INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Identifying and Managing Product Complaints

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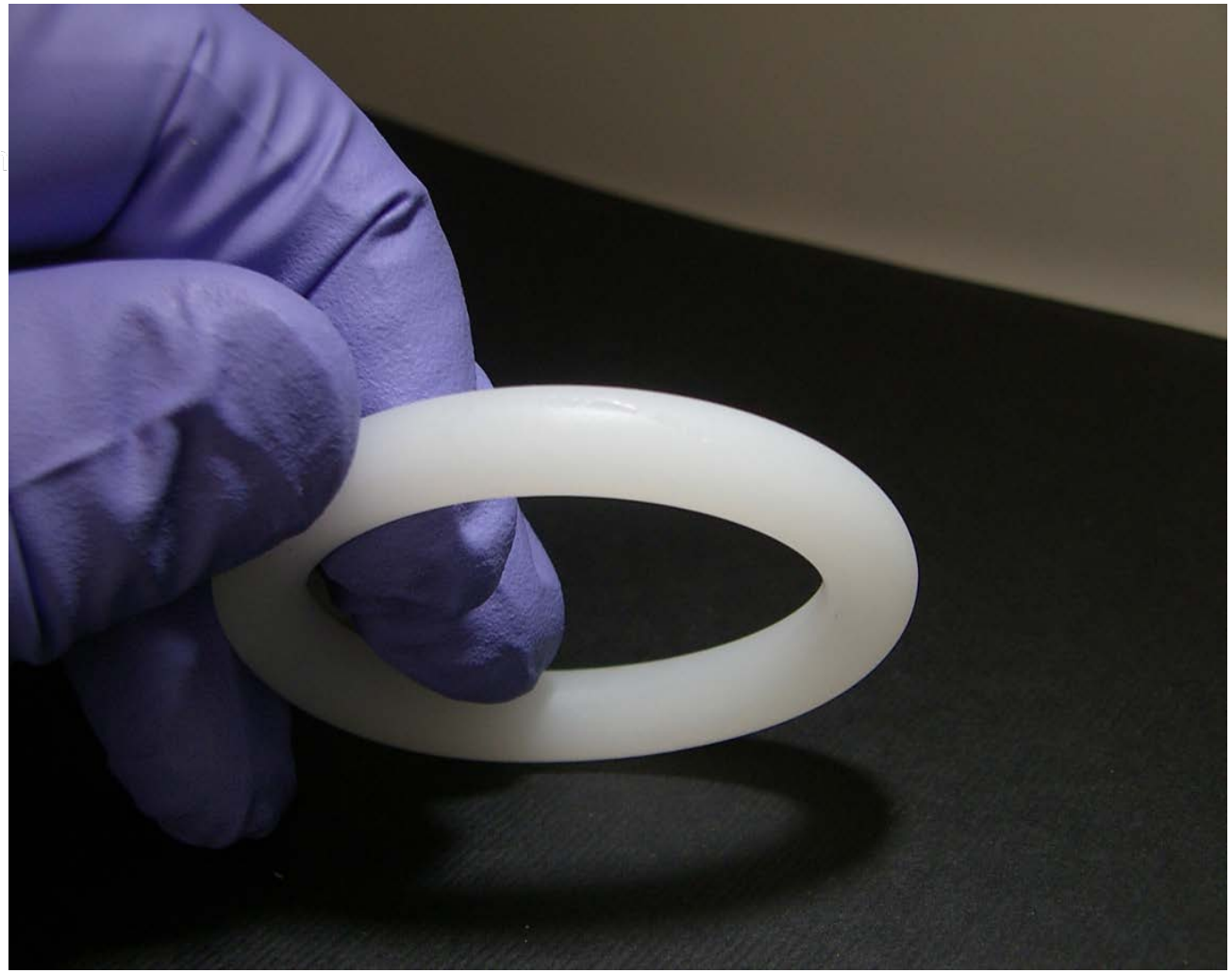
Developing HIV Prevention *Products for* **Women** *worldwide*

Ring

Vaginal Ring:



