ARK Diagnostics, Inc.
Thomas Houts, Ph.D.
Sr. Director, Quality, Regulatory and Planning
48089 Fremont Boulevard
Fremont, California 94538

Re: K232017
Trade/Device Name: ARK Methotrexate II Assay
Regulatory Class: Unclassified
Product Code: LAO
Dated: November 21, 2023
Received: November 22, 2023

Dear Dr. Houts:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Joseph A. Kotarek -S
Digitally signed by Joseph A. Kotarek -S
Date: 2023.12.20 10:31:45 -05'00'

Joseph Kotarek
Branch Chief
Division of Chemistry
and Toxicology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 07/31/2026
See PRA Statement below.

510(k) Number *(if known)*
K232017

Device Name
ARK Methotrexate II Assay

Indications for Use *(Describe)*
The ARK Methotrexate II Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of methotrexate in human serum or plasma on automated clinical chemistry analyzers. The measurements obtained are used in monitoring levels of methotrexate to help ensure appropriate therapy. Specimens from patients who have received glucarpidase (carboxypeptidase G2) as a high dose methotrexate rescue therapy should not be tested with the ARK Methotrexate II Assay.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Section 5: 510(k) SUMMARY

This 510(k) Summary of Safety and Effectiveness information is being submitted in accordance with the requirements of Safe Medical Device Act of 1990 and 21 CFR 807.92.

The assigned 510(k) number is k232017.

807.92 (a)(1): Name: **ARK Diagnostics, Inc.**

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Fremont, CA 94538 USA

Owner Operator Number: 10027663
Establishment Registration: 3005755244

Phone: (510) 270-6270
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Date Prepared: June 28, 2023

807.92 (a)(2): Device name - trade name and common name, and classification

Trade Name: ARK Methotrexate II Assay

Common Name: Homogeneous Enzyme Immunoassay

Classification:

Product Code	Classification	Regulation Section	Panel
LAO – Methotrexate enzyme immunoassay	II	Unclassified	Toxicology (91)

807.92 (a)(3): Identification of the legally marketed predicate device

Predicate Device Name: ARK™ Methotrexate Assay

Predicate 510(k) Number: K111904

807.92 (a)(4): Device Description

The ARK Methotrexate II Assay is a homogeneous immunoassay based on competition between drug in the specimen and methotrexate labeled with the recombinant enzyme glucose-6-phosphate dehydrogenase (rG6PDH) for binding to the antibody reagent. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly related to the drug concentration. Active enzyme converts the coenzyme nicotinamide adenine dinucleotide (NAD) to NADH that is measured spectrophotometrically as a rate of change in absorbance. Endogenous serum G6PDH does not interfere with the results because the coenyzme NAD functions only with the bacterial enzyme (rG6PDH) used in the assay.

The ARK Methotrexate II Assay consists of reagents R1 anti-methotrexate monoclonal antibody with substrate and R2 methotrexate labeled with recombinant G6PDH enzyme.

The test system includes the ARK Methotrexate II Calibrator, ARK Methotrexate II Control, and ARK Methotrexate II Dilution Buffer.

Summary and Explanation of Test

Methotrexate [N-[4[[(2,4-diamino-6-pteridinyl) methyl] methylamino]benzoyl]-L-glutamic acid] is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis.

807.92 (a)(5): Intended Use / Indications for Use

ARK Methotrexate II Assay

The ARK Methotrexate II Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of methotrexate in human serum or plasma on automated clinical chemistry analyzers. The measurements obtained are used in monitoring levels of methotrexate to help ensure appropriate therapy. Specimens from patients who have received glucarpidase (carboxypeptidase G2) as a high dose methotrexate rescue therapy should not be tested with the ARK Methotrexate II Assay.

