FDA U.S. FOOD & DRUG ADMINISTRATION

EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
Procise IFX
DECISION SUMMARY

I Background Information:

A De Novo Number

DEN210056

B Applicant

ProciseDx Inc.

C Proprietary and Established Names

Procise IFX

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QXT	Class II	21 CFR 862.3115 - Anti-tumor necrosis factor alpha monoclonal antibody test system for inflammatory bowel disease	TX - Clinical Toxicology

II Submission/Device Overview:

A Purpose for Submission:

De Novo request for evaluation of automatic class III designation for Procise IFX

B Measurand:

Infliximab (IFX)

C Type of Test:

Quantitative, Time-resolved fluorescence energy transfer immunoassay

III Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
The Procise IFX assay is a time-resolved fluorescence energy transfer immunoassay for the quantitative determination of infliximab levels in venous serum in patients undergoing infliximab therapy, using the ProciseDx Analyzer.

Measurements obtained by this assay can be used to detect infliximab as an aid in the management of patients with inflammatory bowel diseases (IBD): Crohn's disease and ulcerative colitis being treated with infliximab. The test is intended for use in a clinical laboratory.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

For in vitro diagnostics use only

D Special Instrument Requirements:
Procise Dx Analyzer

IV Device/System Characteristics:

A Device Description:
Each Procise IFX assay kit includes Procise IFX reagent cartridges, buffer bulbs, and Procise IFX low and high assay controls as follows:

- Twenty pouched Procise IFX cartridges each containing a lyophilized test-specific reagent bead contains a dry reagent bead located in the cartridge cap comprised of < 50 µg of test-specific conjugates (monoclonal Fab anti-IFX/TNFα complex labeled with acceptor fluorophore and TNFα labeled with donor fluorophore)
- Twenty 1.5mL buffer bulbs
- Two pouched assay IFX Low controls
- Two pouched assay IFX High controls
- Product Insert
- Quick Reference Guide

The Procise IFX assay requires the ProciseDx Analyzer. The ProciseDx Analyzer is designed to detect time-resolved fluorescent signal from both the donor and FRET acceptor emission within the Procise IFX assay.

B Principle of Operation
The Procise IFX assay is a sandwich immunoassay that uses time-resolved fluorescence to detect the presence and quantity of IFX in patient serum specimens. It is a homogenous assay that uses an energy transfer between a terbium cryptate acceptor fluorophore labeled anti-IFX/TNFα

complex Fab' antibody and a terbium cryptate donor fluorophore labeled to TNFα protein. When IFX is present in a sample and tested with the Procise IFX assay, it binds to the donor labeled TNFα protein allowing the anti-IFX/TNFα Fab' antibody bound to an acceptor to bind.

Once the labeled TNFα protein and the anti-IFX/TNFα Fab' antibody are bound together within a complex, their close proximity allows for fluorescence resonance energy transfer (FRET) to occur. The acceptor fluorophore emission created from FRET is measured along with the donor signal. The ratio of the two emissions is used by the ProciseDx Analyzer to determine the concentration of IFX within the sample. The acceptor to donor ratio is proportional to the amount of IFX in the sample.

V Standards/Guidance Documents Referenced:

CLSI EP05-A3, 2015, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition

CLSI EP06 2nd Edition, 2021, Evaluation of the Linearity of Quantitative Measurement Procedures

CLSI EP07 3rd Edition, 2018, Interference Testing in Clinical Chemistry.

CLSI EP09c 3rd Edition, 2020, Measurement Procedure Comparison and Bias Estimation Using Patient Samples

CLSI EP17-A2, 2013, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline

CLSI EP25-A, 2013, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.

CLSI EP37 1st Edition, 2018, Supplemental Tables for Interference Testing in Clinical Chemistry

CLSI EP32-R, 2014, Metrological Traceability and Its Implementation; A Report

VI Performance Characteristics:

A Analytical Performance:

1. Precision/Reproducibility:
   Precision studies were performed using five pools of native serum samples with targeted IFX concentrations at approximately 2.8, 5, 7, 20, and 45 µg/mL. Three lots of Procise IFX assay reagents were paired with three lots of buffer bulbs using three different instruments. The paired assay lot and instruments were changed from the first daily run compared to the second. Samples were tested in replicates of two, two times per day, for twenty days. The precision results characterize the precision of the Procise IFX assay across the measurement range and are summarized below for all lots.

