Medication Safety

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Director of Pharmacovigilance, National Pharmacy and Therapeutics Committee
What is Pharmacovigilance?
Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse drug events or any other drug-related problem.

https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

The process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines.

https://ec.europa.eu/health/human-use/pharmacovigilance_en
IHS Pharmacovigilance Program

IHS National Pharmacy and Therapeutics Committee

IHS Pharmacovigilance
IHS Pharmacovigilance Program Goals

**Mission**: to oversee medication safety within the Indian Health System (IHS). The pharmacovigilance program provides clinicians with knowledge, tools, and resources to reduce the risks associated with medication therapy in an effort to promote safe and rational use.

**Vision**: to prevent adverse medication events from occurring and to use medications appropriately to achieve optimal health outcomes.
Why is the IHS Pharmacovigilance Program Part of the NPTC?
The P&T committee should participate in performance improvement activities... initiate, direct, and review the results of medication-use evaluation programs to optimize medication use and monitor outcomes of formulary decisions... take actions to prevent, monitor, and evaluate adverse drug reactions and medication errors.

https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/gdl-pharmacy-therapeutics-committee-formulary-system.ashx
NPTC Formulary Review Process

Evaluate clinical data related to the medication/class
Efficacy, Safety, Clinical pearls, Experience

Review medication use in the IHS (pharmacovigilance)

Review procurement and distribution costs
NPTC Formulary Review Process Goals

- Improve Patient Health
  - Evaluate clinical data related to the medication/class

- Improve Population Health
  - Review medication use in the IHS (pharmacovigilance)

- Reduce Costs
  - Review procurement and distribution costs
Example Report
Recent Examples

Efficacy

Utilization

Formulary Impact

Direct Oral Anticoagulants (DOAC)

Background: Apixaban was added to the National Core Formulary in November 2017. At that time, data from clinical trials indicated that DOACs were equivalent in efficacy for reducing strokes and thromboembolism, however apixaban was associated with statistically fewer serious adverse drug events (bleeding) than other DOACs.

This Formulary Impact Analysis was conducted to answer three questions:

QUESTION 1: Was there an increase in the use of DOACs compared to warfarin after adding apixaban to the National Core Formulary?

FINDINGS: Although direct causation cannot be determined, an increase in DOAC purchases and a decrease in warfarin purchases occurred in the time period following the addition of apixaban. The benefits of this change are that DOACs are safer alternatives to warfarin in most patients and require less monitoring.

QUESTION 2: Did the addition of apixaban to the National Core Formulary affect the procurement of individual DOACs?

FINDINGS: IHS data show low use of dabigatran, consistent use of rivaroxaban over time, and an increase in apixaban use overall. Possible reasons include that patients previously on rivaroxaban were maintained on this therapy while new or DOAC-naïve patients requiring anticoagulants are being prescribed apixaban. Apixaban is prescribed approximately twice as often as rivaroxaban.

QUESTION 3: Did the addition of apixaban to the National Core Formulary improve patient safety?

FINDINGS: A recently published meta-analysis* showed that the findings from 2017 are consistent today – all DOACs provide similar efficacy; however, major bleeding risks are lower with apixaban. IHS data supports these findings with an absolute reduction in major bleeding events of approximately 4% in patients prescribed apixaban compared to rivaroxaban.

What About Medication Safety and Adverse Drug Events?
Adverse Drug Event (ADE)

• An unwanted effect or harm that occurs after using a medication where the medication is suspected as the cause.
• An adverse event can result from a medication error but often occur with appropriate medication use.
Adverse Drug Event Statistics

• In inpatient settings, ADEs:
  • Account for an estimated 1 in 3 of all hospital adverse events
  • Affect about 2 million hospital stays each year
  • Prolong hospital stays by 1.7 to 4.6 days

• Each year, ADEs in outpatient settings account for:
  • Over 3.5 million physician office visits
  • An estimated 1 million emergency department visits
  • Approximately 125,000 hospital admissions

https://health.gov/our-work/health-care-quality/adverse-drug-events
Adverse Drug Events During Clinical Trials may be Different Than What Happens in Real Life