807.92 (a)(6): Technological Similarities and Differences to the Predicate

SUBSTANTIAL EQUIVALENCE COMPARATIVE TABLES

Comparison between ARK™ Methotrexate Assay and ARK Methotrexate II Assay

Characteristic	**Predicate Device** ARK™ Methotrexate Assay (K111904)	**Candidate Device** ARK™ Methotrexate II Assay
Intended Use	The ARK™ Methotrexate Assay is intended for the quantitative determination of methotrexate in human serum or plasma on automated clinical chemistry analyzers.	Same
Indications for Use	The results obtained are used in monitoring levels of methotrexate to help ensure appropriate therapy.	Same
Sample Matrix	Human serum or plasma	Same
Reagent Components	Two (2) reagent system: Anti-methotrexate Antibody/Substrate Reagent (R1) containing rabbit polyclonal antibodies to methotrexate, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, preservatives, and stabilizers Enzyme Reagent (R2) containing methotrexate labeled with bacterial G6PDH, buffer, bovine serum albumin, preservatives, and stabilizers	Two (2) reagent system: Anti-methotrexate Antibody/Substrate Reagent (R1) containing rabbit monoclonal antibody to methotrexate, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers Enzyme Reagent (R2) containing methotrexate labeled with recombinant G6PDH, buffer, bovine serum albumin, sodium azide, and stabilizers
Methodology	Homogeneous Enzyme Immunoassay (EIA)	Same
Platform Required	Automated Clinical Chemistry Analyzer	Same
User Environment	Professional Clinical Laboratory: Prescription Use Only	Same
Reagents Form	Liquid – Ready to use	Same
Storage	2-8˚ C until expiration date	Same
Analyte	Methotrexate	Same

807.92 (b)(1) and 807.92 (b)(2): Brief Description of Nonclinical and Clinical Data

The following performance characteristics were obtained on the Beckman Coulter AU680® automated clinical chemistry analyzer.

Limit of Quantitation (LoQ)

The LoQ of the ARK Methotrexate II Assay was established as 0.030 µmol/L and may depend on analyzer specific performance. The LoQ was determined according to CLSI EP17-A2 and is defined as the lowest concentration for which acceptable inter-assay precision (≤0.010 SD) and recovery (±0.010 µmol/L) is observed. Pooled human serum was supplemented with methotrexate to give concentrations of 0.030, 0.040, and 0.050 µmol/L. Eight (8) replicates of each sample were tested in each of five (5) runs to give a minimum of 40 replicates of each LoQ sample tested.

Nominal Concentration (µmol/L)	Grand Mean (µmol/L)	SD	CV (%)
0.030	0.034	0.002	4.87
0.040	0.043	0.002	4.01
0.050	0.052	0.003	4.00

Measurement Range

The measurement range of the ARK Methotrexate II Assay is 0.030 – 1.300 µmol/L. Specimens containing methotrexate in higher concentrations (>1.300 µmol/L) may be assayed by dilution of the specimen into the measurement range for a quantitative result or otherwise reported as detected above the measurement range. Multiply the assay result by the dilution factor to obtain the concentration of methotrexate in the undiluted specimen.

Recovery

Analytical recovery throughout the measurement range was performed by adding concentrated methotrexate drug into human serum negative for methotrexate. A certified stock concentrate of highly pure methotrexate was added volumetrically to human serum negative for methotrexate, representing drug concentrations across the assay range. Two analytical runs of three replicates of each sample were assayed on an automated clinical chemistry analyzer. The results of the six replicates of each sample were averaged and compared to the target concentration and percent recovery calculated. Recovery at all concentrations tested was ±10% of the expected sample concentration.

Theoretical Concentration Tested (µmol/L)	Mean (µmol/L)	%Recovery
0.060	0.063	104.4
0.100	0.105	105.2
0.300	0.322	107.2
0.600	0.628	104.7
1.000	1.079	107.9
1.200	1.293	107.8

Linearity

Linearity studies were performed as suggested in CLSI Protocol EP06-Ed2. A methotrexate serum sample was prepared to contain 1.600 µmol/L, and dilutions were made proportionally with human serum negative for methotrexate. Methotrexate concentrations ranged from 0.030 to 1.300 µmol/L. Two analytical runs of three replicates of each sample were assayed on an automated clinical chemistry analyzer. The results of the six replicates of each sample were averaged. A weighted linear regression analysis (intercept set to zero) was performed in which the varying observed standard deviations were weighed into the calculation. A fitted slope was generated (1.087) and used to calculate the predicated results of which the observed results were compared to. A ±10% deviation from linearity was allowable. A linear relationship was demonstrated between 0.030 and 1.300 µmol/L. Results are shown below.

