Refractometers & Polarimeters

APPLICATIONS WITHIN THE PHARMACEUTICAL INDUSTRY

Version 3.3

Restricted Publication:

Official Distributors of
Bellingham + Stanley only

Not for customer use

Bellingham + Stanley

a xylem brand

Bulletin No: ***APP003 – May 2013***
Title: ***Polarimeters and Refractometers for the Pharmaceutical Industry***

Over the past few years, Bellingham + Stanley has widened its potential customer base by introducing industry specific instrumentation with software that takes into consideration changes in legislation.

The pharmaceutical industry has now become a key market for Bellingham + Stanley, as the latest RFM900 refractometers and ADP440+ polarimeter satisfy both measurement and operational requirements of EP/USP/BP and FDA regulations 21 CFR Part 11.

"Pharmacopoeia" is the quality standard for all companies concerned with research, development, and manufacturing or testing of medicinal substances that are used throughout the world today. Medicinal substances do not only include medicines and intravenous drugs but also cosmetics and healthcare products. Although there are different regional versions, most are harmonised and so whether the customer is looking at European or American Pharmacopoeia, there is very little difference between the publications. It is also worth noting that even if located in one region, it is likely that a manufacturing site may be contracted to export to a differing region, so may be working in accordance with more than one pharmacopoeia. For example, a contract laboratory in the UK may adhere to both British Pharmacopoeia and US Pharmacopoeia if product is to be exported to America.

Importantly, Pharmacopoeia contains reference values including refractive index and optical/specific rotation for raw materials as well as specific analytical tests for finished products (called nomograms). USP (version 2005) contains 75 monographs that quote refractive index values and 61 for specific rotation at 20°C with another 20 at 25°C. There are far too many to explain individually but the list at the end of this document offers an insight into the importance of our measurement field and to the number of opportunities in the market!

There is one other important piece of legislation in the pharmaceutical industry that is worth a mention. In December 2003, the European Council introduced Directive 98/79 that governs *In Vitro diagnostic devices*. The directive covers instruments that are *specifically designed for IVD use*, that are sold within member countries. Instruments that are not specifically designed for use in IVD are exempt from the directive and are termed *general purpose*. As refractometers and polarimeters used in the medical field such as the ADP440+ (glucose etc.) are *general purpose laboratory instruments, not specifically designed for IVD use, they do* NOT come under EU legislation 98/79.

This Application Bulletin will try to explain the key features of the instrumentation offered by Bellingham + Stanley along with highlighting the technical attributes in order to beat the competition in the market.

Polarimetry in the Pharmaceutical Marketplace

We have already mentioned the importance of Polarimetry, citing over 80 specific tests for optical rotation of compounds within Pharmacopoeia.

Traditional optical measurements were taken at the sodium wavelength and with the move to digital instrumentation; this wavelength is still most common. However, some monographs will quote measurements at a lower wavelength (even occasionally UV) as the concentration of the sample is extremely low hence optical rotation is reduced. In the event that a particular customer requests such an instrument, then they must be treated as specialist and as such B+S can not offer instrumentation at this stage.

USP dictates the method of measurement for both <781> specific rotation (which quotes a value taking into consideration tube length and concentration at a temperature of typically 25°C) <781A> and optical rotation (the value of the polarimeter itself and assumes a 10dm tube when measuring a neat liquid (100% concentration) at 25°C). For further information about specific and optical rotation, see Technical Bulletin P001.

USP states that for polarimetric measurements, temperatures should be stabilised to 0.5°C of the required value. For many applications, samples are stabilised in a remote waterbath and the reading taken as quickly as possible, in order to prevent a rise in temperature or any chemical changes within the sample. By adopting this method, use of specialist 'water-jacketed' polarimeter tubes may be avoided or at least limited to specific samples where temperature effects are significant.

British Pharmacopoeia has one more caveat when discussing polarimeters. It dictates that the instrument should have a readability of at least 0.01°A. The term readability relates to optical instrumentation and for digital instrumentation, this is known as resolution. By using this statement, BP rules out the use of optical polarimeters, as the lowest readability is typically 0.1°A. (Note: USP2005 permits the use of optical polarimeters but insists on 5 readings being taken, with the mean value being taken as the result)

ADP410 Polarimeter

"Being one or the most economically priced polarimeters on the market, the ADP410 is an important polarimeter for general applications within pharmacopoeia."

Notwithstanding its lower accuracy than the ADP440+, the ADP410 satisfies the minimum requirements of EP/BP/USP for optical and specific rotation at 589nm by having a resolution of 0.01°A. However, for low concentration or samples with a low optical rotation, there may be some restrictions in use.