• Longer duration of therapy
• Different patient populations
  • Pregnant women
  • Children
  • Elderly
• People with other diseases
• People taking other medications
• Use in other conditions
Pharmacovigilance in Action

• Park-Davis submitted an application to the FDA for Troglitazone (Rezulin®) in 1996.
Pharmacovigilance in Action (2)

John Gueriguian, an officer with the FDA assigned to review the Troglitazone studies, did not recommend approval based on observations of increased risk of liver damage.
Pharmacovigilance in Action (3)

- Park-Davis complained to the FDA.
- John was removed from his post and Rezulin® was approved in 1997.
Pharmacovigilance in Action (4)

More than 430 reports of liver failure were traced to Rezulin® use by the NIH, who interpreted the risk of liver failure to be 1,200 times greater in patients taking Rezulin®.
Pharmacovigilance in Action (5)

- Park-Davis was accused of covering up the risks.
- “I believe that the company . . . deliberately omitted reports of liver toxicity and misrepresented serious adverse events experienced by patients in their clinical studies.” – Dr. Janet McGill
Pharmacovigilance in Action (6)

Rezulin® was withdrawn from the market in 2000.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Reason for Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprotinin (Trasylol)</td>
<td>Increased risk of death</td>
</tr>
<tr>
<td>Rimonabant (Acomplia)</td>
<td>Risk of severe depression and suicide</td>
</tr>
<tr>
<td>Drotrecogin alfa (Xigris)</td>
<td>Lack of efficacy (no survival benefit)</td>
</tr>
<tr>
<td>Propoxyphene (Darvocet/Darvon)</td>
<td>Increased risk of heart attacks and stroke</td>
</tr>
<tr>
<td>Pergolide (Permax)</td>
<td>Risk for heart valve damage</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx), Valdecoxib (Bextra)</td>
<td>Risk of myocardial infarction and stroke</td>
</tr>
<tr>
<td>Cerivastatin (Baycol, Lipobay)</td>
<td>Risk of rhabdomyolysis and kidney failure</td>
</tr>
<tr>
<td>Fenfluramine/phentermine</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>QT prolongation and phototoxicity</td>
</tr>
<tr>
<td>Troglitazone (Rezulin)</td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>

Onakpoya et al. BMC Medicine (2016) 14:10
The Role of Pharmacovigilance

Belongs to anyone and everyone that provides patient care.
Reporting Adverse Drug Events (ADE)
Indian Health Manual Chapter 7, 3-7.14

• All adverse drug events will be reported to and reviewed by the SU P&T, quality assurance and/or medication safety committee(s).
  • This includes all allergic responses to drugs, any overextension of therapeutic effects or side effects, and any other unexpected response to a drug that results in actual or potential risk to the patient.
  • In addition, all serious, unusual, or previously unreported adverse effects will be reported directly to the FDA MedWatch program.
  • Adverse reactions to vaccines will be reported to the Vaccine Adverse Event Reporting System. A copy of each report will be filed in the pharmacy with a copy sent to the P&T Committee.
Reporting Adverse Events

Adverse Drug Event (ADE)
MedWatch

Adverse Vaccine Event (AVE)
VAERS
Adverse Drug Events

Adverse Drug Events (ADE) should be documented in the patient’s medical record. If the ADE is serious or unexpected, it will be reported to the MedWatch reporting program or the Vaccine Adverse Event Reporting System (VAERS) as described in the Indian Health Manual.

Documenting Common ADEs

Common adverse events are the anticipated but unwanted experiences that patients have after taking a medication. These adverse events can be documented in the patient’s problem list as a purpose of visit. An Adverse Drug Event pick list has been created to easily find commonly reported adverse events. It is important that the name of the suspected medication be included in the purpose of visit narrative to associate the medication with the finding.

- Documenting Common ADEs [PDF - 224 KB]

Documenting Serious or Unexpected ADEs

Serious adverse drug events can be captured prominently in the patient’s medical record using the Adverse Reaction Tracking System (ART).

