



Methotrexate Test Systems

Chemistry Devices Advisory Panel Meeting
April 25, 2013

Tracey Bosworth, MT (ASCP)
Scientific Reviewer

Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

Classification of Methotrexate Test Systems

- Regulatory History of Medical Device Classification and Methotrexate Test Systems
- Indications for Use for Methotrexate Test Systems
- Overview of Methotrexate
- Safety and Effectiveness of Methotrexate Test Systems
- The Agency's Premarket Review and Postmarket Surveillance
- Summary and Panel Deliberation Considerations

Regulatory History

- Methotrexate test systems are considered pre-amendments devices since they were in commercial distribution prior to May 28, 1976 when the Medical Device Amendment Act became effective.
- Recommendations for the classification of existing medical devices by their risks into Class I, II, or III were determined by a series of classification panel meetings held after the enactment of the Medical Device Amendments.
- However, methotrexate test systems were not classified during the original device classification process.
- Therefore, the purpose of this meeting is to obtain the Panel's recommendation for the appropriate regulatory classification of methotrexate test systems.

...Regulatory History

- The first post-amendments 510(k) for a methotrexate test system was submitted in 1978 and was found to be substantially equivalent to a methotrexate assay that was in commercial distribution since 1974.
- For the last 37 years, methotrexate test systems have been reviewed by the Agency through the premarket notification process, also known as a 510(k) review, as unclassified devices. Seven methotrexate test systems have been FDA cleared in that time.

Classification Considerations

For the purposes of classification, the FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

- The persons for whose use the device is represented or intended;
- The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling of the device, and other intended conditions of use;
- The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
- The reliability of the device.

Indications for Use

A description of the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.

Methotrexate Test Systems

Indications for Use:

Methotrexate test systems are used for the measurement of methotrexate in human samples, typically serum or plasma. The measurements obtained are used in monitoring levels of methotrexate to ensure appropriate drug therapy. These devices generally provide a quantitative drug concentration result.

Methotrexate, the Drug

- Methotrexate is a chemotherapeutic agent which competitively inhibits the binding of folic acid to dihydrofolate reductase to inhibit the growth of rapidly dividing cells.
- FDA approved indications for use are for the treatment of certain types of malignancy, rheumatoid arthritis, and psoriasis.
- To effectively inhibit the growth of tumor cells, a certain degree of toxicity is necessary. However, methotrexate toxicity is non-specific and may be toxic to healthy cells as well.
- The toxic effects may be reversed by administering the folic acid alternate, leucovorin. This is referred to as “leucovorin rescue.”

Adverse Effects of Methotrexate

- Unexpectedly severe (sometimes fatal) bone marrow suppression and aplastic anemia
 - Gastrointestinal toxicity
 - Hepatotoxicity
 - Methotrexate-induced lung disease
 - Tumor lysis syndrome
 - Severe, occasionally fatal, skin reactions
 - Potentially fatal opportunistic infections, especially pneumonia
 - Methotrexate given along with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis
- Patients undergoing methotrexate therapy should be closely monitored so that toxic effects are promptly detected and treated.

High-Dose Methotrexate Monitoring for the Treatment of Malignancy

- High-dose methotrexate therapy may be monitored with one or more methotrexate tests that are typically ordered at 24, 48, and as needed at 72 hours after administering the drug.
- Testing is performed to monitor therapeutic concentrations at these time points and to assure that the drug is being sufficiently eliminated.

Low-Dose Methotrexate Monitoring

- Measurement of methotrexate levels during treatment of rheumatoid arthritis and psoriasis has not been proven to be of much benefit due to the low dosages given, which are often below the detection limit of the assay. Therefore, methotrexate tests are generally not ordered for low dose treatment.
- Instead, low-dose methotrexate treatment is typically monitored by hematology, liver and renal function tests.

Methotrexate Test Systems

- Methotrexate test systems may include enzyme and fluorescence based immunoassays which may be performed on clinical chemistry analyzers.
- More complex and specific methods, such as HPLC, may also be used to measure methotrexate levels.
- This testing is typically performed by laboratory professionals, in a clinical laboratory setting, with a physician's order.
- The measurements are quantitative.

