ICON Laboratory Services, Inc.

Laboratory Manual

Bristol-Myers Squibb
Protocol: CA209908

Version #: 1.0 **Date: 12-Apr-2017**

NORTH AMERICA
123 Smith Street
Farmingdale, NY 11735
USA

(Phone) +1-919-674-5474
(Fax) +1-631-306-5399

EUROPE
South County Business Park
Leopardstown, Dublin 18
Ireland

(Phone) +353-1-291-2355
(Fax) +353-1-291-2777

SINGAPORE
30 Loyang Way
#02-13 Loyang Industrial Estate
Singapore 508769

(Phone) +65-6895-8270
(Fax) +65-6542-0875

CHINA
TEDA International
Cardiovascular Hospital Level 3
61 Third Avenue
TEDA Tianjin China, 300457
(Phone) +86-10-8529-5131
(Fax) +86-22-6520-9008

ICON
A Symbol of Excellence

TABLE OF CONTENTS

Section 1 - Introduction

ICON Laboratory Services is pleased to have been selected by **Bristol-Myers Squibb** to provide the laboratory support for the **CA209908** protocol.

As the central laboratory for this protocol, we are committed to providing quality laboratory and related site support. If you have any questions or concerns regarding the laboratory component of this clinical protocol, please do not hesitate to contact ICON Laboratory Services. Contact information can be found in the following section of this manual.

Please Note: Your site is responsible for ensuring that all site lab staff and clinical trial personnel are properly trained on all procedures outlined in this Laboratory Manual, as defined by the Sponsor or their designee for this protocol. This includes documentation of initial training on the laboratory instructions within this manual, as well as documentation of training provided to site personnel following any changes to the lab procedures outlined in this manual or changes in site personnel. All documentation of such training must be maintained in your site files.

Information Available in this Manual

This manual serves as a comprehensive guide to the central laboratory requirements for this protocol, including information and instructions regarding:

- Laboratory contacts;
- Laboratory supplies;
- Specimen collection procedures;
- Laboratory requisitions;
- Specimen packaging;
- Specimen shipping information;
- Result reporting and alert values.

Additional Information Available on the ICON Website (www.iconplc.com/LabSiteHelp)

The ICON website includes an Investigator Site Resource Center that offers additional information that may prove helpful to you, such as:

- Printable copies of all laboratory licenses and certifications*;
- Links to commercial couriers that serve sites;
- Frequently asked questions;
- Contact information;
- General Information about ICON Laboratory Services' locations and services;
- Training Videos for common collection practices;
- Packaging instructions for common ICON Laboratory Services' shipping boxes;
- Site Newsletters;
- Holiday schedule information for ICON Laboratory Services and Couriers.

* Current Certificates are sent to your Site with initial shipments. Please check the website for updated Certificates as needed.

iSite – ICON Laboratory Services' Secure Web Portal

iSite is ICON Laboratory Services' secure web portal for clinical research sites. When you register with iSite, you gain access to site-specific solutions developed to help make your ICON Laboratory Services experience as efficient as possible. Once registered for iSite, the User Guide will be accessible through the iSite portal. It is strongly recommended that this be read as it will have guidance on all the iSite features listed below.

iSite features currently include:

- **Lab Report eDelivery** – receive email notifications each time a lab report is ready for download and enable you to view all subject reports in an organized manner.
- **Kit and Supply Ordering** – order new kits, view past orders, view your site's kit inventory, find out when your kits expire, and more!
- **Specimen Collection and Shipping Videos** – see our lab manual come to life in easy to follow animations of our most common specimen collections and shipping instructions.
- **E-Requisitions** – electronically receive laboratory visits into the ICON database instead of using paper requisitions. You are also able to edit Subject Demographic or Visit information as needed to automatically update information to ICON.

To ensure security, only email addresses on file with ICON Laboratory Services are able to register with iSite. If you are unsure of the email address that we have for you or your Site, please contact Site Services.

To register or access iSite please visit https://isite.iconplc.com

Section 2 - Contacting ICON Laboratory Services for Assistance

ICON Laboratory Services has global Site Service Specialists who are familiar with your protocol and are available via telephone, e-mail and fax to help you. They routinely help sites by:

- Calling laboratory alert values;
- Resolving any missing/discrepant information;
- Answering questions about specimen collection, packaging and/or shipping;
- Responding to other laboratory-related questions/concerns;
- Sending copies of laboratory reports when iSite is unavailable;
- Processing supply re-order requests when iSite is unavailable.

Query Process

Visits received at ICON Laboratory Services that have missing or discrepant information may result in a query being issued to the site contact on file. These queries will be sent via email and will contain a description of the query and unique record number. Queries may be responded to via email or you may call our Site Service department directly. In addition to an initial query, a summary email of outstanding queries will be sent once daily until the outstanding queries are resolved. Your prompt attention to these queries is appreciated as some queries may delay release of lab reports.

Abnormal Result Notification Process

Abnormal results or results of particular interest that meet a predefined flag determined by the sponsor will be sent to the site contact on file. There are two categorizations of flagging priority; what is considered to be a panic value and a non-panic value.

- Lab values that meet flagging criteria however are *not* considered a panic value will be emailed once and closed
- Lab values that meet flagging criteria and are considered panic values may be telephoned and emailed daily until we have confirmed the value has been received.

Panic values must have a confirmed receipt. You can confirm receipt of a panic value by either reading back the value while on the phone with our Site Service Specialist, reply to the email which contained the value, or signing and faxing back the Urgent Result Report that contained the value. Please refer to Section 15 for definitions of the different types of result flags for this study.

NOTE: ICON Laboratory Services cannot provide medical advice based on subject results. Please contact the Medical Monitor, designated by the protocol sponsor, for such assistance.

Please refer to the Site Services Directory provided below to obtain the appropriate ICON Laboratory Services contact information for your site.

ICON Laboratory Services Global Site Services Directory

Global Call Centre Hours of Operation						
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
8:00 am - 4:30 pm (EST) 1:00 pm - 9:30 pm (GMT)	24 Hours	24 Hours	24 Hours	24 Hours	24 Hours	12:00 am - 4:30 pm (EST) 12:00 am - 9:30 pm (GMT)

Global E-mail Contact: LabSiteHelp@iconplc.com

NORTH AMERICA	Toll Free (U.S. and Canada) +1-877-797-4422 Telephone: +1-919-674-5474	Fax: +1-631-306-5399
EUROPE	Telephone: +353-1-291-2355	Fax: +353-1-291-2777
SINGAPORE	Telephone: +65-6895-8270	Fax: +65-6542-0875
INDIA	Telephone: +91-80-4089-4115	Fax: +91-80-6713-5541
CHINA	Telephone: +86-10-8529-5131	Fax: +86-22-6520-9008

Site Services Toll Free Numbers

Country	Toll Free Number	Country	Toll Free Number
Argentina	0-800-222-2602	**Japan**	00531-13-1504
Australia	1800881823	**Latvia**	800-2461
Austria	0800-295306	**Malaysia**	1-800-815-060
Belgium	0-800-74-152	**Mexico**	001-8002814656
Brazil	8008921061	**Netherlands**	0800-0228527
Canada	1-877-797-4422	**New Zealand**	0800-444-711
Chile	1230-020-4346	**Norway**	80014910
China - North	10-800-713-1446	**Peru**	80054424
China - South	10-800-1301-406	**Philippines**	1-800-1-116-1007
Colombia	01-8005-1-81468	**Poland**	00-800-111-3950
Croatia	0800805916	**Portugal**	800-863-313
Denmark	808-87-278	**Russia**	8-10-8002-8993011
Estonia	800-0111371	**Serbia**	0800190656
Finland	0800-9-18199	**Slovakia**	0800-001673
France	0800915589	**South Africa**	0800-983-142
Germany	0-800-180-6766	**South Korea**	00308-13-2368
Greece	00800-1809-203-9542	**Spain**	900-941-335
Hong Kong	800-93-0646	**Sweden**	020-799-922
Hungary	06800 19035	**Switzerland**	0800-562-591
India	000-800-100-3316	**Taiwan**	00-8011-489-41
Ireland	1800-550-203	**Thailand**	001-800-13-203-9546
Israel	1-809-31-5679	**United Kingdom**	0808-101-3860
Italy	800-87-4092	**United States**	1-877-797-4422

If your Site's location is not listed above, please contact the Global Site Services Call Center directly at +1-919-674-5474 or utilize the Global E-mail Contact address: LabSiteHelp@iconplc.com.

ICON Laboratory Services' Site Services Department is available seven (7) days per week and can provide telephone support in your native language. Simply ask our Site Specialist to conference in an interpreter for the phone call.

Section 3 - Courier Contacts and Documents for Specimen Shipments

Detailed specimen packaging and shipping instructions are provided in this manual. The following table provides helpful contact information and a list of the documents needed to properly ship specimens to our laboratories, based upon your site's location.

NOTE: If your site has received a separately provided Courier Contact Memorandum, please refer to it for your site's specific logistics information.

Shipping Information by Site Location		
Shipping From	**Shipping To**	**Forms Required**
Within U.S.	ICON Laboratory Services Farmingdale, NY, USA	• Domestic Courier Air Waybill
Canada Puerto Rico	Contact FedEx at: 1-800-GO-FEDEX 1-800-463-3339 **Emergency Use Only** Call Marken at: 1-800-MARKEN1 (1-800-627-5961)	• Canadian Air Waybill • International Air Waybill • Commercial (Pro-Forma) Invoice • CDC Permit
Central America South America Caribbean	ICON Laboratory Services Farmingdale, NY, USA Courier information will be provided to each site, based on individual locations	• International Air Waybill • Commercial (Pro-Forma) Invoice • CDC Permit
All European Union (EU) Countries	ICON Laboratory Services Dublin, Ireland Courier information will be provided to each site, based on individual locations	• International Air Waybill
Non-EU Countries Middle East Africa	ICON Laboratory Services Dublin, Ireland Courier information will be provided to each site, based on individual locations	• International Air Waybill • Commercial (Pro-Forma) Invoice
Asia/Pacific	ICON Laboratory Services Singapore Courier information will be provided to each site, based on individual locations	• International Air Waybill • Commercial (Pro-Forma) Invoice
China	ICON Laboratory Services Tianjin, China Courier information will be provided to each site, based on individual locations	• China Air Waybill • Commercial (Pro-Forma) Invoice
India	ICON Laboratory Services Singapore Courier information will be provided to each site, based on individual locations	• International Air Waybill • Commercial (Pro-Forma) Invoice (if required for your site's location)

Section 4 - Laboratory Supplies

Important Reminders for Sites

- Always use the correct kit for the visit.
- DO NOT use an expired kit (The kit expiration date is located on the kit box label).
- Destroy expired and unused kits according to your site's hazardous waste disposal policy.
- Monthly, ICON Laboratory Services sends a Kit Expiration Report of all kits expiring in the near future. Review report and maintain kit inventory so that kits with the earliest expiration dates are used first.
- Please note that Visit kits can be expensive, and sites should be mindful of wastage.

Visit Kits

ICON Laboratory Services has provided the following types of collection kits for use in this clinical protocol:

Collection Kit Type	Use For
Scheduled Visit Kits	The specific visit (s) indicated on the kit label
Non-Sequential Visit Kits	• Visits other than those required by protocol • Retesting for a specific visit • As a substitute for a scheduled visit kit, only when a visit-specific kit is not available for use at the site

Section 5 - Re-Ordering Supplies

Initial shipments will be initiated at the discretion of the sponsor and additional supplies will then need to be managed at the site level and ordered via iSite as appropriate.

Monitor your supply inventory closely. Re-order supplies when needed using the **iSite Portal**.

- Orders placed through iSite are sent directly to the Kit Building department.
- Please access at the following link: https://isite.iconplc.com.

*****If you require an urgent order, please contact ICON Laboratory Services directly using the information available in the Global Site Services Directory of Section 2.*****

Please Note

In addition to study specific items, please also manage standard non kit-orderable items that are provided in bulk and required for sample collection/transport such as:

- Segmented Absorbent Pouches
- 95kPA Biohazard Bags
- Pipettes

Please re-order these items using the iSite Portal when deemed necessary by your site.

Supplies Listing

The following items are provided for the **CA209908** study:

ALL SITES	4 Segmented Absorbent Pouch
	7” x 11” 95 KPA Biohazard Bag
	Bag of 100 3mL Transfer Pipette
	9" x 12"Brown Kraft Clasp(Manila)Envelopes 100/Box
	2 mL Clear No Additive Plastic Simport Graduated Polypropylene Self-Standing
	500uL Single Channel Pipettor Tips (Rack/100)
	Zip-Lock Bag 8x8
	Superfrost White Charged Slide Box/72
	1 Slide Holder w/o Slide (Blue)
	81 Insert (3.6mL Tube) Cryo Box w/Large 95KPA Biohazard Bag
POLAND, GERMANY, FRANCE, SPAIN, NETHERLANDS, UNITED KINGDOM, NORWAY, DENMARK, SWEDEN, ISRAEL, HONG KONG AND RUSSIA ONLY	Shipping Box Refrigerated ROW (2-8) DGP BioTherm 10
POLAND, GERMANY, SPAIN, NETHERLANDS, UNITED KINGDOM, NORWAY, DENMARK, SWEDEN AND ISRAEL ONLY	DHL International Ambient Non-Infectious Airbill
	DHL Saturday Label
NORWAY, ISRAEL, HONG KONG, RUSSIA AND CANADA ONLY	Commercial Invoice Ambient Non-Infectious
	Commercial Invoice Non-Infectious Frozen
FRANCE, HONG KONG AND RUSSIA ONLY	TNT Saturday Label
HONG KONG AND AUSTRALIA ONLY	UN3373 Thermal Ambient Carton w/2 Gel Wraps (ROW)
FRANCE AND HONG KONG ONLY	TNT Ambient Non-Infectious Airbill
USA AND CANADA ONLY	Fed Ex Saturday Label
	Shipping Box Frozen Medium (SG8)
	Shipping Box Refrigerated N. America (2-8) DGP PHT003
USA ONLY	Fed Ex Domestic Ambient Non-Infectious Airbill
	Fed Ex Domestic Ambient Non-Infectious Airbill (Bristol-Myers Squibb NJ)
CANADA ONLY	Fed Ex Canada Ambient Non-Infectious Airbill
	Fed Ex International Airbill Pouch
	Commercial Invoice Ambient Non-Infectious (Bristol-Myers Squibb NJ)
	Fed Ex Canada Ambient Non-Infectious Airbill (Bristol-Myers Squibb NJ)
	CDC Permit
RUSSIA ONLY	TNT Extreme Ambient 3kg
	TNT Airbill Ambient for Russian and Ukraine

Section 6 - Specimen Collection and Labeling Instructions

IMPORTANT NOTE

This manual presumes that persons collecting specimens have had the proper training in venipuncture, safety procedures and disposal of bio-hazardous materials.