- Documenting Serious ADEs [PDF - 202 KB]

Reporting Serious or Unexpected ADEs

Submit an Adverse Drug Event report for a medication with the MedWatch reporting program. There are three options for submitting a MedWatch report:

1. Complete the Online Voluntary Reporting Form on the FDA website.
2. Complete the FDA 3500 form [PDF] and mail or fax the form to the FDA per the instructions on the form.
3. For sites using the RPMS EHR, you can install the IHS Adverse Event EHR note template. This template will help craft your note and create a MedWatch submission at the same time. For sites not using RPMS EHR, a similar template can be developed.

- Submitting ADEs to MedWatch with the RPMS EHR Template [PDF - 134 KB]

When using the online voluntary Reporting Form or the FDA 3500 form, it is essential that the words “IHS” or “Indian Health Service” appear on the form, ideally in the address of the “Reporter” section.

Submit an Adverse Vaccine Event report using the VAERS online reporting tool.

- Reporting Adverse Vaccine Events handout [PDF - 148 KB]
- VAERS Reporting Presentation [PDF - 3 MB]

It is essential that the words “IHS” or “Indian Health Service” appear on the form in item #26 (Immunization Project Report Number).
Adverse Drug Event Reporting
Submitting an Adverse Drug Event

Serious and unexpected ADEs must be reported to MedWatch

• **Serious Adverse Drug Events**: are those that result in death, require hospital admission or prolongation of existing hospital stay, result in persistent or significant disability/incapacity, or are life threatening.

• **Unexpected Adverse Drug Events**: are those that occur but are not found labeled in the package insert, pharmacologic references, or in the medical literature or that occur in a patient where the effect is unexpected.

*If you are uncertain, submit it!*
Submitting an Adverse Drug Event Options

Three options:


2. Download the FDA 3500 form, complete, and mail/fax to MedWatch.

3. Document in the patient’s medical record using the RPMS EHR adverse event template. Print and mail/fax to MedWatch.
MedWatch Options
IMPORTANT: Document IHS

• Place **IHS** at the top of the form or in the Reporter Section (Section G).

• Federal, Tribal, and Urban programs are all encouraged to put **IHS** into this field to help better evaluate adverse events experienced in our patient population.
IHS Pharmacovigilance

Submit MedWatch Report → MedWatch Database → IHS Cases Provided to IHS
Statin Associated Autoimmune Myopathy

• Reports of patients developing severe muscle pain and weakness that appears to be associated with statin therapy
• Pain and weakness continue to progress after discontinuation
• Rheumatologist working with IHS identified this as SAAM
  • The body’s immune system develops antibodies against itself
• Multiple cases referred by members of the NPTC to the NPTC core team
• Cases encouraged to be reported to MedWatch
• FDA has contacted IHS and continues to monitor this effect
Adverse Vaccine Event Reporting
Vaccine Safety: Common Adverse Events

- Vaccines are considered to be safe and effective with most common adverse events being mild and are signs that the body is developing immunity:
  - Pain, swelling, or redness where the shot was given
  - Mild fever
  - Chills
  - Feeling tired
  - Headache
  - Muscle and joint aches
- [https://www.vaccines.gov/basics/safety/side_effects](https://www.vaccines.gov/basics/safety/side_effects)
Vaccine Safety: Serious Adverse Events

• More serious side effects are rare but can occur. Some examples:
  • Anaphylaxis (0.65 cases/1 million vaccinations)
  • Thrombocytopenia from Rubella vaccine (1 case/40,000 vaccinations)
  • Orchitis from Mumps vaccine (0.3 cases/1 million vaccinations)
  • Intussusception from Rotavirus vaccine (1 case/100,000 vaccinations)
  • Guillain-Barre from flu vaccine (1 case/1.25 million vaccinations; association is stronger with flu infection than the vaccine)

Vigilance is Needed Even More Now
The CDC has created a new smart phone tool called v-safe. Once you have signed up and have received the COVID-19 vaccination, v-safe will send you a text message asking you how you are doing and if you have any adverse events.

If you have clinically significant adverse events, the CDC will contact you for more information.

You will also receive a text notification when (if) you are due for a second COVID vaccine.