Procise IFX Assay Precision (20-Day) for All Reagent Lots and Analyzers

Sample	N	Mean (µg/mL)	Between Lot		Between Analyzer		Between Day		Between Run		Within Run		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	240	2.37	0.05	2.3%	0.13	5.6%	0.04	1.5%	0.02	0.6%	0.2	8.5%	0.25	10.6%
2	240	4.91	0.11	2.2%	0.16	3.3%	0.05	0.9%	0.02	0.4%	0.28	5.6%	0.34	6.9%
3	240	6.9	0.10	1.4%	0.16	2.3%	0.04	0.5%	0.03	0.5%	0.33	4.9%	0.39	5.6%
4	240	20.38	0.07	0.4%	0.26	1.3%	0.26	1.3%	0.08	0.4%	0.99	4.9%	1.06	5.2%
5	240	43.77	1.87	4.3%	0.42	1.0%	0.37	0.9%	0.07	0.2%	1.83	4.2%	2.67	6.1%

A reproducibility study was performed at three external sites. Reproducibility studies were performed using five serum samples consisting of three pools of native serum samples with IFX concentrations approximately 5, 10, and 40 µg/mL and two serum quality control samples with IFX concentrations of 3.2 and 20.5 µg/mL. The same Procise IFX assay lot was used at all three sites. At each site, samples were tested in replicates of three, two times per day, for five days by two operators using two instruments. The reproducibility results characterize the precision of the Procise IFX assay across the measurement range and are summarized below for all lots.

Procise IFX Assay Reproducibility for All Sites

Sample	Mean (µg/mL)	Within Run		Between Run		Between Day		Between Instrument		Between Operator		Between Site		Total	
		SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
QC Low	2.86	0.17	5.9	0.08	2.8	0.05	1.8	0.01	0.4	0.04	1.3	0.04	1.3	0.2	7.0
QC High	19.97	0.87	4.3	0.23	1.2	0.3	1.5	0.18	0.9	0.23	1.2	0.66	3.3	1.19	6.0
1	4.38	0.23	5.1	0.05	1.2	0.05	1.1	0.05	1.1	0.08	1.8	0.09	2.0	0.27	6.1
2	8.95	0.33	3.7	0.05	0.5	0.08	0.9	0.05	0.6	0.1	1.2	0.31	3.4	0.48	5.3
3	37.46	1.47	3.9	0.4	1.0	0.24	0.6	0.29	0.8	0.31	0.8	1.28	3.4	2.04	5.4

2. Linearity:

A study was conducted to evaluate linearity across the measuring range of the Procise IFX assay. Samples with thirteen different IFX levels were evaluated: 85.5, 56.4, 38.8, 24.8, 17.5, 11.4, 7.4, 4.4, 3.0, 1.9, 1.2, 0.9, and 0.6 µg/mL. Native serum samples with high IFX concentrations were pooled together to create a High IFX pool. This was mixed with a native serum pool with no IFX to produce samples with the thirteen IFX concentrations tested. The linear regression results and deviation from linearity are shown below.

Claimed Measuring Range	Sample Range Tested	Slope	Intercept	R^2
1.2-50 µg/mL	0.6-80 µg/mL	1.07	-0.21	0.9992

These results support the claimed measuring range of 1.2 to 50 µg/mL for IFX.

3. Analytical Specificity/Interference:
Interference studies were conducted based on CLSI EP37 guideline. Each potentially interfering substance was prepared at twice the CLSI recommended level in pooled IFX negative serum which was then combined at a 1:1 ratio with native IFX serum sample pools to obtain IFX serum concentrations at approximately 2.5, 4 and 7 µg/mL plus the interferent. The control samples without interferent were made by combining the native IFX serum at each level with IFX negative serum at a 1:1 ratio. None of the substances in the tables below showed significant interference, defined as bias ≤10% for each potential interferent and concentration level tested when compared to the nominal condition.