Nominal Concentration (µmol/L)	Observed Results (µmol/L)	Predicted Results (µmol/L)	% Deviation
0.000	0.000	NA	NA
0.030	0.035	0.033	5.78
0.060	0.062	0.065	-4.96
0.130	0.129	0.141	-8.73
0.260	0.296	0.283	4.66
0.390	0.399	0.424	-5.98
0.520	0.549	0.565	-2.89
0.650	0.721	0.707	2.07
0.780	0.877	0.848	3.36
0.910	1.012	0.989	2.32
1.040	1.157	1.131	2.34
1.170	1.261	1.272	-0.87
1.300	1.380	1.413	-2.40

Method Comparison

Measurement procedure comparison studies were performed using CLSI Protocol EP09-A3. Results from the ARK Methotrexate II Assay on the Beckman AU680 were compared with (1) methotrexate determinations by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and (2) results from the predicate ARK Methotrexate Assay on the Beckman AU680. Leftover specimens were obtained from persons receiving high-dose methotrexate therapy.

Clinical accuracy of the ARK Methotrexate II Assay was demonstrated versus the LC-MS/MS reference method. Ninety (90) patient samples were tested. Methotrexate levels ranged from 0.026 to 1.280 µmol/L by LC-MS/MS and methotrexate levels ranged from 0.033 to 1.294 µmol/L by the ARK Methotrexate II Assay. Comparative analysis gave a slope of 1.03, intercept of 0.00, and a correlation of 0.98 calculated using Pearson's Correlation (r^2). The Passing-Bablok regression plot is shown Figure 1 and the Bland Altman analysis is shown in Figure 2.

ARK Methotrexate II Assay vs LC-MS/MS

Sample range: 0.026 to 1.280 µmol/L			
Method	**Description**		**95 % Confidence Interval**
Passing Bablok	Number of samples	90	
	Sample range (µmol/L)	0.026 to 1.280	
	Constant Bias	0.00	-0.01 to 0.01
	Proportional Bias	1.03	1.00 to 1.06
Pearson Correlation	Correlation Coefficient (r^2)	0.98	0.96 to 0.98
Bland Altman	Mean Bias	0.01	0.00 to 0.03
	SE	0.007	
	SD of difference	0.06	
			95 % Limits of Agreement
	Lower	-0.11	-0.14 to -0.09
	Upper	0.14	0.11 to 0.16

