches via an intravenous (IV) administration set equipped with a 0.2-micron inline filter with a polyethersulfone (PES) filtration membrane and having a membrane surface greater than or equal to 10 cm^2. Simultaneous administration of Cyanokit and blood products through the same IV line is not recommended.

Organizations that use this product must ensure vigilance. ISMP recommends securing (i.e., with tape or a rubber band) a 0.2-micron inline filter to the Cyanokit and adding an auxiliary warning to alert practitioners that this product must be administered with the filter. Build clinical decision support into the electronic health record (EHR) to prompt monitoring parameters. Before discharge, educate patients about signs of infection and when to seek emergent care. Report adverse reactions to BTG International, FDA, and ISMP.

Alpha-gal syndrome—evaluate inactive ingredients. Alpha-gal syndrome is a potentially life-threatening allergic condition that can occur after a patient has been bitten by a tick. It is named for a molecule, galactose-alpha-1,3-galactose, that's found in most mammals. Symptoms may then occur after the patient eats red meat or is exposed to other products made from mammals (e.g., gelatin, dairy products). A hospital reported that a patient with alpha-gal syndrome received beef broth with their food tray despite a special diet order in the electronic health record (EHR) stating the patient cannot have beef or pork products. Then, during

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placed or reviewed because the system was only set up to alert for active ingredients. After the event, the organization built a custom alert to screen for this food-drug interaction.

Safe Practice Recommendations: For patients with food allergies, inactive ingredients in medications may create challenges. Consider the following recommendations to prevent patient harm.

For Manufacturers

Specify inactive ingredient content. Manufacturers should explicitly identify a product's inactive ingredient content, including the exact amount, on the package and label, and in the prescribing information to help ensure this information is readily available to practitioners and patients. This is especially important for medications with an inactive ingredient known to be a common food allergen. Drug information providers and EHR vendors will also then be able to take advantage of this information to provide enhanced CDS for practitioners to prevent patient harm.

Avoid allergens. When possible, manufacturers should preferentially use non-allergen inactive ingredients (i.e., avoid the top eight most common food allergens) in pharmaceutical products.

For Drug Information Providers

Provide information about inactive ingredients. Drug database providers should collaborate with manufacturers and ensure inactive ingredient content is captured in the drug information database, especially any that include the top eight most common food allergens.

For EHR Vendors

Enhance EHR systems. EHR vendors should ensure systems have a method for practitioners to clearly indicate that a patient has a coded reaction to an inactive ingredient (e.g., the top eight most common food allergens) so that CDS support can be maximized. Without such safeguards, some organizations have implemented workarounds such as using a free-text entry to document allergies that will not generate an alert (e.g., food-drug interaction checking), but clearly, this is not as effective as automated CDS.

For FDA

Standardize language. To address this issue, on June 21, 2023, the Allergen Disclosure In Non-food Articles Act was introduced to amend the Federal Food, Drug, and Cosmetic Act of 1938. If approved, it would require the label of a drug intended for human use to identify each ingredient in that drug that is derived directly or indirectly from a major food allergen or a gluten-containing grain. In addition, the US Food and Drug Administration (FDA) should also encourage manufacturers to use standard language to convey inactive ingredients on the medication package/label and in prescribing information. For example, patients who have phenylketonuria, a rare inherited disorder, cannot break down phenylalanine and must restrict food and medication that contain protein or aspartame, an artificial sweetener. To avoid a dangerous build-up of phenylalanine in these patients, the FDA requires over-the-counter and prescription drug labels to include the statement, "Phenylketonurics: Contains Phenylalanine (__) mg Per (Dosage Unit)," to alert of the presence and amount of phenylalanine. We encourage similar standard language to be used for other medications with hidden allergens to warn patients and practitioners of inactive ingredients that could cause harm.

For Organizations

Assess medications on formulary. To identify inactive ingredients (i.e., the top eight most common food allergens) in medications on your hospital formulary, review the package/label

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event investigation, the hospital identified their current EHR functionality did not have a mechanism to screen for inactive ingredients in medications and vaccines (e.g., gelatin, glycerin, magnesium stearate, bovine extract) or animal-derived products (e.g., monoclonal antibodies, heparin, certain antivenoms). These may be contraindicated for patients with alpha-gal syndrome (see Products That May Contain Alpha-gal).