List of interferents at their concentration up to which no interference was observed.

Compound	Tested concentration
5-aminosalicylate	2.04 mg/dL
6-mercaptopurine	0.148 mg/dL
Adalimumab	20 µg/mL
Acetaminophen	15.6 mg/dL
Acetylsalicylic Acid	3 mg/dL
Antidrug antibodies to IFX	200 ng/mL
Ascorbic Acid	5.25 mg/dL
Azathioprine	0.258 mg/dL
Bilirubin Conjugated	20 mg/dL
Bilirubin Unconjugated	40 mg/dL
Budesonide	0.0146 µmol/L
Ciprofloxacin	1.2 mg/dL
Hemolysate	800 mg/dL
Human Anti-Mouse Antibody	200x
Methotrexate	1000 µmol/L
Metronidazole	12.3 mg/dL
Prednisone	0.276 µmol/L
Rheumatoid Factors	1285 IU/mL
Sulfasalazine	7.5 mg/dL
Total Protein	15 g/dL
Triglycerides	1500 mg/dL
Vitamin D	300 ng/mL

High Dose Hook Effect
To evaluate the potential for a high dose hook effect in the Procise IFX assay, serum samples were tested at IFX concentrations of 25, 50, 100, 200, 300, and 400 µg/mL. The samples were tested in replicates of five using three matched assay, buffer bulb, and reaction vessel lots. For results above the Procise IFX assay upper limit of quantification (50 µg/mL), the ProciseDx Analyzer displayed >50 µg/mL as a result. Device results are unimpacted by a hook effect at IFX concentrations of up to 300 µg/mL.

4. Assay Reportable Range:

The assay reportable range is from 1.2 to 50.0 µg/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
The Procise IFX assay calibration standards are traceable to the IFX WHO International Standard: 1st International Standard for Infliximab (NIBSC code:16/170).

Procise IFX Assay Recovery Study
A study was performed to assess the functional accuracy of the Procise IFX assay calibration and control methodology. 50 µg of the WHO IS Standard for IFX was reconstituted using 1.0 mL of pooled native negative serum for a starting concentration of 50 µg/mL. Native IFX negative serum was used to dilute the starting sample to create a total of 11 samples, each one-third less than the previous. These 11 dilutions were tested in triplicates using 1 lot of the Procise IFX assay components in singlicate. The results are summarized below individually for three replicates.

Procise IFX Result vs. WHO IS Standard for IFX Linear Regression Results

Analyte	Replicate	Slope	Y-Intercept	Pearson's R
IFX	1	0.95	0.03	1.00
	2	0.96	0.04	1.00
	3	0.97	0.13	1.00

Procise IFX Result Summary When Testing the WHO IS Standard for IFX

WHO IS [IFX] (ug/mL)	Replicate	Procise [IFX] (µg/mL)	% Bias	%CV
50	1	47.4	-5%	1%
	2	48.1	-4%	
	3	48.7	-3%	
33.3	1	31.6	-5%	3%
	2	31.6	-5%	
	3	33.0	-1%	
22.2	1	20.9	-6%	2%
	2	21.5	-3%	
	3	20.9	-6%	
14.8	1	14.4	-3%	4%
	2	13.6	-8%	
	3	14.5	-2%	
9.9	1	9.7	-1%	2%
	2	10.0	1%	
	3	10.2	3%	
6.6	1	6.2	-6%	3%
	2	5.9	-10%	
	3	6.2	-5%	
4.4	1	4.1	-8%	10%

WHO IS [IFX] (ug/mL)	Replicate	Procise [IFX] (µg/mL)	% Bias	%CV
	2	4.3	-1%	
	3	4.9	12%	
2.9	1	2.9	-2%	5%
	2	2.6	-10%	
	3	2.9	-1%	
2.0	1	1.8	-7%	9%
	2	2.1	8%	
	3	2.1	10%	
1.3	1	1.1	-18%	10%
	2	1.2	-4%	
	3	1.3	0%	
0.9	1	0.9	-1%	12%
	2	0.8	-13%	
	3	0.7	-22%	