GLP is not supported within the instrument but a printer with an internal clock can be provided that allows a record to be kept of the output results.

Specification:

- Range: -90 to +90 °A
- Resolution: 0.01 °A
- Accuracy: ±0.02 °A

For full details on the ADP410, see associated literature and comparison documents.

ADP Competitive Edge:

"Unlike some competitor models on the market, ADP Polarimeters continually read and display optical rotation, giving the user the satisfaction of observing the repeatability of the result once the instrument has finished its read cycle (approx. 20-seconds). They have a simple zero feature that allows calibration with air, water or solvent at any point of the scale and may also be calibrated/verified with a quartz control plate. They also incorporate quartz as well as sugar temperature compensation, used in conjunction with an internal temperature sensor."

Model D7 Polarimeter

"If you see an optical polarimeter being used in a pharmaceutical lab, chances are the customer may wish to upgrade to a more compliant instrument!"

Bellingham + Stanley also offer the optical Model D7 polarimeter. This instrument does not generally comply with pharmacopoeia but some smaller laboratories may adopt this model for simple raw material checks or for occasional contract use. The Model D7 is however heavily used in the education field as a teaching tool.

Model D7 Competitive Edge:

Launched in 2007, the Model D7 optical polarimeter is unique in that it has an internal LED light source that is far more convenient than traditional sodium or halogen lamps (bench space, shipping costs, maintenance and heat output!). Relatively it is the HIGHEST ACCURACY optical polarimeter on the market today!

ADP440+ High Resolution Polarimeter

"When it comes to reproducibility, the ADP440+ stands alongside the best polarimeters in the business!"

The ADP440+ is possibly one of the most important instruments to be launched on to the market for a number of years. Replacing the earlier ADP220 polarimeter, the ADP440+ has a higher accuracy (±0.01°A) and an even greater resolution (0.001°A). Although the increase in accuracy is slight, it is significant when it comes to the calculation of specific rotation. The example below shows the effect of accuracy between an ADP220 and the new ADP440+ when calculating specific rotation of a low concentration sucrose solution. Additionally, the ADP440+ has superb reproducibility, offering confidence when working at the low end of the scale and is a major factor when comparing to other manufacturers in the price range.

Example: Sucrose 50g/l	**Theoretical**	**ADP220 Polarimeter**		**ADP440+ Polarimeter**	
Instrument Reading:		**Low**	**High**	**Low**	**High**
Instrument Error	(±0.00)	(-0.02°A)	(+0.02°A)	(-0.01°A)	(+0.01°A)
Measured Rotation °A	6.654	6.63	6.67	6.644	6.664
Tube length in dm	2	2	2	2	2
Concentration in g/ml	0.050	0.050	0.050	0.050	0.050
Calculated Specific Rotation	66.540	66.300	66.700	66.440	66.640
Calculated error due to inst. Spec		-0.24	0.16	-0.10	0.10
Specific Rotation Accuracy (+/-)		0.20		0.10	

The ADP440+ is one of (if not THE) lowest priced high specification polarimeters to support GLP and be compliant to the operational requirements of FDA regulation 21 CFR Part 11. The ADP440+ also has the feature of allowing 5 readings to be taken and the MEAN value reported in accordance with European and British Pharmacopoeia.

Physically the ADP440+ is small and as it utilizes the latest LED technology, the need for periodical lamp changes is eliminated.

"The ADP440+ is one of (if not THE) most economically priced high specification polarimeters in the market that supports GLP and be compliant to the operational requirements of FDA regulation 21 CFR Part 11."

Specification:

- Range: -90 to +90 °A (selectable 0-360°A)
- Resolution: 0.001 °A
- Reproducibility: ±0.002 °A
- Accuracy: ±0.01 °A

Features:

- Multi-scale: °A, °Z
- Methods: specific rotation, concentration, inversion, *5 read MEAN*
- 21CFR Part 11 (See page 9)
- GLP Printout
- Up to 3 OD

For full details on the ADP440+, see associated literature and comparison documents.

Did you know?
The ADP440+ has the same specification above 5°A as many supposedly "high accuracy" polarimeters!!

Polarimeter Tubes

General purpose measurement of optical rotation by polarimeter requires the use of industry standard glass or water-jacketed polarimeter tubes of lengths 50 to 200mm. Both the ADP410 and ADP440+ are supplied with a 200mm centre fill glass tube for normal use as these are easy to fill and have the added feature that the centre arm supports the ADP integral temperature sensor without infringing on the light beam. Metal end caps versions for aggressive samples are also available.