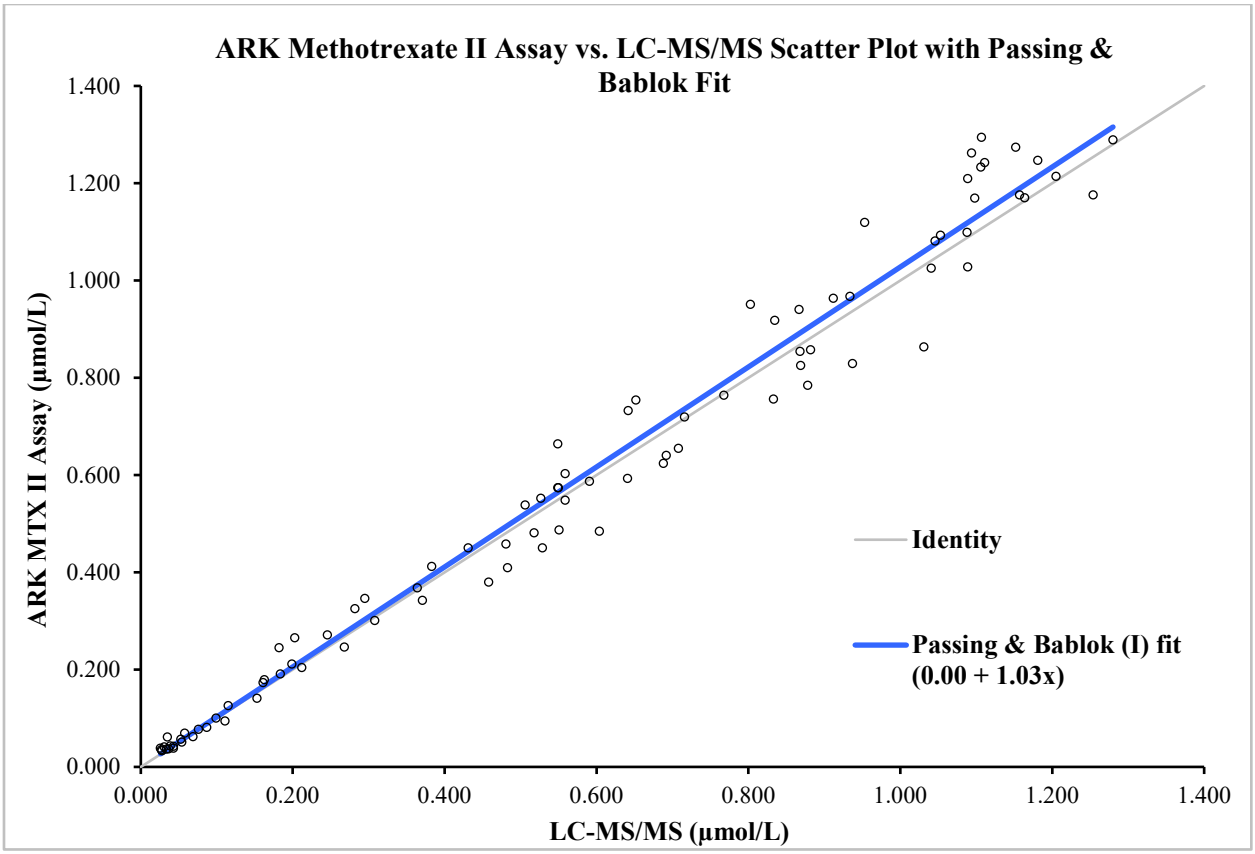

Figure 1. Method Comparison –ARK Methotrexate II Assay versus LC-MS/MS

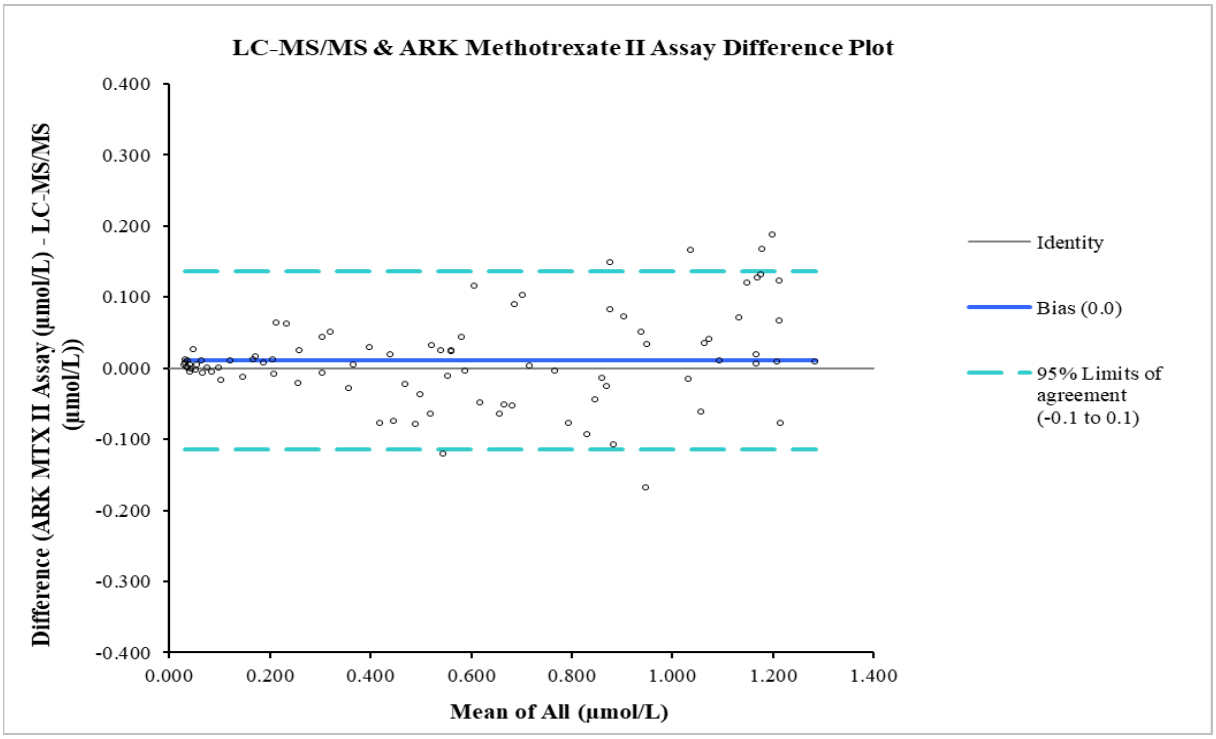

Figure 2. Bland-Altman Difference Plot

Method comparison was also performed against the original ARK Methotrexate Assay for 123 patient samples with methotrexate values ranging from 0.054 to 1.168. Statistics with confidence intervals from the Passing-Bablok comparison are slope = 0.98 (0.95 to 1.01); y-intercept = -0.02 (-0.03 to -0.01); and correlation coefficient (r^2) = 0.97 (0.96 to 0.98).