Sample Stability

Room Temperature and Refrigerated

To test the stability of serum specimens at room temperature or at 4°C, the sponsor performed a stability study using freshly drawn serum from three patients (targeting different IFX concentrations) receiving IFX therapy. Refrigerated (~4°C) and room temperature (~22 °C) specimens were tested in duplicate at baseline, defined as 2-4 hours after draw (Day 0), Day 1, Day 3, Day 5, and Day 7 using three different lots of Procise IFX reagents. The results support the labeling claim of three days of stability at room temperature or refrigerated (4°C).

Frozen Serum Stability

The sponsor performed a frozen serum stability study to demonstrate that serum samples stored at -80°C that contain IFX are stable when measured with the Procise IFX assay. The sponsor performed the stability study using freshly drawn serum from 37 patients, tested by using the Procise IFX assay within a day of draw. Samples were stored frozen at -80°C then thawed and retested in duplicate using one lot of Procise IFX assay reagents. The results show that serum samples with IFX stored at -80°C are stable up to 142 weeks.

Freeze-Thaw Serum Stability

The sponsor performed a freeze-thaw study to test the stability of frozen clinical serum specimens stored at -80°C that contain IFX when the samples undergo multiple freeze-thaw cycles. The sponsor tested five frozen serum samples with IFX concentrations of ~4, 5, 7, 20, and 40 µg/mL, previously measured using the Procise IFX assay when freshly collected. Each sample was tested after 1, 2, 3, and 5 freeze-thaw cycles and the IFX results were compared back to the original pre-frozen value. The results show that IFX is stable in serum samples frozen at -80°C that have undergone up to five freeze-thaw cycles.

6. Detection Limit:
Detection limits were assessed according to recommendations in CLSI EP17-A2.

The limit of blank (LOB) was determined using 4 native serum specimens containing no IFX. Each of the 4 serum samples were tested in replicates of five for over three days using two Procise IFX assay lots for a total of 60 measurements per lot. The 95th percentile from each reagent lot was calculated, multiplied by the standard deviation of the blank and the result was added to the mean of the blank to calculate the LoB for each lot. The sponsor determined the LoB to be 0.08 µg/mL, which was the highest LoB calculation between the two Procise IFX assay lots.

The limit of detection (LOD) was determined using 4 different IFX samples at: 0.1, 0.2, 0.4, and 0.5 µg/mL. Each of the four serum samples were tested in five replicates across three days using two Procise IFX assay reagent lots for a total of 60 measurements per lot. Two operators performed the testing. A one-sided 95% confidence t-distribution table (with a sample size of 60) was used to calculate a multiplier. To calculate the LOD, this multiplier was multiplied by the pooled standard deviations for 60 data points for each assay lot then the result was added to the 0.08 LOB. The sponsor determined the LOD to be 0.28 µg/mL using the assay lot with the highest LOD determination.

The limit of quantitation (LOQ) was determined using four samples above the LOD with IFX concentrations at: 0.5, 0.7, 0.9, and 1.2 µg/mL. Each of the four serum samples were tested in five replicates across three days using two Procise IFX assay reagent lots for a total of 60 measurements per lot. Two operators performed the testing. The LOQ was determined to be 1.2 µg/mL at which they observed 33% total error.

7. Assay Cut-Off:

See Assay Reportable Range section above.

8. Accuracy (Instrument):

See Traceability and Method comparison sections.

9. Carry-Over:

Not applicable, the Procise IFX assay cartridge is single use.

B Comparison Studies:

1. Method Comparison:
A method comparison study was conducted comparing the Procise IFX assay to three validated comparator methods (Comparators 1-3). A total of 53 deidentified serum samples were tested with the Procise IFX assay and the results were compared to results from Comparators 1 and 2. Seventy-seven additional serum samples were tested with the Procise IFX assay and the results were compared to results from Comparator 3. Data was analyzed using Deming regression and Pearson correlation and the results are summarized below.