In 80% of applications, standard glass tubes are adequate; however, where sample volume is extremely low due to its precious nature or where the optical rotation is high, special low volume tubes with a reduced length and internal diameter are available, with or without a water-jacket. Low volume tubes have fixed cover glasses and leur taper connections for easy sample handling by syringe or pump. The instrument temperature sensor may be attached to the polarimeter tube using a specially designed clip.

Low volume and water-jacketed tubes may also require a specially suited slotted lid.

Type	Illustration	Volume (ml)	Length (mm)	Slotted Upper Lid	Code Number
Standard glass sample tube with bulb to clear bubble from field of view *(Preferred for D7)*		2.51 5.02 10.04	50 100 200	Not required	35-28-50mm 35-29 * 35-30
Centre filling glass tube with straight central arm for easy filling. Centre arm holds ADP temperature sensor. *(Preferred for ADP)*		2.51 5.02 10.04	50 100 200	Not required	35-45-50mm 35-46 35-47 *
Centre filling glass tube with cup-shaped centre filler to reduce risk of spillage.		2.51 5.02 10.04	50 100 200	Not required	35-56-50mm 35-57 35-58 *
Centre-Fill tube with water jacket for temperature control. Centre arm holds ADP temperature sensor. *(Preferred for ADP)*		5.02 10.04	100 200	37-010 37-009	36-77 36-78 *
Low volume leur taper continuous flow-through tube. †		0.1 0.2 0.5 1	5 10 25 50	37-010	35-74 35-73 35-72 35-71 *
Low volume leur taper continuous flow-through tube with water jacket for temperature control. † *(Good option for ADP)*		0.5 1	25 50	37-012	35-75 35-76 *
Low volume leur taper continuous flow-through tube for highly acidic samples. †		0.5 1	25 50	37-010	35-77 35-78 *

Spare parts for polarimeter tubes such as windows, rubber washers, temperature saddles are available and can be seen on the relevant PDF literature.

† Sample may also be applied manually by use of a leur taper syringe.

Refractometry in the Pharmaceutical industry

"Wide range with Peltier temperature control that conforms to the technical requirements of 21 CFR Part 11 … an opportunity not to be missed!"

From experience, it could be said that refractometry is less used in the pharmaceutical industry than polarimetry, however, there are still 75 monographs quoted in USP and the need to verify refractive index of raw materials is still very important. In the past B+S has offered traditional Abbe refractometers due to the wide scale range required but with the introduction of the RFM800 series of Peltier temperature controlled refractometers in 2002 and the replacement RFM900 series more recently, more instruments are being sold to the industry than ever before. The addition of GLP software that allows operation in compliance with the technical requirements of FDA regulation 21 CFR Part 11 has given us a technical edge in recent years where more and more companies make this a deciding factor when looking at new equipment. The RFM900 also has rapid user identification by assigned RFID tags and a *5-reading MEAN feature* that complies with European and British Pharmacopoeia.

The RFM900 series comprises 2 models with the RFM960 being most commonly sold, as it has the wide RI range up to 1.70 and meets the minimum requirement quoted in USP, which discusses measurement to ±0.0001 RI at both 25 and 20°C with careful calibration.

For the ultimate in research or for audit laboratories or government institutes within the industry, the higher accuracy RFM970 is an ideal instrument as it offers measurement to five decimal places across the scale range.

All models have Peltier temperature control, which eliminates the need for a waterbath and offers rapid setting and control of measurement temperature.

Abbe Refractometers

"The Abbe 5 refractometer is excellent for use in academia and laboratories that have a low through-put of samples. The 60LR can measure liquid anaesthetic!"

Although Abbe refractometers still meet the minimum requirements of USP/EP/BP, the fact that they need an external waterbath, rely on operator interpretation and can not transmit or record results means that fewer of this type of instrument are being sold to the pharmaceutical industry. Small contract laboratories that only take occasional readings may use the Abbe 5 refractometer as its price makes it viable but for 95% of applications the digital refractometers are the instrument of choice.

There are still some specialist applications for the older Abbe 60 models, especially the Abbe 60ED which may be used at wavelengths other than 589.3nm (sodium) or the Abbe 60LR refractometer that can measure low RI samples such as anaesthetic at approx. 1.27RI to 5-decimal places.

Table of Compliance:

Model	USP	EP	BP	GLP	21 CFR Part 11	Multiple Readings	Certified Calibration
Abbe 5	√	√	√				AG/SS/Oils
Abbe 60	√	√	√				AG/SS/Oils
RFM900	√	√	√	√	√	√	AG/SS/Oils
ADP410	√	√	√				QCP
ADP440+	√	√	√	√	√	√	QCP

PRH Process Refractometer

"PRH refractometers can be supplied in accordance with ISO10204 for production control applications within the pharmaceutical industry."