Precision

Precision was assessed as described in CLSI Protocol EP05-A3. Six-level controls and six samples of methotrexate in pooled human serum were used in the study. Data were collected on a single analyzer over twenty (20) non-consecutive days. One (1) calibration was performed according to requirements for quality control. Each level was assayed in quadruplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The within run, between day, total SD, and percent CVs were calculated. Acceptance criteria: ≤10% total CV.

			Within Run		**Between Day**		**Total**	
Sample	**N**	**Mean (µmol/L)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**
ARK Methotrexate II Control								
LOW	160	0.069	0.002	2.84	0.001	1.23	0.002	3.00
MID	160	0.411	0.006	1.40	0.002	0.43	0.006	1.40
HIGH	160	0.811	0.014	1.79	0.008	0.97	0.017	2.05
5	160	4.868	0.070	1.44	0.036	0.74	0.077	1.58
50	160	49.660	1.108	2.23	0.397	0.80	1.141	2.30
500	160	493.769	8.012	1.62	2.483	0.50	8.012	1.62
Human Serum								
LOW	160	0.070	0.002	2.50	0.001	1.49	0.002	2.88
MID	160	0.404	0.008	1.86	0.003	0.65	0.008	1.92
HIGH	160	0.846	0.016	1.93	0.008	0.95	0.017	2.06
5	160	5.247	0.076	1.45	0.028	0.54	0.078	1.49
50	160	51.614	0.723	1.40	0.285	0.55	0.777	1.51
500	160	507.988	7.632	1.50	4.240	0.83	8.538	1.68

Interference by Endogenous Substances

Interference studies were conducted using CLSI EP07-A3 as a guideline. Clinically high concentrations of the following potentially interfering substances in serum with known levels of methotrexate (approximately 0.050 and 0.500 µmol/L) were evaluated. Two analytical runs of three replicates of each sample (6 replicates total) were assayed using the ARK Methotrexate II Assay, along with a serum control of methotrexate. The mean results of methotrexate were calculated and the percentage recovery relative to the serum control mean result was determined. Elevated concentrations of endogenous substances did not interfere with the measurement of methotrexate at the concentrations tested.

Endogenous Substance	Suggested Concentration to Test	Concentration Tested	± µmol/L from Control (0.050 µmol/L Methotrexate)	% Interference (0.500 µmol/L Methotrexate)
Human Albumin	12 g/dL	12 g/dL	0.002	-1.04
Conj. - Bilirubin	70 mg/dL	72 mg/dL	0.001	1.96
Unconj. - Bilirubin	70 mg/dL	72 mg/dL	0.003	0.23
Cholesterol	500 mg/dL	500 mg/dL	0.005	3.49
Human IgG	12 g/dL	12 g/dL	0.003	2.42
Hemoglobin	1000 mg/dL	1000 mg/dL	-0.006	-2.72
Rheumatoid Factor	1000 IU/mL	1080 IU/mL	0.001	3.52
Triglycerides	1000 mg/dL	1000 mg/dL	-0.007	7.48
Uric Acid	30 mg/dL	30 mg/dL	0.000	1.60

Analytical Specificity

Methotrexate's metabolites, structurally similar compounds, folate derivatives, and potentially co-administered medications were tested to determine whether these compounds affect the quantitative measurement of methotrexate using the ARK™ Methotrexate II Assay.

7-Hydroxymethotrexate (7-OH-MTX) is the main metabolite in serum following high-dose methotrexate (HDMTX) treatment. The concentration of 7-OH-MTX may exceed that of the parent compound by up to 100-fold in plasma shortly after MTX infusion. Methotrexate is also metabolized by intestinal bacteria to the minor, inactive metabolite 2,4-diamino-N_{10}-methylpteroic acid (DAMPA).

Pooled human serum was supplemented with methotrexate prior to addition of potentially cross-reacting metabolites (7-OH-MTX and DAMPA) or other compounds with structural similarity. Preparation of serum pools with 0.050 and 0.500 µmol/L methotrexate were identical to the interference study above. Then the potentially cross-reactive compounds at their respectively solvated concentrations were added to serum containing methotrexate. Appropriate Serum/Solvent Controls containing methotrexate for each potentially cross-reacting interferent sample were also prepared.