Procise IFX vs. Comparator 1

N	Slope	Intercept (µg/mL)	Correlation Coefficient (r)	Sample range tested (µg/mL)
53	1.04	-0.84	0.97	1.96 – 20.25

Procise IFX vs. Comparator 2

N	Slope	Intercept (µg/mL)	Correlation Coefficient (r)	Sample range tested (µg/mL)
53	0.99	-0.50	0.99	1.15 – 18.73

Procise IFX vs. Comparator 3

N	Slope	Intercept (µg/mL)	Correlation Coefficient (r)	Sample range tested (µg/mL)
77	1.05	1.26	0.98	0.9 – 46

2. Matrix Comparison:

   Not applicable. Serum is the only matrix claimed for the Procise IFX assay.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Clinical therapeutic drug monitoring (TDM) for infliximab is based on the understanding that there is a relationship between drug exposure and clinical outcomes when treating patients with IBD with therapeutic biologics. Inter-individual variability exists in the rate of clearance of therapeutic biologics, including for infliximab; therefore, having information that helps clinicians understand whether a patient is clearing the drug faster than expected provides information that aids clinicians in the management of their patients. The Procise IFX assay is intended to quantitatively detect the presence (or absence) of infliximab in patients with IBD receiving infliximab therapy. Published literature and professional society practice guidelines on the use of TDM in patients with IBD receiving infliximab support that the device output (i.e., detecting the presence of infliximab) provides information that is clinically meaningful to aid healthcare providers in the management of patients with IBD.

   In patients with IBD who have active disease, detecting the presence or absence of circulating drug is useful to aid clinicians in clinical decision-making. As noted in the U.S. clinical practice guideline "American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease" (2017), failure of treatment

with infliximab is generally due to one of two possibilities: 1) mechanistic failure or 2) pharmacokinetic failure. Pharmacokinetic failure occurs when therapeutic levels of drug are not achieved/maintained. Pharmacokinetic failure can occur via either immune or non-immune mediated pathways. In immune-mediated PK failure, anti-drug antibody formation results in increased drug clearance and reduced or undetectable levels of the drug. Various publications support the assertion that anti-drug antibody formation is associated with lower infliximab trough concentrations, as well as worse clinical outcomes. This is also reflected in the USPI for infliximab, which notes (for adult patients with Crohn's disease) "*Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy, and to experience an infusion reaction... than those who were antibody negative.*" Published data also support the assertion that an undetectable trough level (irrespective of ADA status) is associated with less favorable outcomes in patients with IBD.

Regardless of the cause of the undetectable drug level, understanding whether a patient has circulating drug present is informative, as therapeutic proteins can exert beneficial clinical effects only when circulating at concentrations that allow interaction between the antibody and the target receptor, leading to downstream pharmacodynamic effects.

In summary, there is available evidence to support that the "detectable" or "not detectable" quantitative output from the Procise IFX assay will provide meaningful information to clinicians to aid in determining whether a lack of therapeutic response may be due, at least in part, to lack of circulating drug. Including the measured quantitative level can help the physician put the result into context.

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

Not applicable.

F Other Supportive Performance Characteristics Data:

Procise IFX Assay Biosimilars

To demonstrate that the Procise IFX assay can accurately detect Infliximab biosimilar drugs, a pool of IFX negative human serum was used to create 7 different levels each of Infliximab, Inflectra, and Renflexis: 2.5, 5, 10, 20, 30, 40, and 50 µg/mL. Each level was tested in replicates of 6 with Infliximab, derived from the Primary Intermediate Dilution for IFX (see traceability section), serving as the control for the expected IFX concentration. The results are summarized below.