Safety and Effectiveness, Risks and Mitigations

- For *in vitro* diagnostic devices, the majority of the risks to health are not from the direct use of the device (chemical burns, electrical shock) as may be the case with other types of medical devices.
- Rather, the risks of *in vitro* diagnostic devices are generally related to the impact of the decisions made in patient treatment based on erroneous test results, such as undetected false positive or false negative results.

False Positive Risks

- A false positive test result is an overestimation of the drug concentration in the sample being tested.
- When an falsely high methotrexate drug concentration goes undetected, the impact will vary based on the clinical situation, testing reasons, and the degree of inaccuracy of the result.

Risk: If the result is being used to determine the dosage of methotrexate, an overestimation could contribute to the decision to decrease the dose below what is necessary for effective treatment. This may result in an increased risk of tumor relapse.

Overestimation Caused by Metabolites

- According to the reviewed scientific literature and our own regulatory experience, false positive results for immunoassay tests are most commonly due to cross-reactivity of the assay with the methotrexate metabolites, 7-OHMXT and DAMPA*.
- The degree of the interference of methotrexate metabolites may be assessed by comparing immunoassay test results to those results obtained by more specific methods such as HPLC.
- HPLC is able to distinguish between methotrexate and its metabolites.

* 4-[[2,4-diamino-6-(pteridinyl)methyl]-methylamino]-benzoic acid

...Overestimation Caused by Metabolites

- Several published articles are based on scientific studies which assess the interference of methotrexate metabolites on immunoassays.
- For example, in one study, the methotrexate levels were measured in 420 blood samples using 4 different manufacturers' immunoassays. The samples were also tested by the HPLC method.
- After comparing the results of each of the immunoassays to those obtained by the HPLC method, there was found to be a 3% to 31% overestimation of methotrexate levels by the immunoassays.

Fotoohi K, et al., *Interference of 7-hydroxymethotrexate with the determination of methotrexate in plasma samples from children with acute lymphoblastic leukemia employing routine clinical assays.* J Chromatogr B Analyt Technol Biomed Life Sci. 2005 Mar 25;817(2):139-44

False Negative Risks

- A false negative test result is an underestimation of the methotrexate concentration in the sample.
- When a falsely low test result goes undetected, the impact will vary by factors including the clinical situation, the reason for testing, and the extent of the inaccuracy.

Risk: If methotrexate testing is being used to determine the treatment strategy, underestimation of methotrexate could contribute to a decision to increase the dose above that which is necessary for therapeutic benefit. This may result in an increased risk of toxicity.

Other Potential Causes of Erroneous Results

- Assay imprecision
- Assay bias
- Interferences
- Test design flaws
- Device malfunctions
- Calibration errors or drifts
- Contaminated or expired reagents
- Pre-analytical errors

Agency Regulation

- FDA regulation **helps to mitigate such potential risks** of in vitro diagnostic devices before they are marketed.
- Since the Agency never called for Premarket Approval (PMA), as required for Class III devices, methotrexate test systems have been cleared through the 510(k) process since 1978.

Class II Devices and Special Controls

- Many therapeutic drug monitoring test systems are regulated as Class II devices and are cleared through the 510(k) process.
- Class II therapeutic drug monitoring systems such as tests for cyclosporine, sirolimus, and tacrolimus have **Special Controls**, which may include a description of the risk(s) to health, study designs, and clinical data requirements necessary to support 510(k) clearance.

The 510k Review

The Agency's 510(k) review of methotrexate test systems for the past 37 years has helped to identify and mitigate many of the performance issues that may lead to erroneous results.

Before a test system is FDA cleared for use and allowed to be marketed, the 510(k) submitted by the manufacturer is thoroughly reviewed by the Agency and must have acceptable **performance characteristics**, such as:

- Accuracy
- Precision
- Specificity
- Linearity
- Detection Limits

... The 510(k) Review

In addition, as part of the review, the Agency ensures that the labeling clearly communicates the information necessary for the safe and effective use of the device such as:

- Indications for use and the intended use
- Specimen collection, handling, and storage
- Step-by-step instructions to obtain accurate test results
- Expected performance characteristics
- Calibration and control procedures
- Limitations which may negatively impact test results
- Warnings or precautions against any known hazards

These labeling requirements, among others, for *in vitro* diagnostic devices, are codified in the Code of Federal Regulations, 21CFR 809.10.