Correct Sequence of Collection Tubes

To minimize the potential for cross-contamination between tubes containing different additives, please collect specimens in the following tube order:

Draw Order	Tube Top Reference	Tube Top Color	Tube Type/Additive [1]
1.		**Red** (Black/White Ring)	**Clot Activator**
2.		**Red or Gold** (Yellow/White Ring)	**Serum Separator Tube (SST) Clot Activator w/Gel**
3.		**Speckled, Tiger Top, Red or Gold**	**Serum Separator Tube (SST)**
4.		**Green/Red**	**(CPT) Heparin**
5.		**Lavender** (Black/White Ring)	**K2/K3 EDTA**
6.		**Clear/Red**	**PAXgene blood RNA**

[1] References: CLSI H3-A6, CLSI H21-A5, BD Diagnostics, Streck-Flow Cytometry, Greiner Bio-One

Centrifugation Table
Ref: Becton Dickinson Vacutainer System, 1996

Please note that centrifuges vary. The radius of the centrifuge "arm" is a critical factor in determining centrifugal force. Based upon the arm radius, the following tables provide the centrifugal speed in revolutions per minute (rpm) that will produce the relative centrifugal force noted. This information is based upon the formula:

$$\textbf{RCF (g) = 0.00001118 x radius in cm x (rpm)}^2$$

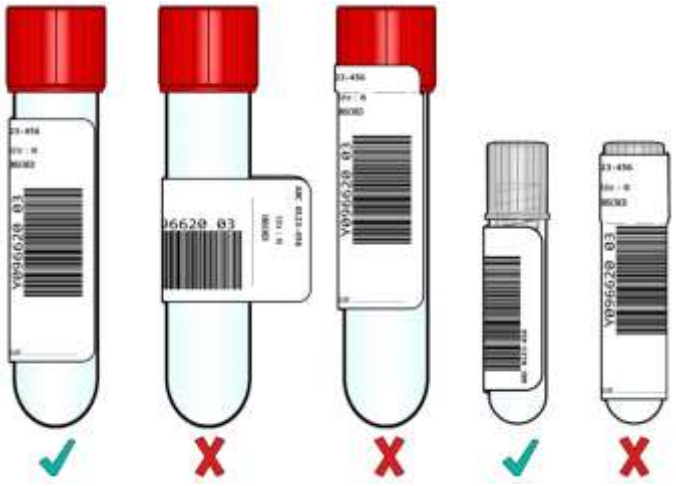
Centrifuge Radius (cm)	Centrifuge Speed (rpm)						
	1000g	1200g	1300g	1500g	1600g	2000g	2500g
7	3575	3916	4076	4378	4522	5055	5652
8	3344	3663	3812	4095	4230	4729	5287
9	3153	3453	3594	3861	3988	4458	4985
10	2991	3276	3410	3663	3783	4230	4729
11	2852	3124	3251	3492	3607	4033	4509
12	2730	2991	3113	3344	3453	3861	4317
13	2623	2873	2991	3213	3318	3710	4147
14	2528	2769	2882	3096	3197	3575	3997
15	2442	2675	2784	2991	3089	3453	3861
16	2364	2590	2696	2896	2991	3344	3738
17	2294	2513	2615	2809	2901	3244	3637
18	2229	2442	2542	2730	2820	3153	3525
19	2170	2377	2474	2657	2744	3068	3431
20	2115	2317	2411	2590	2675	2991	3344
21	2064	2261	2353	2528	2611	2919	3263
22	2016	2209	2299	2470	2551	2852	3188
23	1972	2160	2248	2415	2494	2789	3118
24	1931	2115	2201	2364	2442	2730	3052
25	1892	2072	2157	2317	2393	2675	2991
26	1855	2032	2115	2272	2346	2623	2933

Preparing and Affixing Bar Code Labels to Specimen Containers

ICON Laboratory Services utilizes bar code labels to ensure proper specimen identification and appropriately process each specimen. **Properly affixing the bar code label is critical to expediting each specimen for testing.**

A Sample of the **1 x 1** bar code label is displayed below, along with the proper method of affixing it to the tubes.

1 x 1 Barcode



To properly affix the bar code label:

- Match the appropriate bar code label to the corresponding collection/transport tube.
- **Affix the label with the bar code oriented LENGTHWISE on the tube.**
- Do not cover the stopper with the label.

Important Note: ICON Laboratory Services offers protocol sponsors a variety of bar code label size and formatting options. Therefore, the bar code labels provided in your protocol's collection kit and in the step-by-step collection instructions located in this manual may not look exactly alike. However, the procedure for properly affixing the bar code labels is the same.

A subject identification number is required for proper specimen container identification. **Legibly print the subject identification number on EACH bar code label provided BEFORE collecting specimens.**

Testing and Shipping Requirements by Visit Quick Reference Guide

Protocol # CA209908 / KIT NAME / VISIT NAME / Test/Panel		SCREEN	C1D1-Mono	C1D1-Combo	C2D1-Mono	C2D1-Combo	C3D1-Combo	C4D1-Mono	C4D1-Combo	C5D1-Mono	C5D1-Combo	C7D1-Mono	C8D1-Combo	C10D1-Mono	C13D1	C21D1	C29D1	C37D1
PK Nivo[1]	Predose		F	F	F	F		F	F	F	F				F	F	F	F
	EOI		F	F				F	F									
PK Ipi[1]	Predose			F		F			F		F							
	EOI			F					F									
ADA Nivo Predose[1]			F	F	F	F				F	F				F	F	F	F
ADA Ipi Predose[1]				F		F					F							
Serum Markers[1]			F	F			F	F			F	F	F	F				
PBMC[5,7]			A	A			A	A			A	A	A	A				
DNA		F[6]																
Gene Expression Profiling[1]			F	F			F	F			F	F	F	F				
PK CSF[1]			F[3]*	F[3]*														
Protein CSF[1]			F[3]*	F[3]*														
Tissue Block		A[2*]																
Tissue Slides		R[2*]																
Pathology Report		A																
Shipping Container (US)		A/F /R	A/F	A/F	F	F	A/F	A/F	F	F	A/F	A/F	A/F	A/F	F	F	F	F
Shipping Container (ROW)		A/F /R	A/F	A/F	F	F	A/F	A/F	F	F	A/F	A/F	A/F	A/F	F	F	F	F

* Testing for this visit is optional
[1] Batch Ship Bi-Monthly
[2] Site should submit fresh block/slides or an archived block or slides
[3] Baseline sample strongly recommended for Cohorts 3, 4 and 5 unless clinically contraindicated
[4] Samples obtained at progression are optional, and should only be obtained if a baseline sample was obtained
[5] USA and Canada Cohort do not ship samples to ICON. Ship from Site directly to Bristol Myers Squibb
[6] Batch Ship Monthly
[7] Second 8 mL CPT tube (CPT-2 or VA-PBMC2) is optional

(A) Specimen is to be maintained ambient. Use kit box as ambient shipping container unless otherwise directed.
(R) Specimen is to be refrigerated. Use refrigerated shipping container.
(F) Specimen is to be frozen. Use frozen shipping container.

Testing and Shipping Requirements by Visit Quick Reference Guide

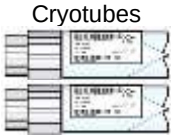
Protocol # CA209908 / KIT NAME / VISIT NAME		C45D1	C53D1	Progression	30D FU-Mono	30D FU-Combo	100D FU-Mono	100D FU-Combo	EOT-Mono	EOT-Combo	UNSCHED
Test/Panel											
PK Nivo[1]	**Predose**	F	F		F	F	F	F	F	F	F*
	EOI										F*
PK Ipi[1]	**Predose**					F		F		F	F*
	EOI										F*
ADA Nivo Predose[1]		F	F		F	F	F	F	F	F	F*
ADA Ipi Predose[1]						F		F		F	F*
Serum Markers[1]				F[4]*							F*
PBMC[5,7]				A[4]*							A*
DNA											F[1]*
Gene Expression Profiling[1]				F[4]*							F*
PK CSF[1]											F*
Protein CSF[1]				F[4]*							F*
Tissue Block				A[1,4*]							
Tissue Slides				R[1,4*]							
Pathology Report				A[1,4*]							
Shipping Container (US)		F	F	A/R/F	F	F	F	F	F	F	A/F
Shipping Container (ROW)		F	F	A/R/F	F	F	F	F	F	F	A/F

* Testing for this visit is optional
[1] Batch Ship Bi-Monthly
[2] Site should submit fresh block/slides or an archived block or slides
[3] Baseline sample strongly recommended for Cohorts 3, 4 and 5 unless clinically contraindicated
[4] Samples obtained at progression are optional, and should only be obtained if a baseline sample was obtained
[5] USA and Canada Cohort do not ship samples to ICON. Ship from Site directly to Bristol Myers Squibb
[6] Batch Ship Monthly
[7] Second 8 mL CPT tube (CPT-2 or VA-PBMC2) is optional

(A) Specimen is to be maintained ambient. Use kit box as ambient shipping container unless otherwise directed.
(R) Specimen is to be refrigerated. Use refrigerated shipping container.
(F) Specimen is to be frozen. Use frozen shipping container.

Specimen Collection – Quick Reference Guide

Protocol # CA209908

Test/Panel		Bar Code Label: Collection Label	Bar Code Label: Transport Label	Collection Container	Transport Container	Shipping Temperature
PK Nivo	**Predose**	PK NIVO	**PK NIVO**	2mL Red Top (White Ring) Serum Tube w/Clot Activator [Per Timepoint] 	4mL Gray Top Screw Cap Nova Biostorage Tube w/2D Barcode [Per Timepoint] 	**Frozen**
	EOI					
PK Ipi	**Predose**	PK IPI	**PK IPI**	2mL Red Top (White Ring) Serum Tube w/Clot Activator [Per Timepoint] 	4mL Gray Top Screw Cap Nova Biostorage Tube w/2D Barcode [Per Timepoint] 	**Frozen**
	EOI					
PK Nivo Predose		PK NIVO	**PK NIVO**	4mL Red Top (Yellow Ring) SST Tube w/Clot Activator 	Two - 4mL Gray Top Screw Cap Nova Biostorage Tubes w/2D Barcode 	**Frozen**
ADA Nivo Predose			**ADA NIVO**			
PK Ipi Predose		PK IPI	**PK IPI**	4mL Red Top (Yellow Ring) SST Tube w/Clot Activator 	Two - 4mL Gray Top Screw Cap Nova Biostorage Tubes w/2D Barcode 	**Frozen**
ADA Ipi Predose			**ADA IPI**			
Serum Markers		SM-1	**SM-1** **SM-2**	3.5mL Gold Top SST Vacutainer Tube 	Two – 1.8mL NUNC Conical Self-Standing Cryotubes 	**Frozen**
<u>USA and Canada Cohort</u> **PBMC**		**VA-PBMC1** **VA-PBMC2**		Two - 8mL Green/Red Sodium Heparin CPT Tube 		**Ambient**
<u>Germany and Netherlands Cohort and All Other Sites Cohort</u> **PBMC**		**CPT-1** **CPT-2**		Two - 8mL Green/Red Sodium Heparin CPT Tube 		**Ambient**

Specimen Collection – Quick Reference Guide

Protocol # CA209908

Test/Panel	Bar Code Label		Collection Container	Transport Container	Shipping Temperature
	Collection Label	Transport Label			
DNA	**SNP-1**		3mL Lavender Top (Black Ring) Tube w/K2 EDTA 		**Frozen**
C1D1-Mono and C1D1-Combo Only **Gene Expression Profiling**	**GENE EXP A** **GENE EXP B**		Two - 2.5mL Clear/Red Blood RNA PAXgene Tubes 		**Frozen**
All Visits Except C1D1-Mono and C1D1-Combo **Gene Expression Profiling**	**GENE EXP A**		2.5mL Clear/Red Blood RNA PAXgene Tube 		**Frozen**
PK CSF	CSF_Collect	**CSF PK**	3mL Clear Top Simport Cryovial w/O-Ring 	Two - 2.5mL Orange Top Corning Self-Standing Cryovials 	**Frozen**
Protein CSF		**CSF Protein**			
Tissue Block	**S-BLCK**		Formalin Fixed Paraffin Embedded Block (Place in Ziplock Bag 8x8) 		**Ambient**
Tissue Slides	**S-SLD1 H&E** **S-SLD2** **S-SLD3** **S-SLD4** **S-SLD5** **S-SLD6** **S-SLD7** **S-SLD8** **S-SLD9** **S-SLD10** **S-SLD11** **S-SLD12** **S-SLD13** **S-SLD14** **S-SLD15** **S-SLD16** **S-SLD17** **S-SLD18** **S-SLD19** **S-SLD20**		Twenty - White Charged Slides (Place in individual Blue Slide Holders) 		**Refrigerated**
Pathology Report	**S-PATH**		Pathology Report (Place in Manila Envelope)		**Ambient**

Sample Collection and Preparation Steps to Ensure Quality Test Results			
Sample Integrity Issue	**Definition**	**Cause**	**How to Prevent**
Clotting	A sequence of complex chemical and physical reactions that results in conversion of blood into a coagulated mass, making specimen unacceptable for coagulation or hematology testing.	• Gauge of needle is too large or too small for the tube vacuum. • Failure to adequately mix the sample with the anticoagulant in the tube following collection.	Use proper collection system as well as phlebotomy and sample handling techniques.
Fibrin Clotting	An elastic, insoluble, whitish protein produced by the action of thrombin on fibrinogen and forming an interlacing fibrous network in the coagulation of blood.	Serum sample did not fully clot prior to centrifugation.	• Ensure sample is placed in vertical position and allowed to clot for the time indicated in the lab manual. • Samples from subjects receiving anticoagulant medication may require additional clotting time.
Hemolysis	Hemolysis results when RBCs are lysed (the cell breaks apart and is destroyed); hemoglobin is released; and serum or plasma, which is normally straw colored, becomes tinged with pink or red. If a specimen is grossly hemolyzed, the serum or plasma appears very dark red.	• Excessive vacuum in vein, causing red cells to be drawn toward the bore of the needle too quickly. • Loose connection of blood collection equipment parts (needle to holder, etc.) • Alcohol used to cleanse collection site not allowed to dry prior to collection. • Gauge of needle is too large or too small for the tube vacuum, or excessive manipulation or improper placement of needle during the collection. • Vigorous mixing or shaking of the filled collection tube. • Tourniquet applied for too long. • Shaking or mixing tubes vigorously.	• Use proper collection system as well as phlebotomy and sample handling techniques. • Ensure collection set is securely assembled. • Before performing the venipuncture, the alcohol should be allowed to air dry. • During phlebotomy, avoid probing to find the vein and achieve blood flow. Excessive probing and/or “fishing” to find a vein can result in a poor quality sample and lead to hemolysis. • Ensure needle bevel is not against the vein wall and the needle is at the appropriate angle. • Ally the tourniquet for a maximum of 1 min. • Gently invert the specimen as specified in the lab manual for appropriate mixing.
Platelet Clumping	Partial clotting of a specimen, or agglutination of platelets, that becomes evident on a blood smear and can affect platelet results.	• Usually due to EDTA preservative not mixing properly with specimen. • EDTA-induced platelet clumping is the most common cause of pseudothrombocytopenia, antibodies in EDTA may react with platelets. • Platelet clumping can rarely be indicative of a medical condition known as thrombocytopenia.	Proper tube inversion immediately after collection. To confirm platelet clumping is not due to clinical thrombocytopenia in the study subject, obtain sponsor approval to collect a blue top tube in addition to the EDTA tube. Refer to collection instructions for “Light Blue Top Tube w/Sodium Citrate (Whole Blood) (PLATELETS)” for additional information.