Most installations carried out within the pharmaceutical industry are laboratory based, however, in recent years a number of on-line refractometers have been installed for specific applications where a control signal is required as part of the production cycle.

Process instrumentation is not specifically covered by pharmacopoeia as customers adopting this type of measurement tend to rely on later laboratory analysis but there are other factors that have to be considered as part of an on-line process installation. One very important factor is that the materials in contact with the sample must be FDA approved. Our job at B+S is to make sure we use only approved and certified raw materials and in accordance with ISO10204, ensure that they are 'traced' through the production process so that a certificate of conformity can be issued with accompanying certificates showing the material compliance. The certificate of conformity also has to show the 'roughness' of any machined parts, which has to meet a very high standard. A copy of a certificate is shown below.

"Some customers have opted to use a laboratory instrument with a flowcell in place of a process refractometer but either way, wetted materials must follow the guidelines of ISO10204!"

Current applications:

1. Process control of sucrose/glucose blends that form the base of a vaccine for bird flu
2. Process control in the production of apramycin & polyacrylamides
3. Process control of a silicon/alcohol blend used as a lubricant on hypodermic needles!
4. Continual monitoring of refrigerants used in cryogenic storage facility

Bellingham + Stanley Ltd.

Material Traceability Certificate

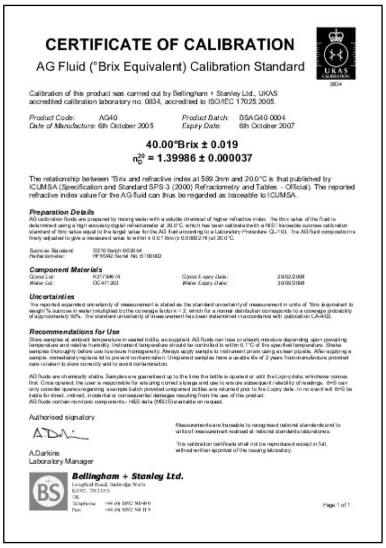
Validation of installations within the pharmaceutical industry

"B+S can supply the necessary documents for IQ/OQ/PQ free of charge when purchased with an instrument and also offer a validation service at extra cost to the customer."

All instruments installed within the pharmaceutical industry must be subjected to a validation process prior to use to ensure the proper performance of the instrumentation. Bellingham + Stanley offer on request the relevant documentation free of charge that can be used by the validation officer of the customer or by a distributor. B+S also offer to carryout the validation on site at extra cost.

When ordering an instrument that requires validation, it is important to supply a new document rather than rely on any you may have on file as they are updated regularly alongside any software changes that may have been made to the instrument. If performing a validation, you will need a complete set of calibration materials such as our service pack for refractometers (code 90-903) or a *quartz plate set*, the latter which may be hired from B+S for a short duration.

Temperature validation is also required during validation. Bellingham + Stanley offer suitable temperature validation kits for hire or for sale that include specifically shaped calibrated temperature sensors and thermal blocks to allow the validation of RFM800, RFM900 and ADP400 series of refractometers and polarimeters. Please contact Bellingham + Stanley for details.


CERTIFICATE OF CALIBRATION

AG Fluid (°Brix Equivalent) Calibration Standard

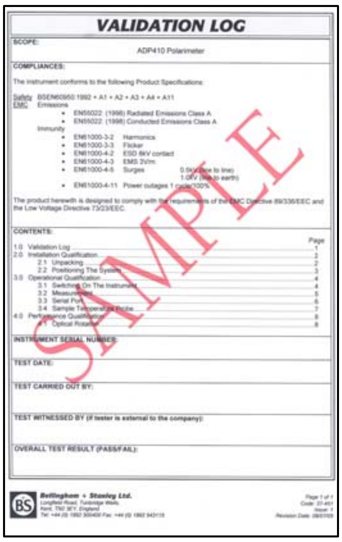
40.00°Brix ± 0.019

n_D^{20} = 1.39986 ± 0.000037

Bellingham + Stanley Ltd.

Calibration verification of refractometers and polarimeters

In addition to the initial validation, customers will need to verify the performance of their equipment on a regular basis. This will involve either self verification, where a customer carries out the check using traceable materials, or they may choose to contract such a function to a calibration house or local distributor. Either way, the importance of calibration materials being traceable to a recognised organisation is essential. B+S , a UKAS certified calibration laboratory No. 0834, can supply CRM's for refractometers and polarimeters that are traceable to NIST, ICUMSA and/or PTB and that are manufactured in accordance with EN ISO/IEC17025:2005


VALIDATION LOG

ADP410 Polarimeter


Reliable Instrument Company Ltd

CERTIFICATE OF VERIFICATION

FDA Regulation 21 CFR Part 11

"Even if customers are not currently operating in accordance with the regulation, foresight dictates that when ordering new equipment, 21 CFR Part 11 is high on the wish list!"