We discussed a similar concern with inactive ingredients in our July 28, 2022, newsletter article, *Hidden pork content in gelatin capsules*. Some medications, including the **COLACE** brand of docusate sodium, have gelatin capsules sourced from pigs, but product labeling doesn't state that. People with food allergies or those who want to avoid animal products need to know the origin of the ingredients contained in their medications. We contacted Avrio Health, the manufacturer of the brand product Colace, and confirmed that the gelatin used is sourced from pigs, which isn't specified in the labeling. It appears that, under current regulations, the product label is not required to detail the animal source of the gelatin.

There is a good chance that staff may be unaware of alpha-gal syndrome and how patients with this condition may react to certain medications and inactive ingredients. Refer them to resources such as the Centers for Disease Control and Prevention (CDC) website. Consider building an alert to notify practitioners when you become aware of a patient with food allergies, or someone known to have alpha-gal syndrome.

Evaluate your EHR functionality to determine if an alert would fire if a patient with an alpha-gal allergy had a documented allergy to an animal-derived product or an inactive ingredient known to trigger this allergy. During transitions of care, specifically ask patients about any reactions they've had from foods, medications, or inactive ingredients, and document the details of the reaction in the EHR. For additional recommendations, refer to this week's feature article, *Food-drug allergies—inactive ingredients taking active roles*. If patients have concerns

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and prescribing information, and/or contact the manufacturer. Evaluate your EHR system to determine if an alert would be triggered if the patient had a documented allergy to that ingredient. Incorporate this as part of the review process when evaluating new drugs or formulations for formulary addition.

Designate a preferred formulation. When possible, purchase medication formulations that do not contain inactive ingredients that are common allergens, especially for the top eight most common food allergens.

Develop a policy and procedure. Develop or enhance the organizational policy and procedure to identify patients with allergies (including to inactive ingredients). Outline a process to notify practitioners and to ensure these patients receive the appropriate medications. Ensure the policy clearly defines the difference between an allergy, intolerance, sensitivity, and preference and how to document each in the EHR.

Enhance CDS. Integrate CDS that differentiates between an allergy, intolerance, sensitivity, and preference. When applying CDS, consider reaction severity and alert fatigue. This helps ensure accurate information is clearly presented to practitioners at the correct time in the clinical decision-making process, limiting nuisance alerts that practitioners may bypass. Standardize documentation for reactions (e.g., date of reaction, substance, reaction type [allergy, intolerance, sensitivity] and status, severity of reaction). Also, consider building additional standardized fields (e.g., contraindication, patient preference, description). If possible, consider removing free-text allergy documentation which will not support coded allergy alerts. If free-text entries are allowed, monitor the data and adjust/build additional coded allergies. Whenever possible, prospectively build documentation strategies that will allow your organization to run useful reports for tracking and trending reactions. Evaluate and implement EHR system updates to ensure the most up-to-date versions are available with any enhancements.

Review and update allergies. During transitions in care, do not assume documented allergies are accurate, and specifically ask patients about any reactions they have had from foods, medications, or inactive ingredients. Gather sufficient details about the causative agent and what the reaction was (e.g., anaphylaxis, mild intolerances) and update this information in the allergy field in the EHR. Allergy, intolerance, and sensitivity entries should be as specific as possible. They should not be considered complete until a reaction and severity are selected.

Educate practitioners. Practitioners should review and understand a patient's allergies, intolerance, or sensitivities including those to inactive ingredients and food allergens. Educate practitioners about the difference between a true allergy, compared to an intolerance, sensitivity, or preference, and how this information should be documented in the EHR.

Monitor patients. If a patient has an anaphylactic reaction after receiving a medication, collect a detailed clinical history to identify possible sources of allergens. Consider referring the patient to an allergy and immunology specialist for a diagnostic workup to identify the responsible allergen. If a patient has been identified as having an allergy, intolerance, or sensitivity to an inactive ingredient, practitioners should document this information in the EHR and follow the organizational policy and procedure as it relates to ordering, dispensing, and administering medications.

Communicate with outpatient pharmacies. When planning for outpatient medication management before discharge, consider if the patient has an allergy to an inactive ingredient. Ask patients for the name of their pharmacy and collaborate to ensure the receiving pharmacists understand the patient's allergy and unique needs. Check if the pharmacy has a method to "flag" the patient's allergy in the system, or how this information will be documented and communicated.