Submitting an Adverse Vaccine Event

• It is required by IHS policy in Chapter 7 of the Indian Health Manual
• Healthcare providers may be required by law to report under certain conditions.
  • Any adverse event listed in the VAERS Table of Reportable Events Following Vaccination that occurs within the specified time period after vaccinations.
  • An adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine.
**VAERS Table of Reportable Events Following Vaccination**

<table>
<thead>
<tr>
<th>Vaccine/Toxoid</th>
<th>Event and Interval** from vaccination</th>
</tr>
</thead>
</table>
| Tetanus in any combination; DTaP, DTP, DTP-Hib, DT, Td, TT, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV | A. Anaphylaxis or anaphylactic shock (7 days)  
B. Brachial neuritis (28 days)  
C. Shoulder Injury Related to Vaccine Administration (7 days)  
D. Vasovagal syncope (7 days)  
E. Any acute complications or sequelae (including death) of above events (interval - not applicable)  
F. Events described in manufacturer’s package insert as contraindications to additional doses of vaccine (interval - see package insert) |
| Pertussis in any combination; DTaP, DTP, DTP-Hib, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV | A. Anaphylaxis or anaphylactic shock (7 days)  
B. Encephalopathy or encephalitis (7 days)  
C. Shoulder Injury Related to Vaccine Administration (7 days)  
D. Vasovagal syncope (7 days)  
E. Any acute complications or sequelae (including death) of above events (interval - not applicable)  
F. Events described in manufacturer’s package insert as contraindications to additional doses of vaccine (interval - see package insert) |
| Measles, mumps and rubella in any combination; MMR, MMRV, MM | A. Anaphylaxis or anaphylactic shock (7 days)  
B. Encephalopathy or encephalitis (15 days)  
C. Shoulder Injury Related to Vaccine Administration (7 days)  
D. Vasovagal syncope (7 days)  
E. Any acute complications or sequelae (including death) of above events (interval - not applicable)  
F. Events described in manufacturer’s package insert as contraindications to additional doses of vaccine (interval - see package insert) |
| Rubella in any combination; MMR, MMRV | A. Chronic arthritis (42 days)  
B. Any acute complications or sequelae (including death) of above event (interval - not applicable)  
C. Events described in manufacturer’s package insert as contraindications to additional doses of vaccine (interval - see package insert) |
| Measles in any combination; MMR, MMRV, MM | A. Thrombocytopenic purpura (7-30 days)  
B. Vaccine-strain measles viral infection in an immunodeficient recipient  
  o Vaccine-strain virus identified (interval - not applicable)  
  o If strain determination is not done or if laboratory testing is inconclusive (12 months)  
C. Any acute complications or sequelae (including... |
Reporting a Vaccine Adverse Event

- Open a web browser and go to https://vaers.hhs.gov
- Scroll down and select Report an Adverse Event.
Reporting a Vaccine Adverse Event Options

There are two options to submit an adverse event to VAERS:

- Using the online report.
- Uploading and submitting a PDF form.

This option enables you to begin the report, save it, and finish it at a later time.

Two Ways to Submit an Online Report to VAERS

Option 1 - Report Online to VAERS (Preferred)
Submit a VAERS report online. The report must be completed online and submitted in one sitting and cannot be saved and returned to at a later time. Your information will be erased if you are inactive for 20 minutes; you will receive a warning after 15 minutes.

Option 2 - Report using a Writable PDF Form
Download the Writable PDF Form to a computer. Complete the VAERS report offline if you do not have time to complete it all at once. Return to this page to upload the completed Writable PDF form by clicking here.

If you need further assistance with reporting to VAERS, please email info@VAERS.org or call 1-800-822-7967.

Checklist

- Patient information (age, d. birth, sex)
- Vaccine information (brand name, dosage)
- Date, time, and location administered
- Date and time when adverse event(s) started
- Symptoms and outcome of adverse event(s)
- Medical tests and laboratory results (if applicable)
- Physician's contact information (if applicable)
Reporting a Vaccine Adverse Event Form

• After clicking the online report icon, a new page will open.
• Begin filling out the report with as much info as possible.
  • Please note that items marked with an asterisk (*) are mandatory.
IMPORTANT: Document IHS (cont.)

