**AMERICAN COLLEGE OF RHEUMATOLOGY**
**POSITION STATEMENT**

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| **SUBJECT:** | Pharmacovigilance |
| **PRESENTED BY:** | Committee on Rheumatologic Care |
| **FOR DISTRIBUTION TO:** | Members of the American College of Rheumatology<br>Food and Drug Administration<br>Medical Societies<br>Centers for Medicare and Medicaid Services<br>Managed Care Organizations/Third Party Carriers<br>Members of Congress<br>Arthritis Foundation |

## POSITIONS:

1. The American College of Rheumatology (ACR) supports robust pharmacovigilance to support the safety of medications used in rheumatology, including pharmacovigilance during pregnancy.

2. The ACR recognizes the vital role of healthcare providers in actively monitoring patients for adverse events and reporting any serious adverse events through MedWatch.

3. The ACR recommends pharmacovigilance systems be readily available and easy to use for patients given the current partial reliance on patients for spontaneous reporting of adverse events.

4. When reporting adverse events related to biologics, the ACR urges the reporting of full product information, including biosimilar suffix, lot information, and indication for using the drug.

## BACKGROUND:

Pharmacovigilance is the science of detection and assessment of adverse effects from drugs, with particular emphasis on effects not recognized prior to licensing.[1] Pharmacovigilance is important because most new drugs receive marketing approval after testing in a limited number of patients (frequently fewer than 1,000) for a limited time period.[2] At time of marketing the safety profile of any new drug is incomplete. After marketing, the drug is used in a much larger and more diverse population, allowing for the detection of rare adverse events, as well as events that are more common, in particular sub-populations of patients. Pharmacovigilance is alsoimportant in detecting bad lots of drug or other unexpected changes to a drug's safety profile.

Pharmacovigilance in the U.S.

Pharmacovigilance, as a formal activity, is primarily carried out by drug manufacturers and the drug regulatory agency of each country (specifically, the FDA in the United States). TheFDA's Office of Surveillance and Epidemiology (OSE) is charged with evaluating product risks and promoting the safe use of products by the American people.[3]

New drugs are often approved in the United States with very few patient-years of exposure; therefore, the FDA takes a continuous life-cycle approach to monitoring drugs for safety. Detection of adverse events essentially occurs in 2 ways: Detection of new adverse eventscan come from reports of individual cases (voluntarily from patients or health professionals, and mandatorily by manufacturers); or through aggregation of observational data in large databases.

The FDA has several programs for monitoring trends in drug safety. The oldest of these is the **Adverse Event Reporting System (AERS)**. This was originally developed in 1969 as the Spontaneous Reporting System and migrated to AERS in 1997.[4] This program collects information on individual reports of adverse drug reactions. The majority of these reports come from manufacturers due to mandatory reporting requirements as they become aware of this information.

Additional information enters AERS from voluntary, direct reports from patients and medical professionals through the **MedWatch** program. Through MedWatch, health care professionals and consumers may submit electronic reports to AERS when they find a problemwith a drug, medical device, biologic agent, or other FDA-regulated product.

Additional programs relevant to pharmacovigilance and managed by the FDA include:

**REMS:** The Food and Drug Administration Amendments Act of 2007 gave the FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks in everyday use. These programs range from medication guides for patients, to restricted prescription and distribution networks. See current examples at REMS@FDA.[5]

**Safe Use Initiative:** This is a system of private and public collaborations with the healthcare community. Its goal is to reduce preventable harm by identifying specific medication risks and developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use.[6]

**Sentinel Initiative:** This is a linked, sustainable system that uses existing automated databases from multiple sources to actively monitor drug safety and rely less on spontaneous case reports. A pilot phase – Mini-Sentinel – was completed and the full system was implemented in 2016.[7] It is particularly important with the advent of accelerated approval of drugs. Sentinel is a distributed system – all data stay in their existing environments, not a central database. FDA identifies safety questions and sends them to participating partners. Data partners (e.g.

potentially RISE for ACR) may then evaluate data in their own systems with appropriate privacy protections and forward results to FDA for aggregation.

Pharmacovigilance during Pregnancy

Although the FDA does not conduct or endorse any pregnancy registries, a list of pregnancy exposure registries, including several anti-rheumatic drugs, can be found on the FDA website.[8]

Pharmacovigilance in the International Setting

The United States also participates in pharmacovigilance on a world-wide level. After nearly 10,000 babies were born with birth defects associated with thalidomide, the World Health Organization (WHO) developed a pharmacovigilance program called Programme for International Drug Monitoring (PIDM) in 1968. Within this program, pharmacovigilance is performed at the national level, with countries reporting adverse events through a protocol called Individual Case Safety Reports. As of January 2016, 127 countries, including the United States, report to the PIDM. Data are stored at the Uppsala Monitoring Centre in a database called VigiBase.

The Importance of Pharmacovigilance in the Biosimilar Era

Due to the complex manufacturing processes of biopharmaceuticals, biosimilars are not identical to their reference products or even between two different biosimilar manufacturers. This may result in differences in adverse events and/or immunogenicity between originator and biosimilar products. As such, adverse event reporting with biologics (including biosimilars) should include the drug name suffix. Furthermore, lot number should be included in the medical record of all patients receiving biologic medications to allow for detailed post-marketing analyses and attribution of adverse events to the correct biologic.

For robust pharmacovigilance of biosimilars to occur, there must be the ability to track the products to the manufacturer. Under the FDA's final naming guidance, all biological products must bear a non-proprietary name that includes a unique four-letter suffix. The ACR additionally advocates for inclusion of lot number for each medication to improve tracking. As the US healthcare system relies heavily on spontaneous reporting of adverse events from patients and/or health care providers, *it is essential that the non-proprietary name and lot number is collected when adverse events are reported to ensure that any post-marketing adverse events are attributedto the correct medication.*

Healthcare providers should be educated to include the biologic product's suffix in all prescriptions; if the suffix is missing, the pharmacist should clarify the desired biologic product to be dispensed. This will help prevent inappropriate substitutions (see Biosimilar PS).

Given the extrapolation of indications that may occur for biosimilar drugs, the indication for which the biosimilar was prescribed should be collected during adverse event reporting to identify potential at-risk populations for a specific adverse event.

Rheumatology Providers and Pharmacovigilance

Pharmacovigilance requires the active participation of a variety of stakeholders including patients, healthcare providers, pharmacies and pharmaceutical companies. The ACR recognizes the importance of the active participation of rheumatology healthcare providers in monitoring patients for adverse events and reporting any serious adverse events through MedWatch. A serious adverse event as defined by the FDA includes an event resulting in death or a life threatening event; an event resulting in hospitalization, disability or permanent damage, or congenital anomaly/birth defect; an event that required medical or surgical intervention to prevent permanent impairment of a body function; or any other serious medical event which may jeopardize the patient.[1] The ACR strongly encourages all rheumatology healthcare providers to report any such adverse events through the FDA website.[9]

**REFERENCES:**


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