Sample Collection and Preparation Steps to Ensure Quality Test Results			
Sample Integrity Issue	**Definition**	**Cause**	**How to Prevent**
Age of Specimen / Sample out of Stability	The elapsed time since specimen collection has exceeded the specimen stability period for the requested test.	• Usually caused by delays in transport time to the laboratory.	Samples need to be shipped as detailed within the lab manual to ensure they are received in a timely manner.
Expired Tube	Tube manufacturer's expiration date has been exceeded.	• Expired tubes are a source of potential patient safety issues. • Results from expired tubes cannot be used, as they may have a decreased vacuum, as well as potential changes in any additives in the tubes.	• Check expiration dates of kits frequently. • Review monthly notifications of expiring kits and miscellaneous supplies. • Kit inventory and expiration can also be viewed via iSite.
Insufficient Sample Quantity	Amount of sample collected would not render the appropriate ratio of sample to tube preservative, or the amount of sample provided not sufficient to perform the test.	Failure to collect the required amount of sample in the collection tube or aliquot the appropriate amount of sample into transport tube.	• Ensure sample collection tubes fill to the appropriate volume. • Carefully review specimen requirements in the lab manual and collect accordingly.
Specimen received at wrong temperature	The sample arrived at the laboratory at a condition that is not consistent with test requirements and therefore could yield inaccurate results.	• Selection of improper shipper. • Improper courier handling.	Ensure frozen specimens are maintained, packed and shipped as indicated in the lab manual.
Interfering substances / Pre-analytical contamination	Interference occurs when a substance or process falsely alters an assay result.	• Incorrect sample tube collected. Example - EDTA (lavender top tube) drawn and aliquotted for chemistry tests rather than speckled red, plain red or gold for serum. • Proper order of draw not followed. • Draw from dialysis port or too close to an IV line. • Other form of contamination or substance introduced into sample during collection process.	• Follow collection and shipment instructions as detailed in the lab manual. • Follow the specified order of draw as detailed in the lab manual. • If drawing from a port, draw a discard tube before collecting test samples.
Integrity of sample in question	Sample is compromised, results are deemed not valid.	• Sample received in a state other than acceptable for the test.	• Follow collection and shipment instructions as detailed in the lab manual.

Sponsor-Specific Detailed Specimen Collection Instructions

Red Top Tube w/Clot Activator (Serum Without Gel) or Red Top (Yellow Ring) SST Tube w/Clot Activator (PK NIVO, ADA NIVO)

CA209-908
Serum PK and Immunogenicity (ADA)
BMS-936558 Collection Instructions
(for subjects receiving Nivolumab)

Supplies

- PK and ADA: one 4 mL SST Vacutainer
- PK only: one 2 mL SST Vacutainer
- Two 4 mL Micronic tubes for PK and ADA timepoints
- One 4 mL Micronic tube for PK only timepoint

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor. If samples are obtained through a heparin lock, sufficient blood (~1 mL) must be withdrawn to remove the heparin solution. PK samples should not be collected from the same line as an infusion. Specifically, if the compound is infused through an IV line, the contralateral arm should be used to collect the PK samples. If a central line is used for dosing, then direct venipuncture in either arm would be appropriate.

2. To ensure sufficient sample volume for the required test is obtained, fill tube until vacuum is exhausted and blood ceases to flow. Blood samples should be collected as follows:
   - On timepoints where both PK and ADA samples are collected, a 4 mL SST tube is used.
   - On timepoint where PK only is collected, a 2 mL SST tube is used

3. Immediately after collection, gently invert each blood sample 5 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).

4. Centrifuge samples at room temperature for 10 minutes (swing out) or 15 minutes (fixed) at 1100-1300 x g until clot and serum are well separated.

5. Aliquot according to the following:
   - PK and ADA- transfer serum equally from the 4 mL SST into 2 appropriately labeled 4ml Micronic tubes (1 for PK, 1 for ADA)
   - PK only - transfer serum from the 2 mL SST into a appropriately labeled 4ml Micronic tube (1 for PK)

6. Store serum samples immediately (within approximately 2 hours of collection) at approximately -20°C or colder (-70°C preferred) to ensure stability of the samples until they are shipped on dry ice to ICON every 2 months.

If multiple tubes are collected at a given time point, the EXACT clock time of the PK sample collection (to the minute) must be recorded on the requisition.

If a sample was not collected, do not send empty tube.

Red Top Tube w/Clot Activator (Serum Without Gel) or Red Top (Yellow Ring) SST Tube w/Clot Activator (PK IPI, ADA IPI)

CA209-908
Serum PK and Immunogenicity (ADA)
BMS-936558 Collection Instructions
(for subjects receiving Ipili)

Supplies

- PK and ADA: one 4 mL SST Vacutainer
- PK only: one 2 mL SST Vacutainer
- Two 4 mL Micronic tubes for PK and ADA timepoints
- One 4 mL Micronic tube for PK only timepoint

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor. If samples are obtained through a heparin lock, sufficient blood (~1 mL) must be withdrawn to remove the heparin solution. PK samples should not be collected from the same line as an infusion. Specifically, if the compound is infused through an IV line, the contralateral arm should be used to collect the PK samples. If a central line is used for dosing, then direct venipuncture in either arm would be appropriate.

2. To ensure sufficient sample volume for the required test is obtained, fill tube until vacuum is exhausted and blood ceases to flow. Blood samples should be collected as follows:
   - On timepoints where both PK and ADA samples are collected, a 4 mL SST tube is used.
   - On timepoint where PK only is collected, a 2 mL SST tube is used

3. Immediately after collection, gently invert each blood sample 5 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).

4. Centrifuge samples at room temperature for 10 minutes (swing out) or 15 minutes (fixed) at 1100-1300 x g until clot and serum are well separated.

5. Aliquot according to the following:
   - PK and ADA- transfer serum equally from the 4 mL SST into 2 appropriately labeled 4ml Micronic tubes (1 for PK, 1 for ADA)
   - PK only - transfer serum from the 2 mL SST into a appropriately labeled 4ml Micronic tube (1 for PK)

6. Store serum samples immediately (within approximately 2 hours of collection) at approximately -20°C or colder (-70°C preferred) to ensure stability of the samples until they are shipped on dry ice to ICON every 2 months.

If multiple tubes are collected at a given time point, the EXACT clock time of the PK sample collection (to the minute) must be recorded on the requisition.

If a sample was not collected, do not send empty tube.

Gold Top SST Tube w/Clot Activator (SM-1, SM-2)

CA209-908 Serum Soluble Biomarkers Collection Instructions

Supplies

- One 3.5 mL SST Vacutainer
- Two polypropylene tubes

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor.

2. To ensure sufficient sample volume for the required test is obtained, fill tube until vacuum is exhausted and blood ceases to flow.

3. Immediately after collection, gently invert each blood sample 5 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).

4. Centrifuge samples room temperature for 10 minutes (swing out) or 15 minutes (fixed) at 1100-1300 x g until clot and serum are well separated.

5. Transfer serum from the 3.5 mL SST into two appropriately labeled screw-capped polypropylene tubes as follows:
   - one aliquot of 1 mL labeled as Serum Soluble Biomarkers 1
   - one aliquot of remaining serum labeled as Serum Soluble Biomarkers 2

6. Store the serum samples immediately (within 2 hours of collection) at approximately -70°C to ensure stability of the samples until they are shipped on dry ice to ICON per the shipment schedule. **If site only has -20°C freezer available (no -70°C freezer on site), MUST ship sample monthly to ICON.**

If a sample was not collected, do not send empty tube.

Green/Red Sodium Heparin CPT Tube (VA-PBMC1, VA-PBMC2) – USA and Canada Cohort

CA209-908
Whole Blood Immunophenotyping for PBMC (Peripheral Blood Mononuclear Cell) Collection Instructions
ALL NA (US/Canada) Sites Shipping to BMS - NJ, USA

SUPPLIES

- 8 mL CPT tube
- 8 mL CPT tube (Optional)

Sample Collection Procedure:

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor.

2. Blood samples must be collected into properly labeled 8 mL CPT tube(s). Second 8 mL CPT tube is optional. Volume of blood collected is critical for analysis; ensure blood collects in tube until vacuum is exhausted and blood ceases to flow.

   Note: The tubes contain chemical additives therefore it is important to prevent backflow from the tube to the patient. Further instructions concerning prevention of backflow may be found in the tube manufacturer's website.

3. Immediately after collection, gently invert tubes 8-10 times to ensure mixing with the anticoagulant. Keep the 8 mL CPT tube(s) upright, **at room temperature at all times.**

4. **DO NOT CENTRIFUGE OR FREEZE the 8 mL CPT tube(s).**

5. **Pack sample thoroughly between insulation material using supplies provided by ICON, including gel wraps and foil bag. Cover every open space in ambient shipper to protect sample from breakage.**

6. **It is very important to attach the 5 ICON aliquot labels from each visit kit to the corresponding requisition (staple or clip). Please fill out the necessary patient and visit information on the aliquot labels and requisition form.**

7. **Please send pre-notification of intent to ship, courier tracking number, and protocol number with BMS study number on the subject line to:**
   bmsbiorepository@bms.com and **mg-notify-bms-flow@bms.com**

8. **Ship samples ambient with requisitions and attached labels immediately for overnight delivery to BMS:**

   Karl Kammerhoff
   BMS Biorepository
   311 Pennington-Rocky Hill Road
   Building 27, Room 101
   Pennington, NJ 08534
   p. 609-818-6398 f. 609-818-7569

9. Ensure the correct BMS-Hopewell, NJ airway bill is provided to courier upon pick up

****Schedule courier for same-day sample pick-up, prior to sample collection****
BMS recommends avoiding Friday visits, sample collection and/or shipping
****If shipping on Thursday or Friday and if the airbill has a Saturday Delivery section**:**
Check "Saturday Delivery" box on airbill - DO NOT check "Signature required" box
Place Saturday Delivery sticker on box
Saturday Delivery instruction steps do NOT apply to Marken

Green/Red Sodium Heparin CPT Tube (CPT-1, CPT-2) – Germany and Netherlands Cohort and All Other Sites Cohort

CA209-908
Whole Blood Immunophenotyping for PBMC (Peripheral Blood Mononuclear Cell) Collection Instructions - All EU, APAC and Brazil Sites

SUPPLIES

- 8 mL CPT tube
- 8 mL CPT tube **(Optional)**

Sample Collection Procedure:

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor.

2. Blood samples must be collected into properly labeled 8 mL CPT tube(s). Second 8 mL CPT tube is optional. Volume of blood collected is critical for analysis; ensure blood collects in tube until vacuum is exhausted and blood ceases to flow.

   Note: The tubes contain chemical additives therefore it is important to prevent backflow from the tube to the patient. Further instructions concerning prevention of backflow may be found in the tube manufacturer's website.

3. Immediately after collection, gently invert tubes 8-10 times to ensure mixing with the anticoagulant. Keep the 8 mL CPT tube(s) upright, **at room temperature at all times.**

4. **DO NOT CENTRIFUGE OR FREEZE the 8 mL CPT tube(s).**

5. **Pack sample thoroughly between insulation material using supplies provided by ICON, including gel wraps and foil bag. Cover every open space in ambient shipper to protect sample from breakage.**

6. **Ship samples ambient with requisitions and attached labels immediately for overnight delivery to *ICON*:**

7. **Ensure the correct *ICON Vendor* airway bill is provided to courier upon pick up**

****Schedule courier for same-day sample pick-up, prior to sample collection****
***ICON* recommends avoiding Friday visits, sample collection and/or shipping**
****If shipping on Thursday or Friday and if the airbill has a Saturday Delivery section**:**
Check "Saturday Delivery" box on airbill - DO NOT check "Signature required" box
Place Saturday Delivery sticker on box
Saturday Delivery instruction steps do NOT apply to Marken

Lavender Top Tube w/K2 EDTA (SNP-1)

CA209-908 Whole Blood DNA Collection Instructions

SUPPLIES

3 mL K_2 EDTA (lavender top) Vacutainer tube

1. Collect blood via direct venipuncture in a 3 mL K_2EDTA lavender-top tube.
2. Invert gently 8 times.
3. **DO NOT CENTRIFUGE SAMPLE**.
4. Store samples in an upright position preferably in a-70ºC freezer (-20ºC is acceptable for short term storage).

   A **step down freezing process is recommended**, if possible. First, refrigerate the whole blood samples at 4°C for at least one day, but no longer than four days. Then the samples should be placed upright in a -70°C freezer.

   Holding samples longer than four days at 4°C may result in decreased recovery of high molecular weight DNA.
5. Complete the requisition and record the date and time of sample collection on the appropriate source document.
6. Ship samples on dry ice to ICON for processing every 2 months. **If a site only has -20ºC freezer available (no -70ºC freezer on site), then Whole Blood DNA sample MUST ship monthly to ICON.**

PAXgene RNA Collection (Red/Clear Cap Tube) (GENE EXP A, GENE EXP B)

CA209-908
Whole Blood mRNA PAXgene Gene Expression Collection Instructions

Supplies

- Two 2.5 mL PreAnalytiX™ PAXgene Blood RNA Tubes **(First visit requires two tubes)**
- One 2.5 mL PreAnalytiX™ PAXgene Blood RNA Tube **(All other visits require only one tube)**

1. Blood samples (2.5 mL each) will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor. ICON may provide the ***discard/throw away tubes as bulk supplies***.