• Place **IHS** in the Item 26 field (Immunization Project Report Number)

- Federal, Tribal, and Urban programs are all encouraged to put **IHS** into this field to help better evaluate adverse events experienced in our patient population.
Final Step

After you have completed the form, click the **Submit** button in the bottom right to send your report to VAERS and complete the reporting process.

*Warning:* Knowingly filing a false VAERS report with the intent to mislead the Department of Health and Human Services is a violation of Federal law (18 U.S. Code § 1001) punishable by fine and imprisonment.
IHS Pharmacovigilance (cont.)

Submit VAERS Report → VAERS Database → IHS Cases Provided to IHS
Indian Health Service  
National Pharmacy and Therapeutics Committee  
Quarterly Adverse Drug/Vaccine Event Report

This Quarterly Adverse Drug/Vaccine Event Report period includes adverse events submitted to the FDA MedWatch or FDA/CDC VAERS programs from January 1, 2020 through November 1, 2020.

<table>
<thead>
<tr>
<th>Medication and Suspected Adverse Event</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine Mouthwash: Throat swelling and hives. Hives persisted for 2 months.</td>
<td>Hypersensitivity reactions, including anaphylaxis, have been reported.</td>
</tr>
</tbody>
</table>
| Remdesivir:  
- 3 reports decreased renal function  
- 3 reports of increased LFTs  
- Severe leukopenia  
- Shivering during infusion  
- Increased O2 requirements followed by STEMI  
- Decreased Hg  
- Hypotension and bradycardia 14th after 2nd dose | Anticipated adverse events include hyperglycemia, increased LFTs, renal failure, and fever. Hypersensitivity or infusion related reactions may include: hypotension, nausea, vomiting, diaphoresis, and shivering.  
From internal IHS remdesivir utilization surveillance, adverse events have included:  
- 8 reports of decreased renal function  
- 13 reports of increased LFTs  
- Leukopenia  
- Allergic reaction  
- Atrial Fibrillation  
- Infusion related reactions (5 reports of nausea, 3 reports of bradycardia, hypotension, & shivering) |
| Semaglutide: Hair loss | Causal relationship is unclear. Hair loss is not reported in the package insert but 11 cases of alopecia have been reported to the FDA MedWatch program. Hair loss is associated with uncontrolled diabetes and may be disease related rather than medication related. |
| Varenicline: Pain in multiple joints | Musculoskeletal pain has been observed in <1% of patients. Joint swelling, stiffness, range of motion, and dislocation have been reported to the FDA MedWatch program. |
| Verapamil: Bradycardia | Common adverse event consistent with pharmacologic action. |

Report suspected Adverse Drug/Vaccine Events:  
- Report suspected adverse drug events to MedWatch: Enter "IHS" in the reporter field  
- Report suspected adverse vaccine events to VAERS: Enter "IHS" in the field for item #26

November 3, 2020
I-STAR and Employees

• Document employee AVEs
• May attach a copy of the VAERS report

https://home.ihs.gov/i-star/
Drug Safety Board

• To help the FDA assess the impact of their safety decisions on the healthcare systems of its Federal Partners
Drug Safety Information

• **Drug Safety Communications**
  • Communications distributed by the FDA regarding the prescribing and monitoring of FDA approved medications and devices.
    • NSAID use and pregnancy warning
    • Lorcaserin withdrawal

• **Drug Safety Alerts**
  • Information about the safe and effective use of one or more medications. Drug safety alerts provide information about current topics and findings to help raise awareness and promote medication safety.
    • Removal of Boxed Warning for Canagliflozin and amputations
    • Metformin Recall
    • Look alike-sound alike medications
Drug Safety Communication

NSAID Use During Pregnancy May Cause Fetal Renal Dysfunction Resulting in Low Amniotic Fluid

The FDA has issued a Drug Safety Communication (DSC) to alert clinicians about risks of NSAID use in pregnant women. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby.

After around 20 weeks of pregnancy, the unborn babies’ kidneys produce most of the amniotic fluid. Amniotic fluid provides a protective cushion and helps the unborn babies’ lungs, digestive system, and muscles develop. Kidney problems can lead to oligohydramnios (low levels of this amniotic fluid surrounding the baby).

Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

FDA recommends that health care professionals limit prescribing NSAIDs between 20 to 30 weeks of pregnancy and avoid prescribing them after 30 weeks of pregnancy.

If NSAID treatment is determined necessary (e.g., the use of 81 mg aspirin for certain pregnancy-related conditions), limit use to the lowest effective dose and shortest duration possible.

Serious Adverse Drug Events associated with the “Benadryl Challenge”

The FDA has issued a Drug Safety Communication (DSC) to alert clinicians about recent reports of teenagers taking higher than recommended doses of diphenhydramine (Benadryl®) in response to a video challenge that appeared on the social medial platform called TikTok.

TikTok is a website and phone application that enables users to share short videos on any topic.

A series of videos called the “Benadryl Challenge” were recently posted on TikTok and encouraged viewers to take 10-20 doses of diphenhydramine to get high and hallucinate.

Higher than recommended doses of diphenhydramine can result in serious heart problems, seizures, coma, and death.

The FDA encourages consumers, parents, and caregivers to store diphenhydramine and other medications out of reach and sight or to lock up medications to prevent misuse or accidental poisonings.

Encourage teens and caregivers to read and follow the Drug Facts label. In the event of suspected overdose, health care professionals should attempt to determine whether a patient took diphenhydramine.
Drug Safety Alerts

Prevent Look-Alike / Sound-Alike (LASA) Medication Errors

Improve medication identification by providing details. Try to include:

- Diagnosis or Intended Use
- Dose or strength
- Route of administration or formulation

Reduce the risk of medication error in patient care areas.

- Keep rarely used or LASA medications in the pharmacy.
- Label bins or shelves with brand names for LASA medications.
- Keep medication dispensing areas clean and organized.
- Have a double check system in place to help prevent accidental errors.

Store medications so they are easily recognized.

- Store LASA medications in separate locations or non-alphabetically.
- Place medications so the label and medication name is always showing.
- Use Tall Man lettering to emphasize differences in medications with sound-alike names: metFORMIN and metoPROLOL.
- Add auxiliary labels to storage bins or shelves or provide labels with information such as route of administration or formulation to more easily identify the correct medication.
- Label bins or shelves with brand names for LASA medications.
- Minimize the availability of multiple medication strengths.

Indian Health Service
National Pharmacy and Therapeutics Committee
Pharmacovigilance Drug Safety Alert

August 26, 2020

FDA Removes Boxed Warning About Risk of Leg and Foot Amputations for Canagliflozin (Invokana®)

Background: Canagliflozin belongs to a class of medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. It is used in patients with Type 2 Diabetes to lower blood glucose.

- 2013 FDA approves canagliflozin for the treatment of Type 2 Diabetes.
- 2017 A Boxed Warning that canagliflozin may increase the risk of leg and foot amputation is added to the package insert.
- 2018 Canagliflozin is approved by the FDA to reduce the risk of major heart-related events such as heart attack, stroke, or death in patients with type 2 diabetes who have known heart disease.
- 2019 Canagliflozin is approved by the FDA to reduce the risk of end-stage kidney disease, worsening of kidney function, heart-related death, and being hospitalized for heart failure in certain patients with type 2 diabetes and diabetic kidney disease.
- 2020 FDA removes Boxed Warning about risk of leg and foot amputations for canagliflozin:
  - Recent clinical trials show that there continues to be an increased risk of leg and foot amputation with canagliflozin; however, the risk is lower than previously described, especially when treatment is appropriately monitored.
  - Recently observed cardiovascular and renal protection effects increases the benefit of canagliflozin therapy in patients with type 2 diabetes.

Recommendation: Although the Boxed Warning will be removed, there is still an increased risk of leg and foot amputations. Health care professionals and patients should continue to recognize the importance of preventative foot care and monitor for new pain, tenderness, sores, ulcers, and infections in the legs and feet. Risk factors that may predispose patients to the need for
How to Get Drug Safety Messages

- NPTC
- Pharmacy
- Public Health Nursing
- Diabetes Coordinators
- NCCMO
- Advanced Practice Nursing
- Midwives
- CCC
- IHS Nursing
- IHS Clinical Directors

https://www.ihs.gov/listserv/topics/signup/?list_id=183
Drug Recalls

Medication Recall Initiated

FDA and Drug Manufacturer(s):
Develop a recall strategy including the process for medication handling, returns, and information for health care providers and consumers.