Procise IFX Serum Biosimilar Drug Results

IFX Biosimilar	Expected [IFX] µg/mL	Observed [IFX] µg/mL (n=6)	% Bias
Inflectra	48.8	50.3	3%
	39	40.3	3%
	28.6	29.1	2%
	19.2	19.6	2%
	9.6	9.7	1%
	4.9	4.8	-3%
	2.5	2.5	1%
Renflexis	48.8	48.6	0%
	39	38.1	-2%
	28.6	29.2	2%
	19.2	19.7	3%
	9.6	9.7	1%
	4.9	4.6	-7%
	2.5	2.4	-5%

VII Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

VIII Identified Risks and Mitigations:

Risks to Health	Mitigation Measures
Incorrect test results	Certain design verification and validation activities and documentation, including certain studies. Certain labeling information, including certain limiting statements.
Incorrect interpretation of test results	Certain design verification and validation activities and documentation, including certain studies. Certain labeling information, including certain limiting statements.

IX Benefit/Risk Assessment:

A. Summary of the Assessment of Benefit:

There are currently no FDA cleared or approved devices for determining infliximab blood concentrations. The accuracy of the device is adequate to support clinical benefit when the device is used solely as noted in the indications for use.

In general, there is a risk of anti-drug antibody (ADA) development during treatment with therapeutic proteins, including infliximab. Although the approved dosing regimen is intended to maintain an acceptable level of circulating drug, development of anti-drug antibodies, or other intrinsic factors affecting clearance, may lead to a reduced drug level or absence of detectable drug level during treatment. The clinical benefit of the Procise IFX assay is that it can quantitatively detect the presence (or absence) of infliximab. This can help determine whether a lack of therapeutic response is due, at least in part, to lack of detectable drug. Providing the "detectable" or "not detectable" quantitative output will provide useful information to physicians and including the measured level can help them put this result into context.

B Summary of the Assessment of Risk:

The risks with use of the device are associated with misclassification due to incorrect test results (i.e., falsely high and falsely low test results) and incorrect interpretation of results such as interpreting a particular target trough concentration as optimal when there is not sufficient data to support this claim.

C Patient Perspectives:

This submission did not include specific information on patient perspectives for this device.

D Summary of the Assessment of Benefit-Risk:

The clinical benefit of the Procise IFX assay is having a determination of the presence or absence of infliximab in IBD patients, with the quantitative level provided for context. In patients with active disease, understanding whether they have detectable trough levels is informative for clinicians to aid in clinical management. Development of anti-drug antibodies can occur at any time during treatment and has the potential to increase drug clearance and lead to an undetectable trough level, which may impact the efficacy of the drug.

When the device is used as intended, the risks are mitigated by the Procise IFX assay indications for use, which do not propose therapeutic or reference ranges or refer to any action a clinician should take, such as dose adjustment, and the special controls. The output of the Procise IFX assay is intended to be used as one piece of information, taking into consideration many other factors such as the patient's clinical status and other laboratory test values. The device provides information regarding whether a patient has circulating drug at the time of testing. It is not intended to be used to make treatment decisions/change in medical management in isolation The indications for use, along with special controls which require appropriate device verification and validation testing to support all clinical and analytical claims, are sufficient to mitigate the risks associated with misclassification due to incorrect test results (i.e., falsely high and falsely low test results) and incorrect interpretation of results.

Device design verification and validation activities, including studies to support all analytical claims, clinical claims, and testing environments to ensure acceptable clinical and analytical performance, as well as certain labeling information will help ensure that the device functions as intended and mitigate the risk of incorrect test results (i.e., falsely low or falsely high test results) or the incorrect interpretation of the test results.

While general controls are insufficient to mitigate the risks of the device, the probable benefits outweigh the probable risks for the Procise IFX assay, considering the indications for use and the mitigation of the risks provided by the special controls. Overall, the probable benefits outweigh

the probable risks of incorrect test results or incorrect interpretation of test results for the proposed indications for use, in light of the special controls and general controls.

X Conclusion

The De Novo request for Procise IFX is granted and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code(s): QXT
Device Type: Anti-tumor necrosis factor alpha monoclonal antibody test system for inflammatory bowel disease
Class: II (Special Controls)
Regulation: 21 CFR 862.3115