Packaging Configuration

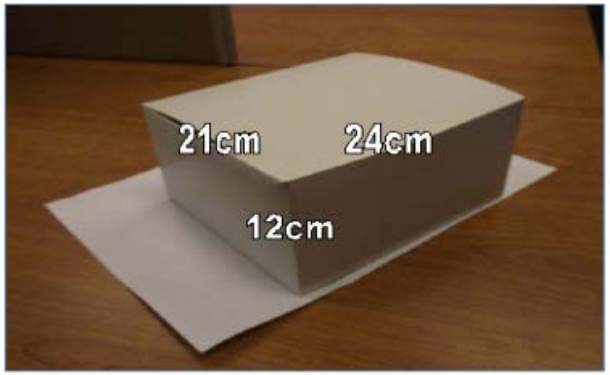
- GMP rings will be manufactured and pouched in Sweden, shipped to Penn UK.
  - Penn Pharma will label each ring pouch and pack into cartons
  - Each pouch will have a sub lot code number with a tear off portion (to be placed in source documents)
  - Each carton will contain 40 dapivirine or 40 placebo rings per carton.
  - Each carton will also indicate on the front label the bin code.
  - Each carton will be tamper sealed in 2 locations

IP Carton Configuration

MATRIX RING BOX MEASUREMENTS

Each carton to hold 40 matrix rings in 4 stacks of 10

Outside measurements of collective ring box: 21cm deep x 24 cm wide x 12cm high



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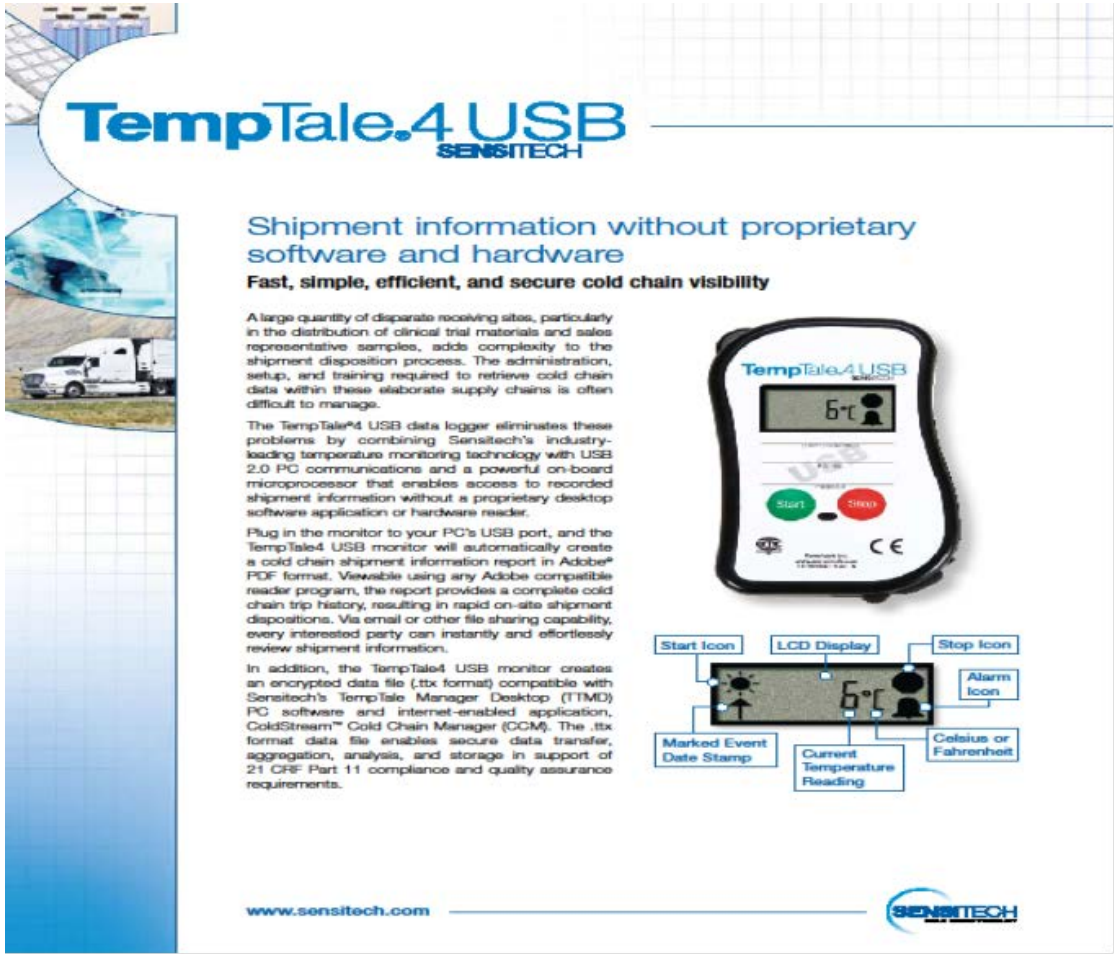
IP Pouch Configuration