IHS Pharmaceutical Prime Vendor (PPV):
Notify the IHS of the medication recall through direct communication or by posting information on their procurement software.

National Supply Service Center (NSSC):
Notifies service units of the recall and provides guidance from the manufacturer(s) and IHS PPV on how to handle the recalled medications.

Service Units:
Follow written drug recall procedures per the IHS Indian Health Manual (https://www.ihs.gov/hmp/pdf/part-3/3b7/04-3_7.pdf)

Indian Health Service
URGENT: Metformin ER Recall

Dear PATIENT,

This letter is to inform you that there is a medication recall for metformin ER (also called Glucophage®). Metformin is a tablet that is normally used to manage diabetes. The Food and Drug Administration (FDA) found a chemical called NDMA in some brands of metformin ER tablets. Based on our information, we believe that you may have received a prescription for metformin ER that could contain small amounts of NDMA.

What is NDMA? NDMA (N-nitrosodimethylamine) is a chemical that is classified as a probable cancer-causing agent based on laboratory test results when ingested in large amounts.

Is the NDMA in the metformin ER dangerous? The NDMA in metformin ER products does not pose any immediate health risks. NDMA can be found in water and foods. The FDA has determined that the levels of NDMA in metformin ER are similar to the levels you would expect to find in common foods like grilled and smoked meats.

What can you do?
Do not stop taking your metformin ER until you talk to a health care provider.

You should continue taking metformin ER. It could be dangerous to stop taking metformin ER without first talking to your health care provider. You can return the contaminated metformin ER and have it exchanged for another brand (if available) or discuss treatment options with your health care provider.

If you have any questions, please call our pharmacy staff at #.#.#.#.

Thank you,

FACILITY
Some General Principals to Reduce the Risk of ADEs
Remove Medications

• Remove medications when not needed
  • Identify medications causing adverse drug events and consider stopping or alternatives.
  • Identify medications used to prevent or treat side effects.
  • Reassess the need for chronic medications.
• Stop one med at a time
Anticholinergic Medications

- Risk of delirium, cognitive impairment, falls, constipation, urinary retention, dry mouth
  - Avoid first generation antihistamines (diphenhydramine)
    - Use loratadine or non-pharmacologic therapy (sleep hygiene)
  - Avoid tricyclics or paroxetine
    - Other SSRI or SNRI
  - Limit overactive bladder (oxybutynin)
    - Emphasize non-drug (caffeine, alcohol, fluids before bed)
Medications and Hypoglycemia

**Risk factors for drug induced hypoglycemia**

- Advanced age
- More than one glucose lowering medication
- Interactions
- Tight control
- Excessive alcohol intake
- Reduced carbohydrate intake
- Exercise
- Hepatic dysfunction
- Renal dysfunction
- History of hypoglycemia
- Recent hospitalization

- ACE Inhibitors
- Fluoroquinolones
- Quinine/quinidine
- Tyrosine kinase inhibitors
Sulfonylureas

- Increased risk of hypoglycemia
  - 1st generation > glyburide (especially in the elderly or renal impairment) > glipizide > glicazide

- Secondary failure (5+ years)

- Cardiovascular neutral
  - TOSCA.IT
  - CAROLINA


Conclusion

1. Report adverse drug events to MedWatch
   • Put IHS in the **Reporter Section** (section G)

2. Report adverse vaccine events to VAERS
   • Put IHS in field #26

3. Sign up for the NPTC listserv
It Took More Than 430 Reports

Dr. John L. Gueriguian, records show, voiced concern to Warner-Lambert as early as January 1994 about Rezulin's "potential toxicities."

Photo: Chuck Kennedy, for the Times

You can make a difference. You can improve medication safety. You are the pharmacovigilance team.
Thank you!