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about the inactive ingredients contained in a medication, the pharmacy should review the package/label and prescribing information or contact the manufacturer for more information. Additional resources include the following: *What medications are contraindicated with an alpha-gal allergy? What mammal by-products could be listed as inactive ingredients on the package insert (i.e., magnesium stearate, gelatin)?* (InpharmD.com) and *Alpha-gal Syndrome* (VEGANMED.org).

This is how easily bad things can happen. An elderly patient with acute coronary syndrome was admitted to the emergency department (ED). The ED provider ordered four tablets of chewable aspirin (81 mg each); however, the patient did not have their dentures and was unable to chew. Since oral syringes were not readily available, the nurse dissolved the aspirin in water and drew it up in a parenteral luer-lock syringe. The nurse then handed the syringe to a student to administer to the patient without communicating the intended route, and the student started to administer the medication intravenously (IV). After half of the dose had been administered, the nurse realized the error and stopped the student from injecting the remaining dose.

We have previously warned about wrong route errors. To prevent these types of errors, organizations should purchase, store, and maintain an adequate supply of oral/ENFit syringes in all patient care areas where oral/enteral medications may be prepared and administered. Pharmacy should verify that oral/ENFit syringes are in stock and readily available with every monthly unit inspection. In our experience, even in hospitals that are committed to stocking oral/ENFit syringes, they are not consistently available. Educate staff about why parenteral syringes should never be used to prepare oral medications. If a medication is not administered immediately by the individual who prepared it, the syringe should be labeled (e.g., medication name, dose, route, expiration). In addition, if a syringe is handed to another practitioner to administer, this information also needs to be verbally communicated, and the syringe needs to be labeled.

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Educate patients. Engage patients and use each transition of care as an opportunity to collaborate and ensure accurate allergy reconciliation. Educate patients about the difference between a true allergy, compared to an intolerance, sensitivity, or preference, and why it is important to document them accurately. For patients with multiple allergies, intolerances, and/or sensitivities, it is especially important to review the patient's history (including any food allergies) in the EHR and with the patient or family. Do not minimize "bad reactions" based on non-IgE mediated effects. Consider using patient-facing applications to permit patient-initiated participation in keeping their records updated. Empower patients to become stewards of their healthcare by ensuring accuracy in their medical records.

Monitor alerts. Evaluate allergy alert frequency and alert override rates, considering the appropriateness of the overrides. This process will help identify opportunities to adjust alert functionality and reduce unnecessary alerts. Ensure alerts are actionable and triggered at the appropriate times (e.g., prescribing, verification, prior to administration).[9]

Learn from errors. Encourage staff to report close calls as well as errors that have reached the patient to ISMP. Review internally reported allergy-related errors as well as published external events. For tracking and trending purposes, categorize the severity of voluntary error reports detailing reactions using the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index.

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Special Announcements

Apply for New Fellowship

Applications are now being accepted for the first ***Ochsner Children's & ISMP Safe Medication Management Fellowship***! This unique one-year program for pharmacists offers the opportunity to learn from and work with top experts in medication safety while supporting error-prevention strategies in pediatrics at Ochsner Health. The fellowship begins in the summer of 2025 and requires **working onsite at Ochsner Health in New Orleans, LA**, and remotely with ISMP. The deadline to apply is **May 2, 2025**. For more information and to apply, please visit: *Safe Medication Management Fellowships*.

Human Factors Engineering (HFE) training course

ECRI's human factors engineers will be providing an in-person training course, ***ECRI Human Factors Engineering for Medical Procurement Safety***, on **May 15, 2025**, in Herndon, VA (near Washington, DC). This one-day course will describe and demonstrate how to apply HFE techniques to the selection and evaluation of medical and drug-delivery devices and other equipment and supplies. For more information and to register, click here.

Virtual MSI workshop

Join us for our next ***ISMP Medication Safety Intensive (MSI)*** workshop on **May 8 and 9, 2025**. For more information and to register, please click here.

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Editors: Shannon Bertagnoli, PharmD; Ann Shastay, MSN, RN, AOCN; Rita K. Jew, PharmD, MBA, BCPPS, FASHP; Editor Emeritus, Michael R. Cohen, RPh, MS, ScD (hon), DPS (hon), FASHP. ISMP, 5200 Butler Pike, Plymouth Meeting, PA 19462. Email: ismpinfo@ismp.org; Tel: 215-947-7797.