Background Information:

FDA Regulation 21 CFR Part 11 is written for pharmaceutical/medical/healthcare industry laboratories and not for instrument manufacturers. It is concerned with the security and authentication of experimental data and information, in particular validation and security of electronic records. It is sometimes incorrectly referred to as 'electronic signatures;' incorrectly as the scope of the regulation covers far more than just recording operator identifiers.

The document is aimed at pharmaceutical companies and is not simply to do with operating scientific instruments. It is concerned with all procedures and controls for obtaining, keeping and protecting electronic data and information.

21 CFR 11 is written and issued by the Food and Drug Administration (FDA) in the USA. It therefore strictly applies to the pharmaceutical industry in the USA. However, American companies operate all over the world and so they will be seeking compliance in all locations. Non-American companies will also probably try to adopt the ruling, as they have done with other US legislation. Therefore, we should assume it will become a global requirement.

Instrumentation:

- RFM800 series of refractometers from August 2006 to January 2009
- RFM900 series of refractometers
- RFM300+ series of refractometers (as an optional extra)
- ADP440+ polarimeter

The RFM900 series of refractometers and ADP440+ polarimeter are particularly suited to pharmaceutical applications and have recently been adapted to provide a measurement solution in a laboratory environment regulated by the FDA. Instrument configuration has to be set in accordance with the instruction manual as part of the installation (validation).

When configured for use in an FDA controlled environment, no measurement data is stored within the instrument (Reading Log) and certain operating procedures within the company have to be in place within the laboratory for full compliance to be achieved.

Audit Trails:

- No readings are stored within the instrument when configured to high security (21 CFR Part 11)
- An audit trail (formerly known as System Log) records all changes to instrument configuration, calibration log etc. This may be extracted using PC software (Data acquisition code 26-303). An SOP is required to extract the records every week in order for data not to be lost.
- A printed version of the last calibration details is obtainable by instrument keystroke entry.

External Software – LIMS within an FDA Controlled Environment:

Bellingham + Stanley do not provide software for capturing and recording data that complies with FDA CFR 21 Part 11. In the event that a customer requests software, they should be advised to contact a specialist software supplier.

Disclaimer:

This section of this document and any other documents issued by Bellingham + Stanley in relation to 21 CFR Part 11 is based on interpretation of the original FDA text and other third party documentation and as such, Bellingham + Stanley take no responsibility for its content.

This document provides an overview to the FDA regulation and gives an insight as to how compliance is achieved using B+S refractometers and polarimeters.

Printout in accordance with GLP (via Parallel Port) in event that LIMS is NOT used

```
RFM840 Serial No BY05018
Last Z: 08/07/05 16:21
     S: 06/07/05 14:44

Scale:    ri
TC:       no
Set Temp: 20.0'C

Date:     14/07/05
Time:     14:45:56
Batch:    12345678901234
Reading:  1.54389
Temp:     24.0'C
Quality:  101

Reviewed and
 authorised by: R Smith
```

Other topics of interest:

This bulletin features applications for refractometry and polarimetry within the pharmaceutical market place. Other documents relating to the use of instruments in other sectors of manufacturing include, amongst others not listed, the below:

1. Technical Bulletin P001 - *Polarimetry and Polarimeters – a simple explanation, including 'specific rotation'*
2. Technical Bulletin R001 – *Principles of Refractometry*
3. Application Bulletin AP001 – *Refractometers and Polarimeters in the sugar industry*
4. Application Bulletin AP002 –*Uses of Refractometers and Polarimeters in the confectionery industry*
5. Pharmaceutical Mailing Leaflet – *in a number of languages for use as a mailing to your potential customers*
6. Polarimeter Application List – *Internationally recognized uses of polarimeters (fragrance flavours, essence, Ewers method for starch, etc.)*
7. Instrumentation Literature – full colour in English and PDF in foreign language where available
8. Instrument Comparison Charts – old vs. new and some competition comparisons*