***The PAXgene tube should be collected last if multiple vacutainer tubes are collected for protocol related analysis.**

2. Blood samples will be collected into properly labeled, **room temperature**, **PreAnalytiX™ PAXgene Blood RNA Tube(s).** Volume of blood collected is critical for analysis. Fill tube until vacuum is exhausted and blood ceases to flow.
3. Because the tube contains chemical additives, it is **important to prevent back flow** from the tube to the patient. To guard against back flow, the following precautions may be used when drawing blood into the tube:

    a. Keep the patient's arm in the downward position during the collection procedure.
    b. Hold the collection tube with the stopper at the top end.
    c. Release the tourniquet as soon as the blood starts to flow into the tube, within 2 minutes of application.
    d. Make sure the tube contents do not touch the stopper or the end of the needle during the collection procedure.
    e. Further instructions concerning prevention of backflow may be found at the tube manufacture's website.

4. Following blood collection, the PAXgene Blood RNA Tube must be **gently** inverted 8-10 times. **Do not shake.**

5. Hold the PAXgene samples upright at **room temperature** for a **MINIMUM** of 2 hours, preferably overnight. Store samples in a wire rack at -20°C (**-70°C preferred**) until shipped on dry ice to ICON every 2 months.

DO NOT CENTRIFUGE SAMPLE

DO NOT FREEZE PAXGENE TUBES IN STYROFOAM TRAYS

PK CSF, Protein CSF (CSF PK, CSF Protein)

CSF Sample collection and Processing instructions

General Requirements

- Details in this instruction manual must be followed and materials will be provided by the Central Lab. ***Discuss deviation of LP procedure with the BMS Medical Monitor and refer questions related to sample collection to the BMS Biomarker Lead prior to procedure if alternatives must be used.***

  Jaclyn Neely (BMS Biomarker Lead)

  jaclyn.neely@bms.com

- **Source documents** required include a Sample Harvest Log and Sample Processing Log
- Sample Collection Processing forms must be completed with **actual** CSF sample collection **stop** time and documentation of when samples are frozen.
- **Chilling** must be performed by storing sample tubes in a refrigerator prior to collection procedures and placing tubes on ice while collecting and aliquoting procedures occur. Pre-label tubes, or label immediately after each collection tube is complete
  - Available health care facility to perform blood patch for treatment of severe headache
- **All *collection* tubes must be sterile and made of polypropylene. Aliquot tubes should be made of polypropylene but do not need to be sterile**.
- Any collection materials that CSF will be in contact with must **not** be made of glass or polystyrene.
- CSF filters (including bacterial filters) should not be used in the collection set up.

2 STANDARD MATERIAL

2.1 ICON will provide the following:

- Sample Harvest Log and Sample Processing Log
- Supplies for collection of samples including, pipette tips, requisition forms and pre-labeled polypropylene transport tubes for each Lumbar Puncture as follows:
  - 1 x 3 mL sterile polypropylene tube for bulk CSF

- 1 x 2.0 mL polypropylene cryovial transfer tubes for PK-CSF Sample (0.20 mL aliquot)
- 1 x 2.0 mL polypropylene cryovial transport tubes for Protein-CSF (0.5 mL aliquot)
- 500 µL polypropylene pipette tips (bulk supply in packs of 60)
- 2 x 2.0 mL sterile polypropylene tubes for CSF collection *(if gravity flow [rather than syringe] is used)*

2.2 Clinical Site will supply the following:

- Lumbar Puncture supplies and trained staff
  - **Whitacre pencil point spinal needle: 25G x 3.5"**
    - **Recommended supplier: Medline, product ID# PAIN8019**
    - **www.medline.com/sku/item/MDPPAIN8019**
    - Atraumatic needle of a different size (i.e., 22G) may be considered at PI's discretion
    - Atraumatic needle of a different length (i.e., 4.5" or 5") may be considered at PI's discretion for heavier individuals
  - Introducer needle: 20G x 1 3/8"
    - Recommended supplier: B. Braun, ID# SI2000
    - www.bbraunusa.com/products.html?id=&basePrid=PRID00003905&prid=333370
  - 10cc sterile polypropylene syringes
    - Recommended supplier: BD, "Luer-Lok" tip, ID#309604
    - catalog.bd.com/nexusecat/getProductDetail?productId=309604
  - Adult lumbar puncture tray
    - Recommended supplier: CareFusion, ID# 4301C
- A sample processing laboratory space with the following equipment and trained staff is required:
  - Calibrated Pipettes for 100-1000 µL
  - Dry ice and appropriate buckets
  - Freezers set to maintain approximately -70°C/-80°C
  - Tube racks and storage racks suitable for dry ice and freezer

3 Procedures

3.1 Timing

- The **first LP** will be performed on all subjects on **C1D1**.
- A **second LP** will be performed on **Module-A (Nivolumab Monotherapy)** subjects only when spinal tap is clinically indicated, for cytokines.
- A **second LP** will be performed on **Module-B (Nivolumab + Ipilimumab Combination)** subjects For Cohorts 3, 4, 5 when spinal tap is clinically indicated, for cytokines.
- A **third LP** will be performed on all subjects **upon progression**
- Each LP collection will occur at approximately the same time of day as that subject's previous LPs.

3.2 Lumbar Puncture

- The procedure may be performed with the subject in the sitting or decubitus position. Maximize flexion of the spine, as tolerated. Patient positioning is of utmost importance in accessing the space necessary to obtain CSF.
- Using sterile technique, insert a spinal needle in the subject's lumbar region through the skin and between two of the lower lumbar vertebrae (e.g. L3-L4, L4-L5; L5-S1 is acceptable for elderly subjects). ***Record exact location of LP site on source document and CRF. If CSF is visually pinkish after the initial puncture, record as a traumatic LP at PI's judgment.***
- A 25G Whitacre needle is recommended to be used for penetration of dura and collection of CSF.
- If needed, prepare a pre-graduated CSF polypropylene CSF collection tube for guidance on volume.
- LP may be performed under fluoroscopy or with CT guidance if the initial LP attempt or screening LP proved difficult.

3.3 CSF Sample Collection

- The default procedure for collection of CSF will be via sterile, 10cc polypropylene syringes. Gravity flow may also be used to collect the CSF, at the discretion of the physician.
    - ***After obtaining a successful LP, Record start time in source document, this is the start time for CSF flush sample described in bullet 1 below***

1. First, collect ~0.5 mL of CSF into a polypropylene syringe or tube. Visually examine the CSF color, and document on the Source whether or not there is any pink color due to blood contamination. Then aspirate this as waste.

- ***If blood contamination was evident in the opening CSF, notify the BMS medical monitor and BMS Biomarker Lead of this by email as soon as logistically possible. It should be noted in the CRF that the LP was traumatic.***

  Jaclyn Neely (BMS Biomarker Lead)
  jaclyn.neely@bms.com

2. If blood contamination was noted in the initial CSF sample, collect an additional ~1 mL of CSF and examine for continued blood contamination.
   - ***If that sample is clear, proceed with collecting the remaining total CSF sample.***
   - ***If the CSF fluid does not appear to be clear of blood after the additional 1 mL is collected, sample collection may still proceed if there are no other medical concerns. The BMS medical monitor and BMS Biomarker Lead should be notified of this by email and LP should be noted in the CRF as traumatic.***

     Jaclyn Neely (BMS Biomarker Lead)
     jaclyn.neely@bms.com

3. Collect approximately 1-2 mL of CSF in polypropylene syringe or tubes. Total volume **should not exceed 2 mL**, including any initial wasted aliquots.
   - ***Record <u>end time</u> of CSF collection in the Source document.***
   - ***Visually inspect CSF in the collection container. CSF should have a clear and colorless appearance. Record any deviation in the harvest log.***
4. Transfer the entire CSF samples from procedure room to the clinic laboratory.
5. Combine all samples contained in individual collection tubes (if used) into a 3 ml polypropylene tube. If a syringe was used, express all of the CSF into a 3 ml polypropylene tube. The entire sample contained in the 3 ml polypropylene tube is referred to as "**bulk CSF**".
6. Gently vortex or invert the bulk sample to remove cells from side of tube
7. Centrifuge the bulk CSF (1000 x g, or equivalent) for 10 minutes at 4^{o}C (or room temperature if centrifugation at 4^{o}C is not possible) to remove "cellular debris"

8. After centrifugation, aliquot centrifuged CSF liquid into appropriately labeled, **pre-chilled** polypropylene tubes, using a pipette, as follows:
    - 1 x 0.2 mL for **PK-CSF**
    - 1 x 0.5 mL into polypropylene tube labeled **Protein-CSF**

    Note: Do not pipette the pellet.
9. Cap all tubes tightly and ensure labels are securely attached
10. Place the **PK-CSF** and **Protein-CSF** tubes upright on dry ice within 15 minutes after end of collection
11. Store the frozen CSF samples upright in racks or boxes in a freezer set to maintain approximately -70°C or colder until shipment on dry ice.
12. Note: CSF samples must be frozen in the -70°C/-80°C freezer *for at least 4 hours* before being shipped. Ship samples on dry ice only on Monday-Wednesday (to avoid chance of weekend delivery), according to a previously agreed shipment schedule.

Caution: CO_2 from the dry ice can acidify samples so tubes MUST BE tightly capped before shipping.

4. Other considerations

Subject restrictions:

- Use of anticoagulants within 90 days of screening is prohibited. Patients in whom use of anticoagulants is anticipated should not be enrolled. Low dose aspirin is permitted. Discontinuation of aspirin or NSAIDS prior to LP (e.g. 7 days before and 2 days after the LP) is at the discretion of the investigator if not contraindicated.
- Use of dipyridamole (Persantine), clopidogrel (Plavix) or warfarin (Coumadin) within 7 days prior to and 2 days after the LP procedure is prohibited.

4.1 Suggestions to minimize AEs for subject retention:

- Topical and subcutaneous/intramuscular anesthetics (e.g. Lidocaine) are permitted to alleviate pain during LP procedures.

When the procedure is over:

- Subjects are required to remain in the clinical facility for at least 2 hours after each lumbar puncture.
- If subject has an ongoing AE after they are discharged from the site (eg, spinal headache), the site will follow-up with the subject via phone calls until the AE has resolved.
- In many cases, headache may be ameliorated with bed rest, hydration (IV/oral), administration of analgesics (or antiemetics to treat nausea associated with spinal headache). An additional period of bed rest could help resolve the headache.
- Moderate consumption (typically, up to than 3 cups/ 24 hours) of caffeine-containing beverages is permitted to treat headache after LP procedure, as long as it is not consumed within 2 hours prior to ECG assessments.
- If these measures fail, other treatment modalities (e.g. opioids), intravenous caffeine, epidural blood patch) may be considered after consulting with the study director and medical monitor.
- If a persistent severe headache occurs, a "blood patch" should be performed. This is done by injecting a small amount of the patient's blood into the region of the original procedure. This can be performed with or without the aid of fluoroscopy. Blood patch procedure can be repeated once if necessary.

5. Shipment INFORMATION

- Completed requisition forms must accompany the samples. Lack of paperwork or illegible information will delay sample login and project initiation. Samples that are unclearly or incompletely labeled may be subject to additional handling fees.
- Frozen samples should be shipped on dry ice via overnight courier **Monday through Wednesday** to ICON.

Tissue Block, Tissue Slides (S-BLCK, S-SLD1 H&E - S-SLD20)

CA209-908
Fresh Tumor Biopsy Collection Instructions
for Screening, On Treatment and Upon Progression Tissue

SUPPLIES PROVIDED BY CENTRAL LABORATORY

- Plastic slide Holder
- Confidential envelope for the Pathology Report
- Zipper bag for blocks and slide holders
- Gel Packs

SUPPLIES PROVIDED BY SITE

- 20mL Vials containing 10% Neutral Buffered Formalin
- Positively-charged glass slides
- Plastic slide holders
- FFPE supplies and SOP

BIOPSY PROCEDURE GUIDELINES

Sites will follow their own institutional guidelines and operating procedures regarding the biopsy sample collection.

FOLLOW THE SAMPLE PROCESSING PROCEDURE BELOW ACCORDING TO THE APPROPRIATE TUMOR COLLECTION TECHNIQUE THAT IS USED:

I. SAMPLE COLLECTION FOR CORE NEEDLE BIOPSIES:

A. Collect up to four core needle tumor biopsies
   a. Needle gauge of 16-18 should be used to obtain biopsies.
B. **Immediately** upon collection, place samples into the vial pre-filled with 10% Neutral Buffered Formalin
   * Do not place or wrap biopsies in any material (paper, gauze, etc.) prior to submersion.

II. SAMPLE COLLECTION FOR EXCISIONAL OR RESECTION BIOPSIES:

A. Collect up to four 3-5 mm excisional or resection tumor biopsies.

B. **Immediately** upon collection, place samples into the vial pre-filled with 10% Neutral Buffered Formalin
   a. * Do not place or wrap biopsies in any material (paper, gauze, etc.) prior to submersion.

SAMPLE PROCESSING FOR ALL COLLECTION TECHNIQUES:

C. **Allow the sample to remain in the 10% Neutral Buffered Formalin (NBF) for a minimum of 24-48 hours but no more than 96 hours**. **Embed block per FFPE standard.**

   NOTE: Do not ship biopsies in formalin.

D. Secure caps firmly and ensure biopsy samples are completely contained and/or submerged and are not adhering to the vial cap or to the sides of the cryovial.

E. **Ship samples to ICON. If submitting slides, they should be shipped on <u>day of collection.</u>** Complete all the information on the requisition form for biopsy samples shipped, including Processing Date, Number of Slide Holders Sent and Diagnosis (if available at time of shipment).

F. Note that Diagnosis of **Progression, Pseudo-progression, or Indeterminate/Other** is to be entered as soon as possible on the ICON Web Portal (contact ICON PM with any portal concerns).
* Site pathologist should give their determination to the investigator.

Site pathologist should give their determination to the investigator.

G. For FFPE Blocks

a. Ensure cassette is appropriately labeled in pencil
b. Place labeled cassette in the Zipper lock bag provided
c. Place ICON sample ID barcode label provided in kit onto zipper bag
d. Complete requisition form
e. **Attach extra ICON sample ID barcode label to Pathology report.**
f. Enter Diagnosis on ICON Web Portal (contact ICON PM with any portal concerns).

H. At least twenty slides (or more) will be required. **<u>Sectioning of slides is not required</u>.**

a. Place slides in the plastic slide holder(s) provided
b. Place ICON sample ID label provided on the slide holder
c. Place the slide holder in the Zipper lock bag provided
d. If more than four slide holders are required, use additional ICON labels provided
e. Complete requisition form.
f. **Attach extra ICON sample ID barcode label to Pathology report**
g. Enter Diagnosis on ICON Web Portal (contact ICON PM with any portal concerns).