Metabolites

7-Hydroxymethotrexate (7-OH-MTX)

Measurement of methotrexate by the ARK Methotrexate II Assay was not substantially affected by the presence of its major metabolite, 7-Hydroxymethotrexate (7-OH-MTX), when tested at 50 µmol/L.

Metabolite	7-OH-MTX (µmol/L)	(Percent Interference) Methotrexate 0.050 µmol/L	Methotrexate 0.500 µmol/L
7-OH-MTX: 7-Hydroxymethotrexate	50	8.72%	0.58%

2, 4-Diamino-N(10)-methylpteroic acid (DAMPA)

Minor, inactive metabolite DAMPA is not expected to circulate at concentrations that would interfere in measurements of methotrexate. However, for patients at risk of renal toxicity, glucarpidase rescue therapy may be administered to rapidly convert extracellular methotrexate to DAMPA. This can cause the serum concentration of DAMPA to be significant and interfere with the ARK Methotrexate II Assay substantially. The assay should not be used during glucarpidase (carboxypeptidase G2) rescue therapy.

Metabolite	DAMPA (µmol/L)	(Percent Cross-reactivity) Methotrexate 0.000 µmol/L
DAMPA: 2, 4-Diamino-N(10)-methylpteroic acid	0.040	57.50%
	0.100	51.50%
	0.500	42.93%
	0.800	23.42%
	1.000	18.80%

Other Compounds

Methotrexate-selective antibody did not cross-react with potentially co-administered drugs, folate derivatives, and other compounds of similar structure. The interference by trimethoprim and triamterene seen in the predicate assay was avoided by selection of an improved antibody. A high concentration of each compound was spiked into normal human serum with known levels of methotrexate (approximately 0.050 and 0.500 µmol/L) and assayed along with a serum control of methotrexate. All compounds tested were within ±10% interference.

Compound	Conc. Tested (µmol/L)	% Interference (0.050 µmol/L MTX)	% Interference (0.500 µmol/L MTX)
Adriamycin	1000	-3.92	-0.03
Cyclophosphamide	2200	0.00	-1.24
Cytosine	1000	-0.66	-0.78
Dihydrofolic Acid	1000	8.60	1.15
Tetrahydrofolic Acid	1000	6.79	-0.64
DL-6-Methyl-5,6,7,8-Tetrahydropterine	1000	-0.71	-1.03

Compound	Conc. Tested (µmol/L)	% Interference (0.050 µmol/L MTX)	% Interference (0.500 µmol/L MTX)
Folic Acid	1000	2.50	5.05
Folinic Acid	1000	-0.65	0.15
5-Fluorouracil	3000	-0.33	0.90
6-Mercaptopurine	1000	2.31	-1.99
5-Methyltetrahydrofolic Acid	1000	0.00	-0.25
Prednisolone	1000	-2.50	1.35
Pyrimethamine	1000	-2.14	-3.02
Sulfamethoxazole	1600	0.36	-0.29
Vinblastine	1000	-3.57	-0.45
Vincristine	1000	-0.42	-0.24
Trimethoprim	150	0.97	-0.95
Triamterene	25	-0.65	0.79

Sample Stability

Serum specimens were shown to be stable for at least fourteen (14) days when refrigerated (2-8 °C), fourteen (14) days at room temperature (25 °C), frozen (-20 °C) for at least 15 months (k111904), and after three (3) successive freeze/thaw cycles based on supporting data.

Product Stability

Accelerated stability studies and real time stability studies support a shelf-life stability claim of up to 18 months for the ARK Methotrexate II Reagents when stored unopened at 2-8°C.

On-Board Stability

Reagents were stable up to 100 days when stored on-board the instrument based on supporting data.

Calibration Curve Stability

A stored calibration curve was effective up to at least 100 days based on supporting data. Calibration curve stability may depend on individual laboratory performance.

807.92 (b)(3): Conclusions from Nonclinical Testing

As summarized above, the ARK Methotrexate II Assay is substantially equivalent to the legally marketed predicate device k111904. Reasonable assurance of safety and effectiveness for its intended use was shown for the ARK Methotrexate II Assay based on performance studies.