List of Abbreviations Frequently Used by B+S

AG	AG Calibration Fluid (UKAS)
BP	British Pharmacopoeia
CFR	Code of Federal Regulations (USA)
EP	European Pharmacopoeia
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points
ICUMSA	International Commission for Uniform Methods of Sugar Analysis
IQ	Installation Qualification
ISO	International Organization for Standardization
JP	Japanese Pharmacopoeia
NBS	National Bureau of Standards (USA) now called "NIST"
NIST	National Institute of Standards and Technology (USA) formerly NBS
NPL	National Physical Laboratory
Oil	Calibration Oil (UKAS)
OQ	Operation Qualification
PQ	Performance Qualification
PTB	Physikalisch-Technischen Bundesanstalt (Germany)
QCP	Quartz Control Plate
SS	Sucrose Solution (UKAS)
UKAS	United Kingdom Accreditation Service
USDA	United States Department of Agriculture.
USP	United States Pharmacopoeia
UV	Ultraviolet (norm. referring to spectrum)
VIS	Visible (referring to spectrum)

Ten Points to Remember

1. Calibration materials are the easiest way to open the door to an instrument sale.

2. Unlike others in the market, B+S calibration materials are traceable to ICUMSA and
NIST or PTB and are manufactured in accordance with ISO17025 in our UKAS accredited laboratory.

3. Optical instruments such as Abbe refractometers are prime targets for replacement

4. The RFM960 covers all aspects of pharmacopoeia for <831>

5. The ADP440+ offers one of the highest resolution measurements at an extremely good price compared to other manufacturers. It has the same accuracy as some of the "top-end" polarimeters for measurement above 5°A.

6. Featured instruments offer use in applications that require (or will require) conformance to FDA regulation 21 CFR Part 11.

7. On request, B+S supply validation documentation free of charge and can perform such installations at additional cost. *Calibration kits* are available for hire and/or purchase.

8. Process refractometers can be supplied with materials traceability in accordance with ISO10204.

9. Use detailed *instrument specifications sheets* to 'lock out' competitors when making a quotation and make sure you list all accessory items, calibration materials and validation requirements.

10. B+S instruments are manufactured by a company that has been in the business for 95-years; a truly respected marque.

List of Customers using B+S Refractometers & Polarimeters within the Pharmaceutical, Cosmetic & Healthcare Sector

3 M Healthcare
3M Pharmaceuticals
Aarhus Hospital
Abbot Pharmaceutical SA

Actavis
AgriQuality
Alpina Productos Alimenticios S.A
Arab Pharmaceutical Ltd
Ariston Ind. Quims. Farms
Arrow Pharmaceuticals
Aspen Pharmaceutical
Aventis
Bristol Meyer Squibb
Butterworth Laboratories Ltd
CDM Lavoisier
Centrafarm BV
Ciba Specialty Chemicals
Cirrus Laboratories
Cognis Chemical
Colgate Palmolive
Consulchem
Courtaulds Acetate & Films
Croda Colloids (Singapore) PVT
Ego Pharmaceuticals

El Nile Pharmaceutical Co
Eli Lilly
Essex Rivers Healthcare
Farmea
Fresnius
General Nutrition Product
G-Pharm
GSK
GSK - Glaxo Welcome Ceyton Ltd
Haemopharm Biofluids
Haupt Pharma
Hi-Tech Pharmaceutical
Hoechst Marion Roussel
Intercytex Ltd
Ipsen Manufacturing Ireland
Ipswich Hospital NHS Trust
Kin Master Produtos Quimicos Ltda
Laboratorios Alcala Farma

Labtech
Leiner Health Products
Leo Laboratories
Libbs Farmaceutica
Lipa Pharmaceuticals
Macfarlane Smith UK
Matrix Laboratories
Mayne Health Consumer Products
Melbourne Scientific
Merck Farma Equimica S.A.
Merck Pty Ltd
Ministry of Health
Multi Apex Pharmaceutical
Murray Goldbourn
Narcotics I Laboratory Centre for Forensic Science
National Veterinary Laboratory
Novo Nordisk
Ou Est-Doma
Pan Pharmaceuticals
Passiflora Colombiana S.A.
Payan Bertrabnd
Penn Pharmacentical Services Ltd
Pfizer
PFMP API
Pharmaceutical Lab Co.
Pharmacia & Upjohn A/S
Pharmacy Quality Control Laboratory
Pirpmal Organics Ltd
Pro Med
Proctor & Gamble
PT Sanbe Farma
PT. Alpharma Pharmaceuticals
Purac
Queens Hospital London
Research Institute for Chemical Procedures (Czech Rep)
Rhodia
Rhone Poulenc (Rhodia SA)
Sanofi Aventis
Sanofi Pasteur
Sanofi Sythelabo
Schering Plough Farma
Scottish Healthcare Supplies
Seneca Analytical
Serum Products Ltd
Sigma Pharmaceuticals
Sochinaz
Soul Patterson
Steifel Laboratories (Ireland) Ltd
Stepping Hill Hospital
Synthite Ltd
Synthomer Ltd
Taiwan Shiseido Co. Ltd
The University Hospital Of North Staffordshire Nhs Trust
Torbay Hospital NHS Trust
UCB-Biproducts
Uintercell Biomedical Ltd
University of Georgia
WEHI (Medical Research Institute)
Wellcome Foundation
Wyeth
Zeneca SA (part of ICI)
Novartis