I. **Biopsy <u>FFPE blocks</u> are to be shipped to ICON <u>ambient</u> temperature on day of collection.**

J. **<u>Biopsy Slides</u> are shipped to ICON at <u>refrigerated</u> temperature on day of collection.**

Handling Instructions for Archived Tumor Biopsy Block or Slides

SUPPLIES PROVIDED BY ICON

- Zipper bags for blocks and slide holders
- Confidential envelope for pathology report
- Gel packs (refrigerated)
- Plastic slide holders (bulk)

SUPPLIES PROVIDED BY SITE

- Positively-charged glass slides (if cutting is required)

BIOPSY PROCEDURE GUIDELINES

Sites will follow their own institutional guidelines and operating procedures regarding the biopsy sample collection. Every attempt should be made to biopsy lesions that are NOT index/target lesions. It is encouraged to maximize the amount of tissue if medically and technically feasible.

Note: Archived tissue samples should be in the form of 2 (a minimum of 1 is required) paraffin embedded tissue block (preferred) or minimum of 20 unstained slides from the tissue block **accompanied by a copy of the pathology report**. **Reports must be de-identified (removed of any confidential patient information) prior to submission**.

1. **If sending paraffin block (PREFERRED):**

   g. Ensure cassette is appropriately labeled in pencil
   h. Place labeled cassette in the Zipper lock bag provided
   i. Place ICON sample ID barcode label provided in kit onto zipper bag
   j. Complete requisition form to indicate the items sent
   k. Be sure to include copy of pathology report (**required for archived samples**). Reports **MUST** be de-identified (removed of any confidential patient information) prior to submission. **Attach extra ICON sample ID barcode label to Pathology report.**

2. **If sending Archived slides:**

   h. Ensure each slide is appropriately labeled in pencil
   i. Place slides in the plastic slide holder provided
   j. Place ICON sample ID label provided in kit on the slide holder
   k. Place the slide holder in the Zipper lock bag provided
   l. Complete requisition form to indicate the items sent
   m. Be sure to include copy of pathology report (**required for archived samples**). Reports **MUST** be de-identified (removed of any confidential patient information) prior to submission. **Attach extra ICON sample ID barcode label to Pathology report.**

3. Complete all remaining information and **ALL required questions on the requisition form**.

   Reminder: Record original biopsy collection date and time for archival sample

4. **Biopsy FFPE blocks are to be shipped to ICON ambient temperature on day of collection.**

5. **Biopsy Slides are shipped to ICON at refrigerated temperature on day of collection.**

Section 7 - Completing the Laboratory Requisition

Each specimen collection kit contains its own requisition form. The requisition form is visit and protocol specific.

Instructions for Completing the Laboratory Requisition Form:

1. Place a "**REQUISITION**" bar code label on each copy of the requisition form in the space provided.

2. Using a black or blue ball point pen, complete the following sections of the requisition form:

   a. Subject ID Number
   b. Subject Date of Birth (DD-MMM-YYYY)
      - USA and Canada Cohort and All Other Sites Cohort - Will collect full Date of Birth
      - Germany and Netherlands Cohort - Default of 01-JUL-YYYY will be noted on requisition and captured within ICON's database
   c. Subject Gender
   d. Sample Collection Date and Time
      - Corresponds to the time when first sample is collected for the visit/timepoint
   e. Additional Required Information:
      - Visit Type
      - Tissue Type
      - Pathology Reference ID
      - Date of Surgery/Biopsy
      - Collection Method
      - If Collection Method is Other, specify
      - Site of Biopsy
      - If Site of Biopsy is Other, specify
      - Clinical Setting
      - Time of surgical excision to immersion in fixative or frozen
      - Fixation Time
      - Specimen Storage Temp
      - If Specimen Storage Temp is Other, specify
      - Slide Sectioning date
      - Thickness of section
      - If Thickness of section is Other, specify
      - Fixation Method
      - If Fixation Method is Other, specify

3. Include the appropriate copy of the ICON Laboratory Services requisition form when shipping samples to the laboratory. **All required information must be accurate and complete to avoid a delay in receiving the laboratory report.**

Section 8 - Reporting Missed Visits

It is essential to inform ICON Laboratory Services of missed visits. This procedure is required to ensure proper sequencing of protocol visits.

If a study subject misses a scheduled laboratory visit, contact an ICON Laboratory Services Site Services Specialist via phone or email. Informing an ICON Laboratory Services of a missed scheduled visit will potentially avoid a future query. Refer to the information provided in the Laboratory Contacts section of this manual for the appropriate toll free telephone number. Emails may be sent to **LabSiteHelp@iconplc.com**.

Reporting a Missed Visit via Telephone or E-Mail

When reporting a missed visit by telephone or e-mail, please provide the following information:

1. Bristol-Myers Squibb
2. Protocol #
3. Site #
4. Subject Identification #
5. Name of Missed Visit

Section 9 - Properly Packaging Specimens for Shipment

Proper specimen packaging is critical to specimen integrity and accurate laboratory test results. This section contains comprehensive packaging instructions for each type of shipper provided by ICON Laboratory Services for this protocol. If your site utilizes a commercial courier that provides its own specimen shippers, please refer to the instructions that accompany those shippers. Many of the instructions for commercial couriers' shipping containers can be found on the Investigator Site Resource Center page of our website at **www.iconplc.com/LabSiteHelp.**

You may also contact your ICON Laboratory Services Site Services Department (see listing in Contacts section of this manual) for additional assistance with specimen packaging questions.

Some important general reminders for properly preserving and packaging specimens are provided below:

- Maintain collected specimens at the appropriate temperature prior to shipment.
- If your protocol includes frozen specimens, make certain that you have a sufficient supply of dry ice available for proper packaging of specimens. (See detailed instructions for Frozen Shippers in this section.)
- If you are not working with a courier that supplies dry ice, information on how to obtain dry ice is available at www.dryicedirectory.com.
- Refrigerated shippers require the use of pre-refrigerated and pre-frozen gel paks. If you must utilize this type of shipper for your protocol, please ensure that gel paks are removed from the shipper and properly refrigerated or frozen, as indicated, **for at least 24 hours prior to shipment**.
- Verify that the requisition has been thoroughly and accurately completed.
- Prior to packaging specimens in shippers, make certain that each specimen container is properly labeled and identified.
- Ensure that the tube caps and screw tops are well secured.
- For shipments of the same destination and temperature, please note that two of the multi-segmented pouches can fit inside of one 95KPA Biohazard Bag.

IMPORTANT:

Please consolidate specimen shipments of the same shipping temperature whenever possible/as appropriate, including if you are sending specimens across different protocols or sponsors to ICON Laboratory Services. Pathology samples, blocks, slides and CSF should NOT be consolidated.

Detailed Specimen Packaging Instructions

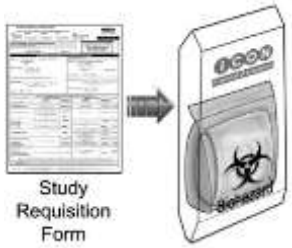
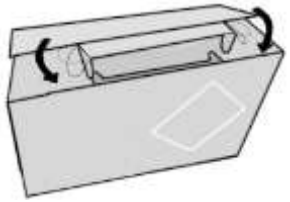
Note: The following instructions are for shippers provided by ICON Laboratory Services. If your site uses courier-provided shippers, please reference any instructions that are provided by that courier. Packaging instructions for many commercial couriers are also provided on the Investigator Site Resource Center page of our website at www.iconplc.com/LabSiteHelp.

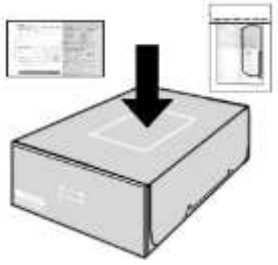
In a case where your courier did not provide packing instructions, and they are not present on the Investigator Site Resource Center, please use the instructions below as a reference

Please also reference the Testing and Shipping Requirements Quick Reference Guide in Section 6 of this Manual for a guide to Visit-Specific boxes to use for your sample shipments.

Note: Please reference Section 5 for the proper product name when re-ordering Shipping Boxes

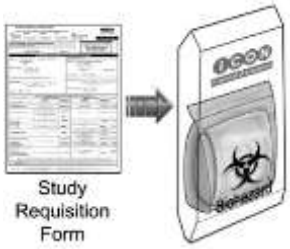
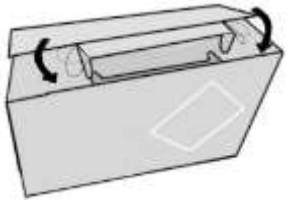
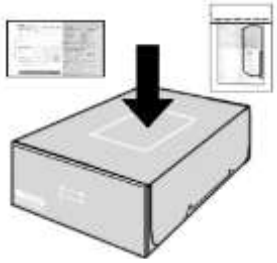
Ambient Packaging – Collection Kit Box

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
					
Place labeled tubes in segmented absorbent pouch. Kits can include a 4 or 6 segmented pouch. Tubes too large for segmented holder should be rolled inside absorbent pouch.	**Roll up the tube-filled segmented absorbent pouch.**	**Insert rolled pouch into the (95kPa) biohazard bag. Note that 2 pouches of the same temperature and destination can be placed in each biohazard bag.**	**Fold completed requisition and insert into outer pocket of biohazard bag. Press bag to remove air, roll up and seal with adhesive strip.**	**Place sealed specimen bag into kit box.**	**Fold tabs of box lock.**

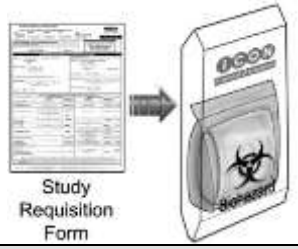
Step 7	Step 8	
		**Note: Ensure the lock is fastened as this is what will prevent the box from opening during shipping.** **Diagnostic Courier Bags are not required.**
Close kit box by inserting folded tabs into designated slots.	**Affix the appropriately completed Air Waybill sticker or courier pouch to the box.**	

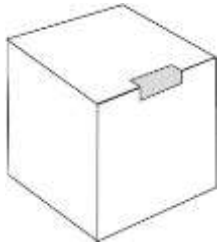
Ambient Packaging – Collection Kit Box (Block)

Step 1	Step 2
	
Place the Block into the Ziplock bag	**Insert Ziplock bag into the (95kPa) biohazard bag. Place only 1 Ziplock bag in each biohazard bag.**

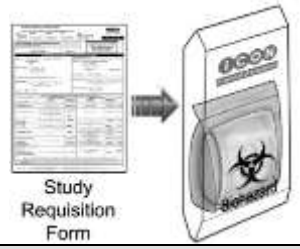
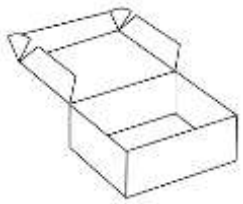
Step 3	Step 4	Step 5	Step 6	Step 7	
					**Note: Ensure the lock is fastened as this is what will prevent the box from opening during shipping.** **Diagnostic Courier Bags are not required.**
Fold completed requisition and insert into outer pocket of biohazard bag. Press bag to remove air, roll up and seal with adhesive strip.	**Place sealed specimen bag into kit box.**	**Fold tabs of box lock.**	**Close kit box by inserting folded tabs into designated slots.**	**Affix the appropriately completed Air Waybill sticker or courier pouch to the box.**	

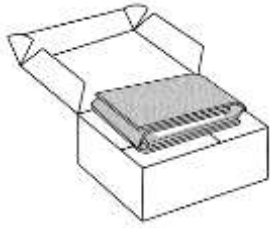
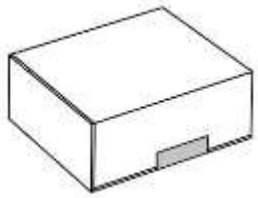
Extreme Ambient Packaging

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
					
Place labeled tubes in segmented absorbent pouch. Kits can include a 4 or 6 segmented pouch. Tubes too large for segmented holder should be rolled inside absorbent pouch.	**Roll up the tube-filled segmented absorbent pouch.**	**Insert rolled pouch into the (95kPa) biohazard bag. Note that 2 pouches of the same temperature and destination can be placed in each biohazard bag.**	**Fold completed requisition and insert into outer pocket of biohazard bag. Press bag to remove air, roll up and seal with adhesive strip.**	**Select the insulated cardboard shipper containing a foam container with 3 gel paks inside. NOTE: gel paks should remain at room temperature at all times.**	**Remove 2 gel paks from container. Set aside for later use. Keep the remaining gel pak in bottom of container.**

Step 7	Step 8	Step 9	Step 10	Step 11
				**Affix the appropriately completed Air Waybill to the shipper.**
Place up to 3 (95kPa) biohazard bags on top of the gel pak. NOTE: Placing more than 3 bags in container will adversely affect shipping temperature.	**Place remaining 2 gel paks on top of the (95kPa) biohazard bag(s).**	**Place the lid to the foam container into position.**	**Close the flaps of the shipper box and seal the box with the enclosed sealing strip.**	

Thermal Ambient Shipper

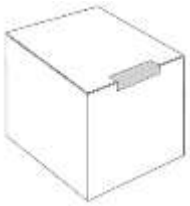
Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
					Assemble the shipper according to the directions printed on the box.
Place labeled tubes in segmented absorbent pouch. Kits can include a 4 or 6 segmented pouch.	Roll up the tube-filled segmented absorbent pouch. Tubes too large for segmented holder should be rolled inside absorbent pouch.	Insert rolled pouch into the (95kPa) biohazard bag. Note that 2 pouches of the same temperature and destination can be placed in each biohazard bag.	Fold completed requisition and insert into outer pocket of biohazard bag. Press bag to remove air, roll up and seal with adhesive strip.	Select the Thermal Ambient Shipper box and obtain 2 gel wraps, provided in your lab supplies. Note: Gel wraps should have been stored in a cool place but NOT frozen, prior to their use.	

Step 7	Step 8	Step 9	Step 10
			Affix the appropriately completed Air Waybill to the shipper.
Using the 2 gel wraps provided, wrap the (95kPa) biohazard bag containing the specimens, as shown above.	Place the wrapped (95kPa) biohazard bag in the shipper box.	Close the flaps of the shipper box and seal the box with the enclosed sealing strip.	