Postmarket Surveillance and Medical Device Reports

- In addition to premarket review, postmarket surveillance is another way that the Agency is able to mitigate risks **after a device is marketed.**
- Medical Device Reports are used by the FDA to monitor the **post-market performance** of a device and to **identify those devices that are not safe and effective for their intended use.**
- The medical device industry and healthcare facilities submit mandatory medical device reports to the FDA. In addition, the Agency receives and reviews voluntary reports from the public.
- Medical device reports may include **deaths, serious injuries, and product malfunctions.**
- Medical device reports are analyzed by FDA healthcare clinicians, engineers, and scientists.
- Follow up actions may include: additional investigation of the incident, manufacturer facility inspections by the Agency, the issuance a public health advisory or a safety alert, as well as enforcement actions.

Medical Device Report Database Query

- The Agency's Medical Device Report Database currently lists a total of 6 reports for methotrexate test systems. These incidences resulted in either an underestimation of, or invalid methotrexate test results.
- One incident did result in an adverse patient outcome. As a consequence of an underestimated test result, the patient was overdosed with methotrexate and subsequently required leucovorin rescue. The patient did fully recover.
- There have been no reported deaths or permanent injuries associated with the use of methotrexate test systems.

Summary

- The technologies used in the quantitative measurement of methotrexate in human serum and plasma are well established.
- The technology has been cleared by the Agency and used for nearly 4 decades with few negative consequences as indicated by medical device reporting and published literature.
- FDA premarket review and post-market surveillance of these devices has helped to assure the safety and effectiveness of these tests when used as intended.
- The FDA believes that General Controls and Special Controls used for Class II devices would be sufficient to support a reasonable assurance of safety and effectiveness of methotrexate test systems.

Considerations for Panel Deliberation

In an effort to determine the appropriate classification of methotrexate test systems, the Chemistry Devices Advisory Panel will be asked to discuss:

- The key risks associated with methotrexate test systems due to undetected false positive and false negative test results.
- Any additional risk(s) that may have been omitted.
- How the risks may be addressed and mitigated (e.g., labeling, additional studies, etc.)
- Whether the evidence allows for methotrexate test systems to be classified as Class I, II or III in accordance with the medical device regulations.



Thank you!

Tracey.bosworth@fda.hhs.gov

301-796-2981



Methotrexate Test Systems Panel Discussion Questions

Chemistry Devices Advisory Panel Meeting

April 25, 2013

Tracey Bosworth, MT (ASCP)

Scientific Reviewer

Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

Panel Discussion

Question 1

The Agency has provided a summary of some key risks to health due to potential false positive and false negative methotrexate test results. Using your own knowledge and expertise, please identify any additional risk(s) to health you feel may have been omitted with regards to methotrexate test systems and how they may be addressed and mitigated (e.g., labeling, additional studies, etc.).

Panel Discussion

Question 2

Which classification, class I (general controls), class II (special controls), or class III (premarket approval), is most appropriate for methotrexate test systems?

Panel Discussion

Question 2(a)

If Class I is recommended, please explain why you believe that there is sufficient information to determine that general controls alone are sufficient to provide reasonable assurance of safety and effectiveness of methotrexate test systems. Should premarket notification be one of the general controls required for methotrexate tests?

Panel Discussion

Question 2(b)

If Class II is recommended, please explain why you believe that there is sufficient information to determine that general and special controls are sufficient to provide reasonable assurance of safety and effectiveness of methotrexate test systems? What special controls would you recommend (e.g., performance standards, labeling, etc.)?

Panel Discussion

Question 2(c)

If you believe the device should be classified into class III and made subject to Premarket Approval (PMA), discuss the important clinical and analytical study design features necessary to demonstrate that the device is safe and effective.