USP listings for Optical Rotation <781>

Alcohol in Dextrose Injection
Allantoin
Alteplase
Anethole
Anhydrous Lactose
Anise Oil
Anticoagulant Citrate Dextrose Solution
Atropine
Atropine Sulfate
Bisoprolol Fumarate
Bretylium Tosylate in Dextrose Injection
Bupivacaine Hydrochloride in Dextrose Injection
Caraway Oil
Cardamom Oil
Ciprofloxacin Injection
Clove Oil
Compressible Sugar
Confectioner's Sugar
Coriander Oil
Dextran 40 in Dextrose Injection
Dextran 40 in Sodium Chloride Injection
Dextran 70 in Dextrose Injection
Dextran 70 in Sodium Chloride Injection
Dextromethorphan Hydrobromide Oral Solution
Dextromethorphan Hydrobromide Syrup
Dextrose and Sodium Chloride Injection
Dextrose Injection
Diatrizoate Meglumine and Diatrizoate Sodium Injection
Diatrizoate Meglumine Injection
Dobutamine in Dextrose Injection
Dopamine Hydrochloride and Dextrose Injection
Ephedrine Sulfate Oral Solution
Ephedrine Sulfate Syrup
Epinephrine Bitartrate
Estrone Injectable Suspension
Estrone Injection
Eucalyptol
Fennel Oil
Fructose
Fructose and Sodium Chloride Injection
Fructose Injection
Iothalamate Meglumine and Iothalamate Sodium Injection
Ioxaglate Meglumine and Ioxaglate Sodium Injection
Lactic Acid
Lactose Monohydrate
Lemon Oil
Levorphanol Tartrate Injection
Levorphanol Tartrate Tablets
Lidocaine Hydrochloride and Dextrose Injection
Mannitol Injection
Mefloquine Hydrochloride
Meropenem
Methyl Salicylate
Metronidazole Benzoate
Multiple Electrolytes and Dextrose Injection Type 1
NF Monographs: Sugar Spheres
Norgestrel
Oral Rehydration Salts
Orange Oil
Oxandrolone Tablets
Paroxetine Tablets
Peppermint Oil
Potassium Chloride in Dextrose and Sodium Chloride Injection
Potassium Chloride in Dextrose Injection
Propoxyphene Hydrochloride Capsules
Propoxyphene Napsylate Oral Suspension
Propoxyphene Napsylate Tablets
Quinidine Sulfate
Ringer's and Dextrose Injection
Rose Oil
Sodium Chloride and Dextrose Tablets
Stavudine
Tetracaine Hydrochloride in Dextrose Injection
Tetracycline Hydrochloride
Theophylline in Dextrose Injection
Tubocurarine Chloride Injection & Vitamin E

USP Listings for RI <831>

Acetyltriethyl Citrate
Alkyl (C12-15) Benzoate
Allantoin
Anethole
Anise Oil
Atropine
Atropine Sulfate
Benzaldehyde
Benzonatate
Benzyl Alcohol
Benzyl Benzoate
Caraway Oil
Cardamom Oil
Cherry Juice
Clove Oil
Cocoa Butter
Coriander Oil
Cranberry Liquid Preparation
Dibutyl Phthalate
Dibutyl Sebacate
Diethanolamine
Diethyl Phthalate
Diethylene Glycol Monoethyl Ether
Dimethicone
Ephedrine Sulfate Oral Solution
Ephedrine Sulfate Syrup
Ethyl Oleate
Eucalyptol
Fennel Oil
Hexylene Glycol
Isopropyl Myristate
Isopropyl Palmitate
Lactic Acid
Lemon Oil
Linoleoyl Polyoxylglycerides
Medium-Chain Triglycerides
Methyl Salicylate
Monothioglycerol
Norgestrel
Oleyl Alcohol
Orange Oil
Padimate O
Peanut Oil
Peppermint Oil
Phenylethyl Alcohol
Phytonadione
Pilocarpine
Propofol
Rose Oil
Soybean Oil
Squalane
Triacetin
Triethyl Citrate
Trolamine
Trolamine Salicylate
Undecylenic Acid

USP does not include raw 'base' materials such as:

Pastes
Syrups
Honey
Detergent mixes
Creams
SLES
Fragrance
Flavours
Essences
etc.