DGP Biotherm 10 Shipper Refrigerated Slide (Summer Packout)

Step 1	**Place one BIOCHILL 2020 and three BIOCHILL 1515s in a -18ºC freezer for 48 hours.** (Ensure the BIOCHILLs are kept flat while being frozen and are spread out to allow air to reach all their sides) **Ensure that the BIOCHILLs are fully frozen. Take the BIOCHILLs out of the freezer and leave them at room temperature for approximately 10 minutes**

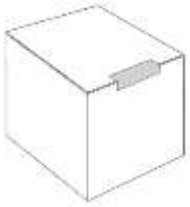
Step 2 (Collect Slides)	Step 3	Step 4	Step 5
 			
Place the slides into the (95kPa) biohazard bag with a single absorbent sheet. **Note: Maximum of 20 slides per biohazard bag.**		**Fold completed requisition and insert into outer pocket of biohazard bag. Press bag to remove air, roll up and seal with adhesive strip.**	**Select the DGP Biotherm 10 Shipper (Summer Packout) and remove insulated lid.**

Step 6	Step 7	Step 8	Step 9	Step 10	Step 11
					**Affix the appropriately completed Air Waybill to the shipper.**
Place the biohazard bag inside the payload carton in the centre of the BIOTHERM 10 box.	**Place a side cut spacer and a BIOCHILL 1515 along each of the two short sides of the shipper and ensure that the spacer falls between the product and the BIOCHILL.**	**Place a top spacer on top of the payload carton and place a BIOCHILL 1515 and 2020 on top of it.**	**Shut the box with the insulated lid.**	**Close the side flaps of the shipper box and then the main flap. Seal the box with the enclosed sealing strips.**	

DGP Biotherm 10 Shipper Refrigerated Slide (Winter Packout)

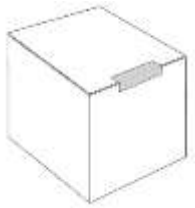
Step 1	**Place 3 BIOCHILL 1515s in a -18ºC freezer and a BIOCHILL 2020 in a +5ºC refrigerator for 48 hours.** (Ensure the BIOCHILLS are kept flat and allow air to reach all their sides.) **Before assembling, ensure the BIOCHILL 1515s are fully frozen.** **Take the BIOCHILL 1515s out of the freezer and leave them at room temperature for approximately 10 minutes.**

Step 2 (Collect Slides)	Step 3	Step 4	Step 5
 			
Place the slides into the (95kPa) biohazard bag with a single absorbent sheet. **Note: Maximum of 20 slides per biohazard bag.**		**Fold completed requisition and insert into outer pocket of biohazard bag. Press bag to remove air, roll up and seal with adhesive strip.**	**Select the DGP Biotherm 10 Shipper (Winter Packout) and remove insulated lid.**

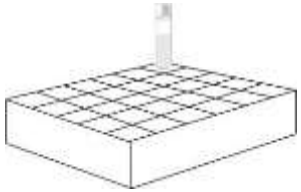
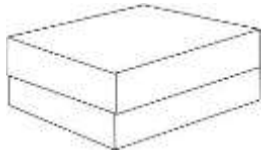
Step 6	Step 7	Step 8	Step 9	Step 10	Step 11
					**Affix the appropriately completed Air Waybill to the shipper.**
Place the biohazard bag inside the payload carton in the centre of the BIOTHERM 10 box and on top of a chilled BIOCHILL 2020.	**Place a side cut spacer and a frozen BIOCHILL 1515 along each of the two short sides of the shipper and ensure that the spacer falls between the product and the BIOCHILL.**	**Place a top spacer on top of the payload carton and place a BIOCHILL 1515.**	**Shut the box with the insulated lid.**	**Close the side flaps of the shipper box and then the main flap. Seal the box with the enclosed sealing strips.**	

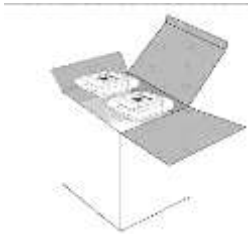
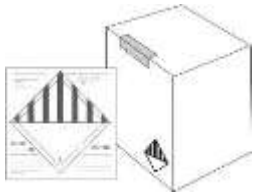
DGP PHT003 Refrigerated Shipper - Slides (North America)

Step 1	Step 2	Step 3	Step 4
Chilled BIOCHILLs should be conditioned at +5ºC for a minimum of 24 hours before use. **Frozen BIOCHILLS should be conditioned at -18ºC for a minimum of 24 hours and then approximately 20 minutes at factory ambient +20ºC (± 5) before system assembly.**	  		
	Place the slides into the (95kPa) biohazard bag with a single absorbent sheet. **Note: Maximum of 20 slides per biohazard bag.**	**Fold completed requisition and insert into outer pocket of biohazard bag. Press bag to remove air, roll up and seal with adhesive strip.**	**Select the DGP PHT003 Refrigerated Shipper and remove insulated EPS3 Lid.**

Step 5	Step 6	Step 7	Step 8	Step 9	Step 10
					**Affix the appropriately completed Air Waybill to the shipper.**
Place one chilled (+5ºC) BIOCHILL 1212 into the center of the EPS 3 base.	**Add the payload directly on top of the BIOCHILL.**	**Add one chilled (+5ºC) BIOCHILL 1212.**	**Add two frozen (-18ºC) BIOCHILL 1212's.**	**Apply the EPS 3 box lid, then close and seal the outer carton. The system is now ready to be shipped.**	

Medium Frozen Shipper – Cryobox Shipments

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
					
Select a medium frozen shipper box. NOTE: This shipper is appropriate for shipping up to 2 cryoboxes.	**Remove the lid of the insulated foam container located inside of the shipper box.**	**Place 4 lbs (1.82 kg) of dry ice in the bottom of the insulated foam container. NOTE: Dry ice pellets are recommended for optimal performance.**	**Place cryovials into the sections of each of the cryoboxes.**	**Place the lid securely on each cryobox.**	**Place each cryobox and an absorbent sheet into its own large (95kPa) biohazard bag. Remove adhesive strip and seal bag. NOTE: Do not place requisition forms in (95kPa) bags.**

Step 7	Step 8	Step 9	Step 10	Step 11	Step 12
					**Affix the appropriately completed Air Waybill to the shipper.**
Place the two (2) sealed (95kPa) biohazard bags on top of the dry ice in the insulated foam container.	**Place 10 lbs (4.54 kg) of dry ice on top of the (95kPa) biohazard bags.**	**Place the lid securely on top of the insulated container. Place the completed requisition forms on top of the lid of the insulated container.**	**Close the flaps of the shipper box and seal the box with the enclosed sealing strip.**	**Enter the amount of dry ice used (in kg) in the space provided on the dry ice label of the shipper box.**	

Note: If Shipper is provided by ICON Laboratory Services, it is qualified for 48 Hr. transits. For information on where to obtain dry ice, visit www.dryicedirectory.com

Section 10 - Specimen Shipping Instructions

Important information when preparing specimen shipments:

- Correct completion of shipping documents and appropriate use of packaging are critical steps in ensuring the timely delivery of your site's samples.
- Improper document completion and packaging can result in delayed reports or cancelled tests.
- ICON Laboratory Services cannot be responsible for delayed reports or cancelled tests as a result of improper document completion and packaging.
- International Air Transport Association (IATA) regulations require that persons responsible for packaging and shipping dangerous goods (such as dry ice) be properly trained. Such training/certification is the responsibility of the investigator site. For more information regarding IATA and its regulations, you may visit their website at www.iata.org or visit us on the web at **www.iconplc.com/LabSiteHelp** and see our "Site Training" link for other available options.

How to Book A Shipment

- Please refer to Section 3 of this lab manual, or to your Courier Contact Memo for complete contact information.
- Contact the courier before the specified cut-off time when you have a specimen for pickup.
- When booking your shipment be prepared to provide your account number and protocol number from your Air Waybill.
- **For all FROZEN shipments, please notify your courier at least 1 day prior to the day of pickup**
    - Please note: Booking frozen shipments may require advanced notice.

Collections and Deliveries on Weekends/Holidays:

ICON Laboratory Services accepts specimen shipments on Saturdays.

The following scenarios will result in a Saturday delivery:

- Sites that ship on Thursday and have 48 hour transit times to our laboratories
- Sites that ship on Friday and have 24 hour transit times to our laboratories

To Ensure Saturday Deliveries:

- When booking the shipment with the courier, state "Saturday Delivery" is required
- Place "Saturday Delivery" stickers on courier bag or shipping container
- Mark the "Saturday Delivery" check box on the Air Waybill. If no check box is provided on the Air Waybill, clearly write "Saturday Delivery" on the Air Waybill

Friendly Reminders:

In the event your site requires Sunday or Holiday pickup

- Be mindful of customs restrictions on the required shipment dates

Section 11 - Completing Courier Air Waybills and Related Shipping Documents

This section contains instructions and examples of courier Air Waybills and other shipping documents that may be necessary when shipping specimens to our laboratories. These include:

- **Sample Courier Air Waybills for:**
  - DHL
  - FedEx
  - Marken
  - QuickSTAT
  - TNT

- **Samples for:**
  - Pro-forma Commercial Invoice
  - CDC Permit

- Additional documents *may* be required based upon your site's location and the type of specimens being shipped. A guide to when such documents are required is provided below: **Failure to include these documents when required may mean that the shipment is rejected or delayed, thereby preventing the laboratory from performing the laboratory tests.**

FORM REQUIRED	WHEN FORM IS REQUIRED
Pro-Forma Commercial Invoice	Anytime specimens are shipped between countries unless both the shipping and receiving countries are members of the European Union (EU).
Centers for Disease Control (CDC) Permit	When specimens contain or are suspected of containing the specific pathogens listed in CDC guidelines

Please reference the Courier Contacts section (Section 3) of this manual to determine the specific forms that are required to accompany your site's specimen shipments. If you have questions regarding these requirements, please contact the Site Services Department at ICON Laboratory Services.

DHL Air Waybill Completion Instructions (International)

***The actual AWB provided to you may differ slightly from the one shown above**

To avoid any delays with your shipments please ensure the number of packages being shipped match the number of packages captured on the Air Waybill

DHL Dry Ice & Ambient Pick-up Request Form

To book a Frozen or Ambient Shipment with DHL, please complete all details below and send the completed form to DHL before the specified cut off time as per your Courier Contact Memo Sheet.
Email – icon.ekas@dhl.com Telephone – 00800 11 33 11 34 Fax - 00800 11 31 11 32

Study Reference: CA209908 **Site No**: _____

Contact Person Details	Name:		
Tel. No: Fax No:	Email Address:		
Name of Hospital			
Department / Wing			
Name Principal Investigator			
Address			
	Country	Postcode	City Name

*Please indicate number of **BOXES** of DRY ICE Required*

1 Box of dry ice will hold 12 samples

Please indicate number of Ambient samples to be collected
*(*If no ambient collection required please leave blank*)*

Please provide DHL Airway Bill Number for ambient collection

Date Dry Ice and packaging are required _ _ - _ _ _

Date required for pick-up of shipment: _ _ - _ _ _

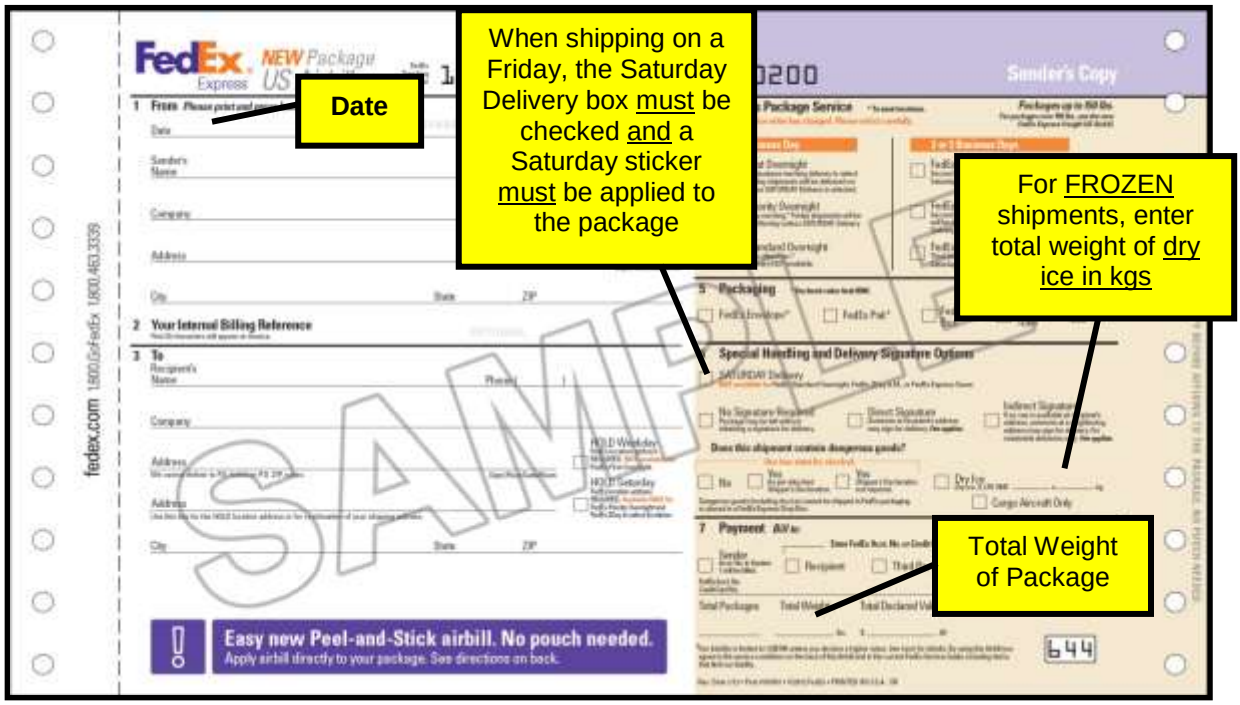
Time shipment will be ready for pickup _ _: _ _

State your office closing time _ _: _ _

***Note:** An email or fax notification will be sent to you to confirm receipt of your order. Please ensure the delivery address and contact details are complete and correct in order to prevent any delays.*

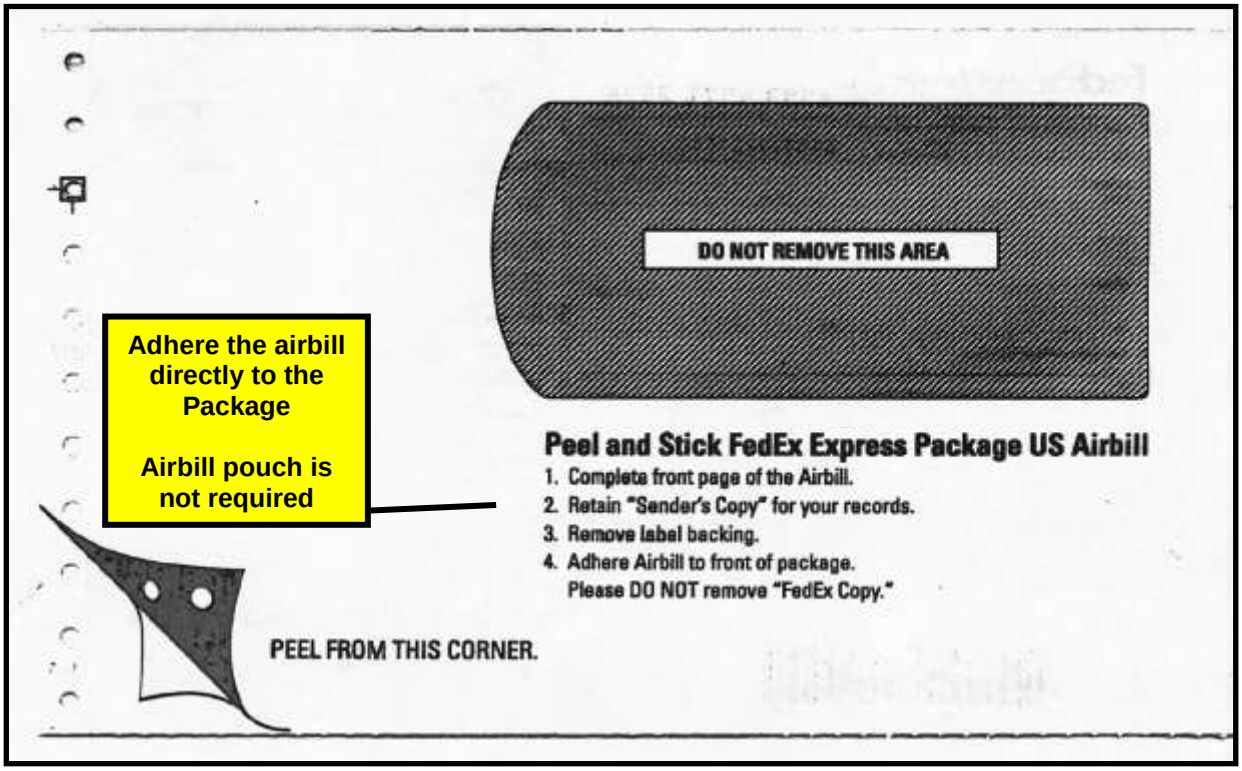
DHL internal information:
Payment terms: RECEIVER PAYS **ICON account number:** 960500204
1 box - 8 kg, 31x 30 x 33 cm **Spec. Instr:** UN3373,Biological Substance, Category B, UN1845, Dry Ice, Class 9, Net 1 x 6Kg
Content: Biological Substance, Category B (UN3373)
Delivery Address: **ICON Laboratory Services**
South County Business Park
Leopardstown, Dublin 18, Ireland
CONTACT: Dublin.Logistics@iconplc.com

FedEx Frozen Air Waybill Completion Instructions (US Only)

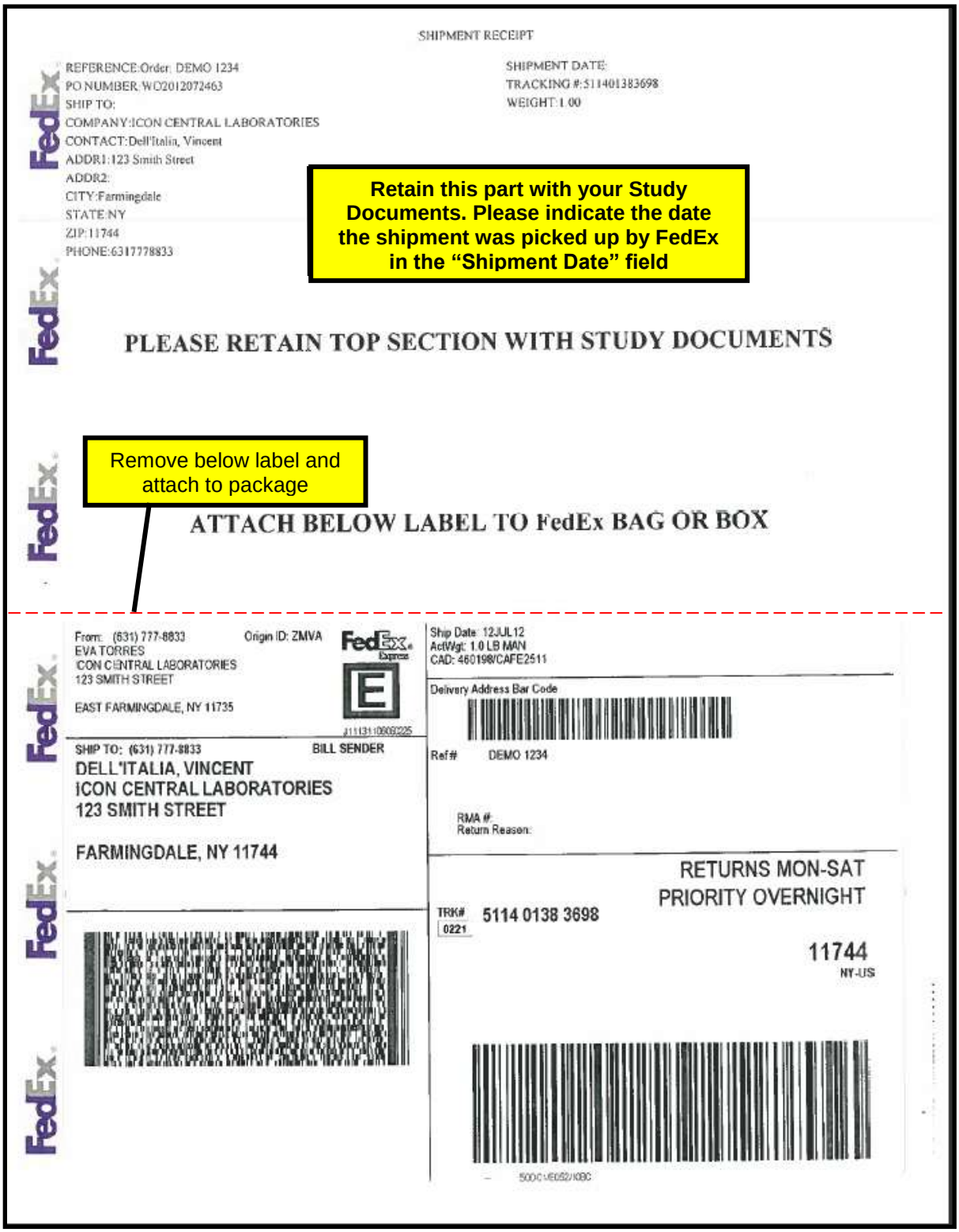


To avoid any delays with your shipments please ensure the number of packages being shipped match the number of packages captured on the Air Waybill

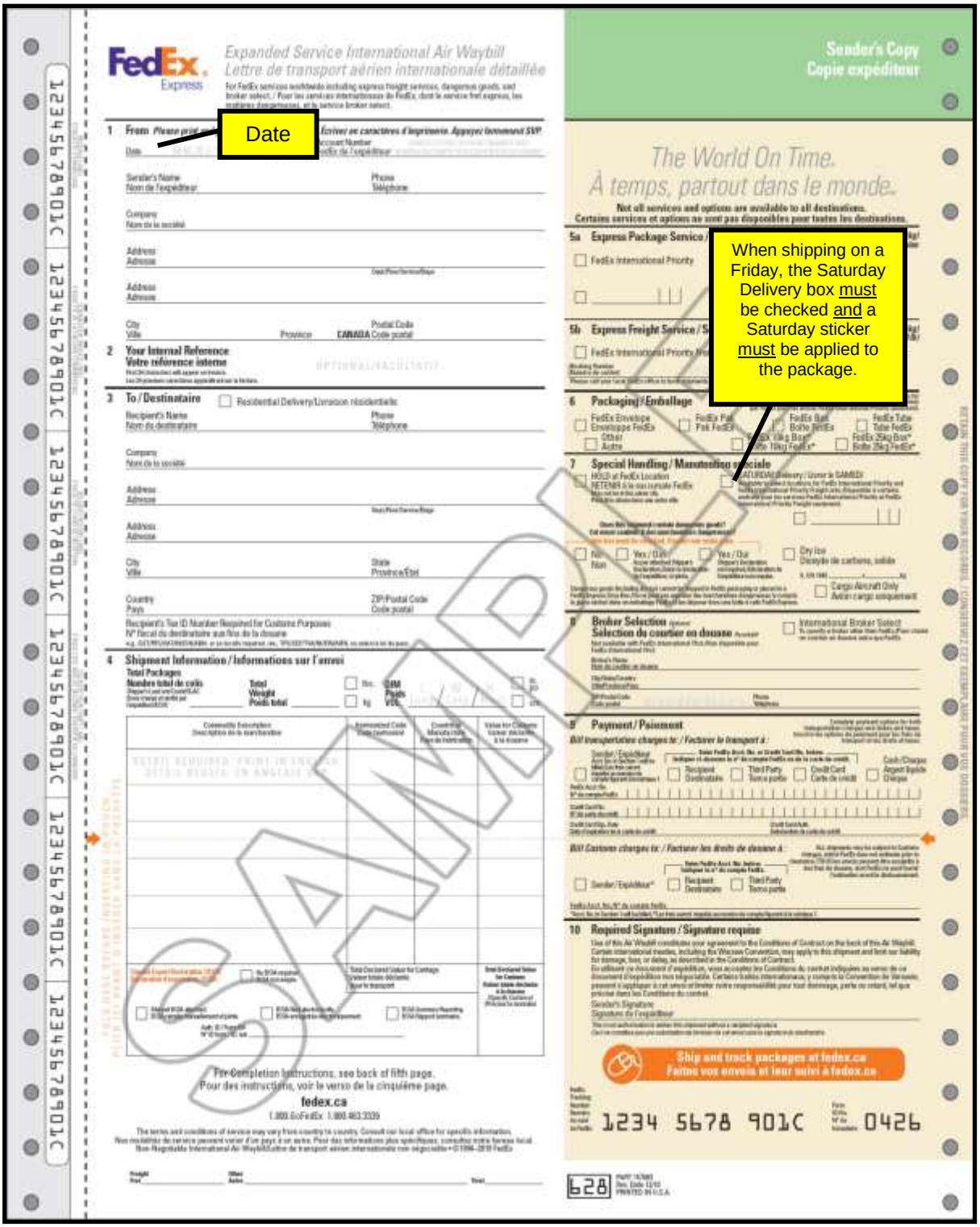
BACK



FedEx Ambient/Refrigerated Air Waybill Completion Instructions
(US shipments to ICON Laboratory Services only)



FedEx Air Waybill Completion Instructions (Canadian)



To avoid any delays with your shipments please ensure the number of packages being shipped match the number of packages captured on the Air Waybill

Marken Air Waybill Completion Instructions

AIRWAYBILL

605X03694486

MARKEN

Marken New York
521 RXR Plaza, East Tower, Uniondale, NY, 11556, United States

Shipper	Consignee	Waybill Number
ICON LABORATORIES 123 Smith St Farmingdale, NY 11735 United States	ICON LABORATORIES 123 Smith St Farmingdale, NY 11735 United States	605X03694486
		Schd Collection: 06 Apr 2015
		Schd Delivery:
Contact:	Contact:	Client Account: US537
Reference: Demo	Reference: Demo	
Telephone: 631-123-4567	Telephone: 631-123-4567	

Content Description	Pcs	Range (°C)	Kgs	Packaging	Supplier	Dimensions (cm) L	W	H	DG	UN	Probe	Num
Human Plasma	1		8.20	Client Packaging								
TOTALS Pieces	1	Actual Kgs	8.20	Volu Kgs		Value (USD)	10.00					

Special Instructions	Collected in good order & condition	Received in good order & condition
Replenish dry ice as necessary Box Dims: 1	Signature	Signature
Shippers signature	Printed name	Printed name
Printed Name	Date / Time	Date / Time
Date / Photo ID Type	NOTE: The goods described above are accepted in apparent good order and condition (except where noted by shipper or noted above) for delivery to the stated consignee, subject to the trading conditions set forth on the attached sheet, which limit Marken's liability.	

Sign and Date

MARKEN

605X03694486

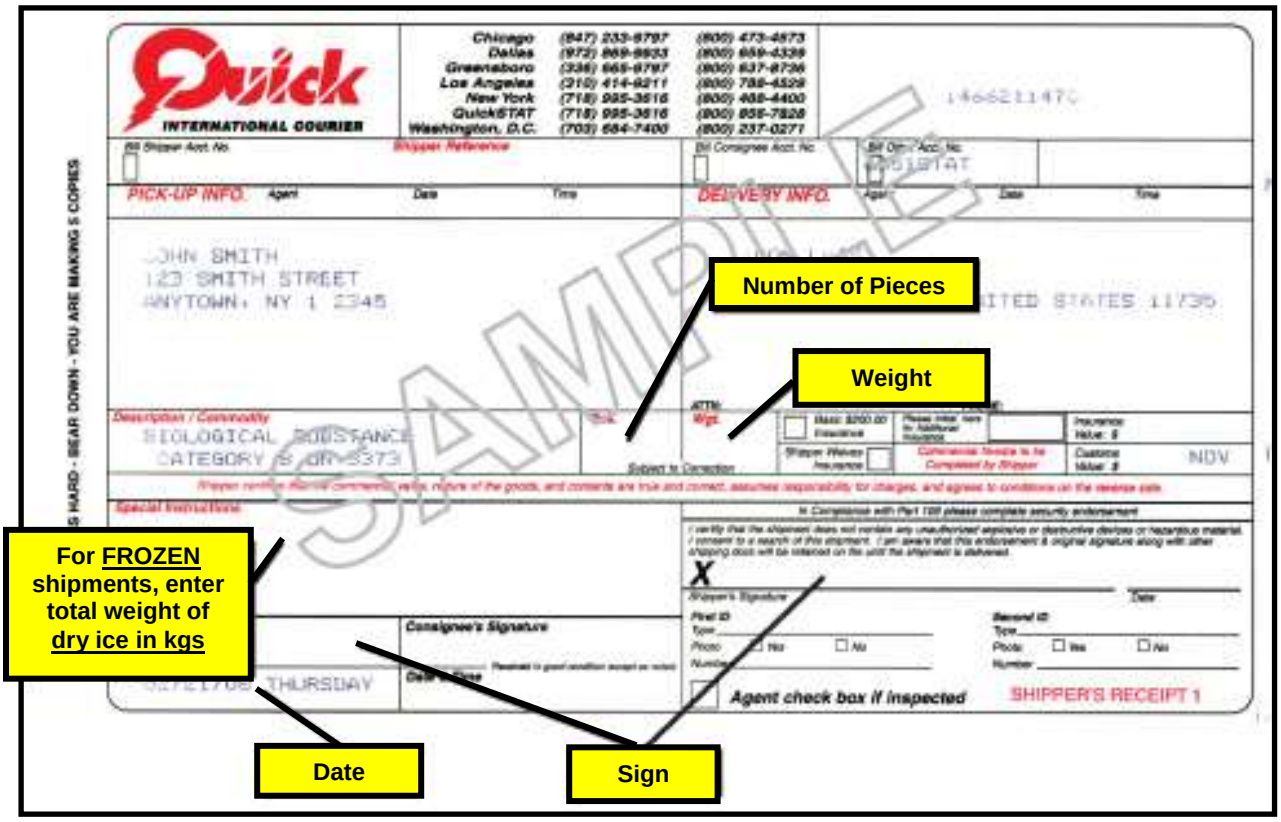
ICON LABORATORIES
123 Smith St
Farmingdale, NY 11735
United States