Example:

Optical Rotation of Fructose at 25°C in accordance with US Pharmacopoeia

A request was received from a customer to evaluate the measurement of a supplied Fructose sample using an ADP410 Polarimeter at 25°C. An accompanying procedure provided details of sample preparation and measuring conditions.

Equipment Details

- ***Apparatus***

Instrument: ADP410 Polarimeter

Span Quartz Control Plate: Reference No. PTB 4.21-554/00: 99.95°Z at 20.0°C and 589.44nm

Polarimeter Tube: 100mm Stainless Steel Centre-Fill Water Jacketed Polarimeter Tube (B+S Code 35-02)

Temperature Control of Polarimeter Tube: Adjustable Electronic Peltier Thermostat, providing temperature control to within 0.1°C.

Balance: Analytical - resolution 0.0001g
Volumetric Flask: 100ml Volumetric Flask
Additional Equipment: Small funnel, plastic disposable pipettes

- ***Supplied Sample***

Plastic container of Fructose Regular Granular, supplied by customer.

Method of Analysis

Optical rotation measurement of the Fructose sample was carried out in accordance with the supplied procedure:

"**Assay** - Transfer about 10g of Fructose, previously dried and accurately weighed, to a 100-mL volumetric flask, and dissolve in 50 ml of water. Add 0.2mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. After 30 minutes, determine the angular rotation in a 100-mm tube at 25° (see *Optical Rotation* <781>). The observed rotation, in degrees, multiplied by -1.124, represents the weight, in g, of $C_6H_{12}O_6$ in the Fructose taken."

9.9901g of Fructose were weighed into the volumetric flask and the solution prepared as detailed above.

Prior to commencing measurements, the polarimeter had been switched on and allowed to stabilise. The ambient temperature in the Laboratory during the course of the tests was 22°C.

An initial calibration of the ADP410 was followed by a measurement of the empty water-jacketed polarimeter tube, then three separate applications of the prepared Fructose solution. On completion of the three applications, the calibration of the instrument was again verified on accordance with USP 2005.

Results

Calibration was performed with the instrument configured to read in °Z, with Quartz Temperature Compensation active. The PTB Certified Quartz Control Plate used for spanning was fitted with a thermal saddle and three minutes allowed for thermal stabilisation.

Calibration Point	Expected °Z	Measured °Z	Optical Density	Sample Probe (°C)
Zero - Empty Chamber	0.00	0.00	0.0	21.9
Span - PTB QCP	99.95	99.95	0.0	21.5

Table 1: Initial Calibration of ADP410 Polarimeter

To ensure that no measurement errors were introduced as a result of stresses in the end caps of the centre-filling tube, a measurement was taken of the empty tube prior to introducing the Fructose solution.

Sample	Expected °Z	Measured °Z	Optical Density	Sample Probe (°C)
Empty 100ml Tube	0.00	0.00	0.1	24.7

Table 2: Measurement of Empty 100ml Centre-Filling Water Jacketed Polarimeter Tube

Before taking measurements of the Fructose solution, the Quartz Temperature Compensation used during calibration of the instrument was turned off and the scale changed to Angular Degrees (°A). The sample temperature probe was immersed in the centre-filling tube and the reading allowed to stabilise before recording the optical rotation in Angular Degrees. For each repeat application, the tube was emptied and fresh solution introduced.

Application	Measured °A	Optical Density	Sample Probe (°C)
1	-8.95	0.1	25.0
2	-8.95	0.1	25.0
3	-8.95	0.1	25.0

Table 3: Measurement of Fructose Solution in 100ml Centre-Filling Water Jacketed Polarimeter Tube

On completion of the Fructose solution measurements, the calibration of the polarimeter was verified. The scale was changed back to °Z and Quartz Temperature Compensation turned back on for these measurements.

Calibration Point	Expected °Z	Measured °Z	Optical Density	Sample Probe (°C)
Zero - Empty Chamber	0.00	0.00	0.0	24.7
Span - PTB QCP	99.95	99.95	0.0	21.7

Table 4: Final Calibration of ADP410 Polarimeter

Conclusion

The measured angular rotation of the prepared Fructose solution at 25.0°C was -8.95°A. Repeatability between the three applications of the solution was excellent, with no variation in readings to 2 decimal places observed.

Bellingham + Stanley

a xylem brand

International
Longfield Road
Tunbridge Wells, Kent
TN2 3EY
United Kingdom
Tel: +44 (0) 1892 500400
Fax: +44 (0) 1892 543115
sales.bs.uk@xyleminc.com

United States
1000 Hurricane Shoals Road
Building D, Suite 300
Lawrenceville, GA 30043
United States of America
Tel: 770 822 6898
Fax: 770 822 9165
sales.bs.us@xyleminc.com

www.bellinghamandstanley.com