Tel: 631-123-4567

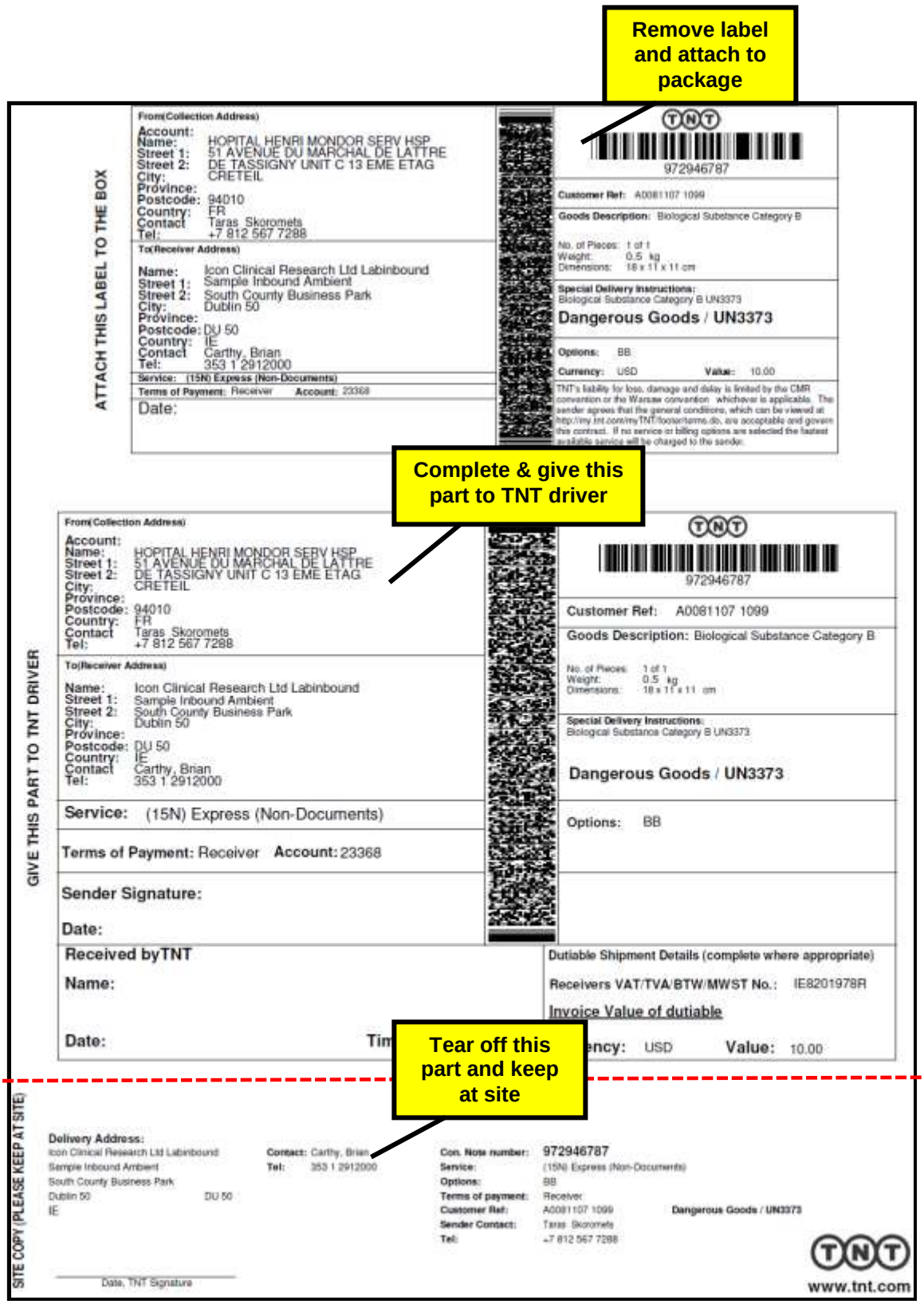
Package
1 of 1

SAMPLE

QuickSTAT Air Waybill Completion Instructions



TNT Air Waybill Completion Instructions



TNT Dry Ice & Pick-up Request Form

Please complete all details below and fax or email the completed form to TNT before the specified cut off time as detailed in your Courier Contact Memo

Collection Details *(to be completed by site)*:

Study Reference: CA209908 Site No:_____

Contact Person	Name:		
Tel. No:	Email Address:		
Hospital/Clinic			
Department / Wing			
Principal Investigator			
Address			
	Country	Postcode	City
Additional Collection Information:			

Date required (dd-mmm-yyyy): _ _ - _ _ _ - _ _ _ _
Pre-printed Air Waybill will be included with packaging and dry ice

Shipment Type and number of boxes and/or pieces required: (TNT Frozen 5 box supplied as standard):
(Note: 1 cryo box or 12 samples will fit into 1 TNT Medpak Frozen 5 shipping box)

No. of Frozen Boxes Required: _ _ BOXES

No. of Ambient Pieces: _ _ PIECES

Air Bill Number: _ _ _ _ _ _ _ _ _

Date required for collection of shipment (dd-mmm-yyyy): _ _ - _ _ _ - _ _ _ _

Time shipment will be ready for collection (Use Local Time 24h): _ _ : _ _

State your closing time (Use Local Time 24h): _ _ : _ _

Note: ***Please ensure the delivery address and contact details are complete to prevent any delays.***

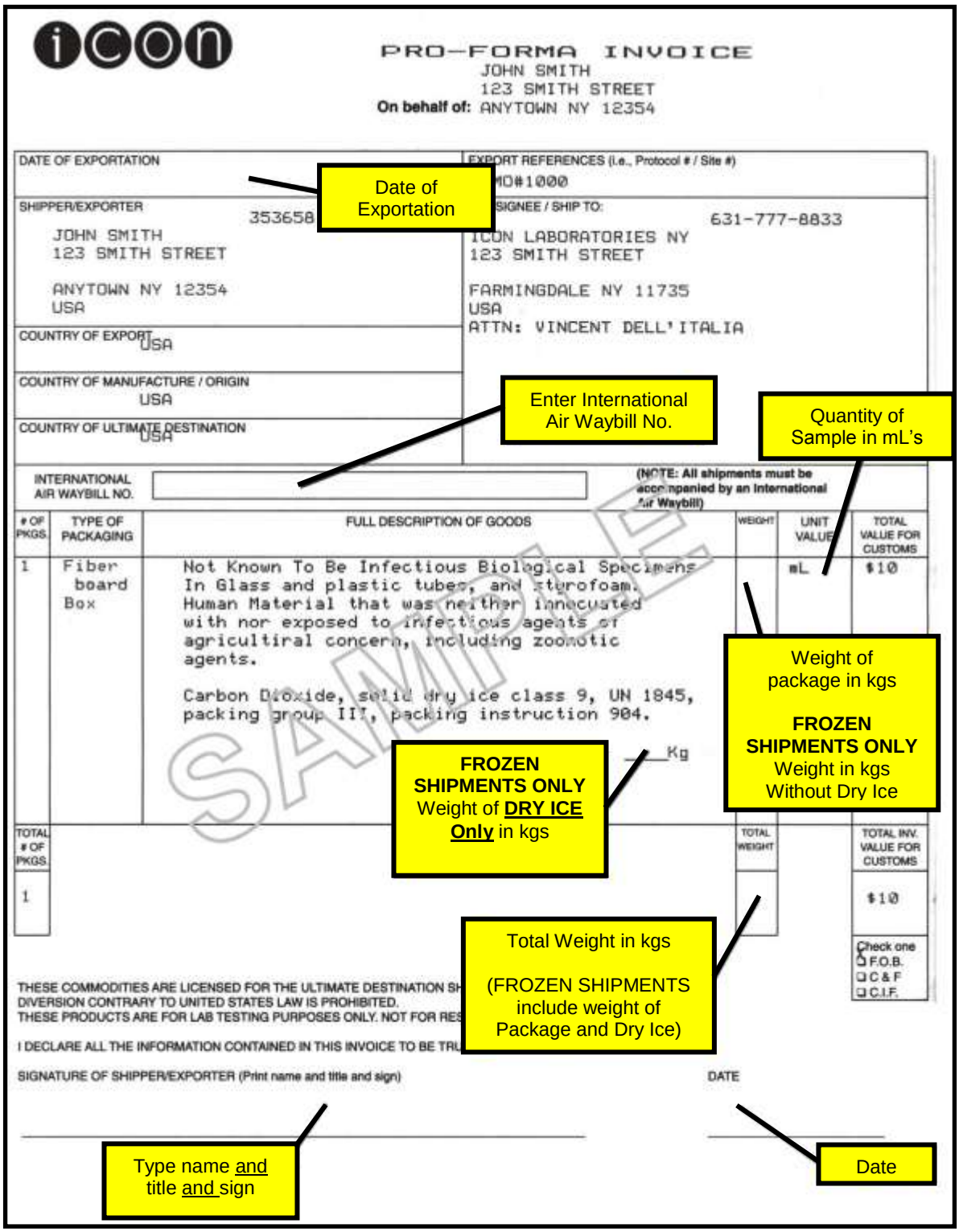
TNT INTERNAL INSTRUCTIONS:

Use Medpak Frozen 10 on Friday's for Monday Delivery to sites

Customer Ref No: CA209908

Payment terms: R **ICON account number**: 58507
Shipment Details: 1 Piece 5.5 kg, 30x30x29 cm **(**Medpak Frozen 5**)**
Service: S1EN BB DI SYS for Network Shipments and **S1EN BB DI SY** for Exclusive Shipments
Special Instructions: Biological Substance, Category B, UN3373 on Dry Ice, Class 9, UN1845, 1 x 5 kg
Content: Biological Substance, Category B (UN3373)
Delivery Address: ICON Laboratory Services
South County Business Park
City: Dublin 50, Postcode DU50, Ireland
Contact: Raivis Perdijaks Tel: +353 1 2912091

Pro-Forma Commercial Invoice Completion Instructions



CDC Permit

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

Centers for Disease Control and Prevention
Office of Health and Safety, MS A-46
Atlanta, Georgia 30333
TEL: 404-718-2077; FAX: 404-718-2093; Email: importpermit@cdc.gov

SAFER • HEALTHIER • PEOPLE

Permit to Import Infectious Biological Agents, Infectious Substances, and Vectors

In accordance with 42 CFR Section 71.54 of the Public Health Service Foreign Quarantine Regulators, cited on the bottom of this permit, permission is granted the permittee to import into any port under control of the United States, or to receive by transfer within the United States, the material described in item 1 below.

PHS PERMIT NO.	2013-12-055	
DATES	ISSUED: Tuesday, December 10, 2013	EXPIRES: Wednesday, December 10, 2014
1. DESCRIPTION OF MATERIAL	BLOOD/BLOOD PRODUCTS, ISOLATES, BODY FLUIDS AND TISSUES FROM HUMANS THAT MAY CONTAIN HEPATITIS A – E, HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 AND 2, STAPHYLOCOCCUS AUREUS, STAPHYLOCOCCUS EPIDERMIDIS, ESCHERICHIA COLI, KLEBSIELLA SPECIES, ENTEROCOCCUS SPECIES, PSEUDOMONAS AURIGENOSA, STREPTOCOCCUS PYROGENES, STREPTOCOCCUS PNUEMONIAE, STREPTOCOCCUS SPECIES, BACTEROIDES SPECIES, FUSOBACTERIUM SPECIES, CLOSTRIDIUM SPECIES, CLOSTRIDIUM ALBICANS.	
2. PERMITTEE (NAME, ORGANIZATION, ADDRESS AND CONTACT INFORMATION)	THERESA BOWMAN-COTTEN ICON CENTRAL LABORATORIES 123 SMITH STREET FARMINGDALE , NY 11735	TEL: 631-306-5521 FAX: 631-694-2524
2a. OTHER AUTHORIZED PERMIT USERS	VINCENT DELL'ITALIA ICON CENTRAL LABORATORIES 123 SMITH STREET FARMINGDALE , NY 11735	TEL: 631-306-5355 FAX: 000-000-0000
	EVA TORRES ICON CENTRAL LABORATORIES 123 SMITH STREET FARMINGDALE , NY 11735	TEL: 631-306-5501 FAX: 000-000-0000
3. SOURCE OF MATERIAL (NAME, ORGANIZATION, ADDRESS, COUNTRY)	WORLDWIDE	
4. TYPE OF PERMIT AND INSTRUCTIONS FOR USE	☐ Single Importation into the U.S. ☐ Single Transfer Within the U.S. ☑ Multiple Importation into the U.S. ☐ Multiple Transfer Within the U.S. A. Record of each importation shall be maintained on permanent file by permittee. B. Enclosed label(s) must be forwarded to the shipper(s). C. One label shall be affixed to shipping container. Enclosed labels may be photocopied.	
5. CONDITIONS OF ISSUANCE ITEMS APPLICABLE WHEN CHECKED	☐ A. Subsequent distribution, within the U.S., of the material described in this permit is prohibited without prior authorization by the Public Health Service. ☑ B. All material is for laboratory use only - Not for use in the production of biologics for humans or animals. ☑ C. All material is free of tissues, serum and plasma of domestic and wild ruminants, swine and equines. ☐ D. Additional Requirements: ☐ IATA Packaged to preclude escape. ☑ USDA permit may be required (Telephone: 301-851-3300). ☑ E. Work with the agent(s) described shall be restricted to areas and conditions meeting requirements in the CDC/NIH publication "Biosafety in Microbiological and Biomedical Laboratories." ☑ F. Packaging must conform to 49 CFR Sections 171-180.	
	6. Signature of Issuing officer Robbin S. Weyant, PhD, RBP (ABSA) Captain, USPHS (Ret.) Etiologic Agent Import Permit Program	

CDC 0728 (F 13,40) REV. 4-13

42 CFR 71.54. Permit to Import Biological Agents, Infections Substances, and Vectors

Section 12 - Test Result Reporting

Reporting method will be sent as defined by the Protocol Sponsor. Lab results will be reported to your site as follows:

No Reports:

- At the request of the protocol sponsor, your site will not be receiving any lab reports.

Section 13 - Version History Table

VERSION NUMBER	DATE	BRIEF SUMMARY OF UPDATES
1.0	12-Apr-2017	Original Document