IP Shipment Contents

- Upon Research Centre (RC) activation, IP shipment process will be initiated
- RC contacted to confirm shipment is on its way
- Shipment will include:
  - Shipper
  - IP Cartons
  - Used Ring Bags
  - Temperature Monitoring Device
  - Temperature Monitoring Device Form
  - Packing List and Acknowledgement of Receipt

Temperature Monitors



Enclosed Temperature Monitor Instructions

WARNING - Immediate Action Needed

Temperature monitor needs to be stopped immediately

Does the alarm bell show on the monitor? Yes / No *Please circle as applicable

Order/Job No. C..... / .....

Instructions for reading the TempTale 4 temperature monitor

Stopping the Monitor

Remove TT4 monitor from box and press the red stop button for 3 seconds until the stop icon appears

Alarms:

If the Bell icon does not appear on the screen, products have traveled in good condition.

Information on LCD screen:

Press and hold the green start button and write down the numbers that appear in sequence on the screen:

1.		= average temperature recorded
2.		= highest temperature recorded
3. *		= cumulative time above high temperature alarm
4.		= lowest temperature recorded
5. *		= cumulative time below low temperature alarm

*If box 3 or 5 is anything other than 0 please inform MTN immediately

To review the numbers again, press and hold the start button again

Retrieving TempTale-4USB Monitor reports and data files

- Pull out the USB connector cable from the side of the TempTale-4USB monitor and insert the plug into a USB port on the computer.
- The monitor will automatically begin creating the Adobe® PDF report and Scriptech .ttx data file within the monitor.
- Copy and paste the two files shown in the pop up screen and print hardcopy to place on file.

In the event of an excursion details should be e-mailed to:

Cindy Jacobson e-mail: cjacobson@usmc.edu

Tracie DiPasquale e-mail: tdipasquale@ipmglobal.org

Anita Garg e-mail: Agarg@ipmglobal.org

Rita Young e-mail: rita.young@pennpharm.com

Please title your e-mail as follows:

(Order job number as stated at the top of this form, site number) - Site temperature download

Date / Time received:	
Serial Number:	
Your details:	
Your Name:	
Site No / Name:	

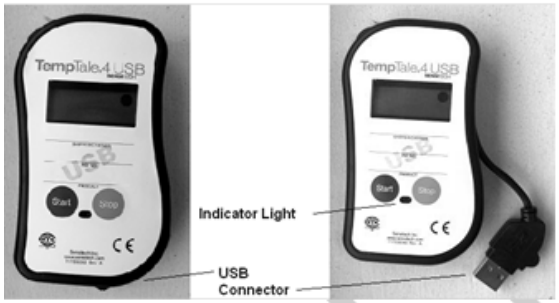
Please fax this page to Penn Pharmaceuticals

on +44 (0) 1495 713743 or e-mail: rita.young@pennpharm.com

Penn Instructions:-

Temperature Monitor Instructions

USB TEMPTALE DOWNLOAD AND EMAIL INSTRUCTIONS FOR INVESTIGATIONAL SITES



1. As soon as the TempTale is removed from the shipper, **immediately press the "Stop" button** until the stop sign icon appears. Note: an "alarm bell" icon will appear under the stop sign icon if an excursion occurred during transit. If there is no alarm, the shipment traveled within temperature range.
2. Remove the USB connector from the bottom right of the TempTale. Plug the connector into a computer USB port.
3. **It will take several seconds for the file icons to appear. Wait for the red indicator light to stop flashing and turn to green. At this point, "Found New Hardware" and other messages may appear on the computer screen. Wait until they disappear.**
4. A window showing two files will appear – one with a "PDF" symbol and another with a round "S" symbol or series of squares:

5. Right click on the PDF file.
6. Click "Send To", then click "Mail Recipient."
7. In the "To" box type: e-mail addresses as specified in temperature monitor form
8. In the subject line, type the study protocol, site number and order number.
9. Click "Send"
10. Disregard the monitor as it is a single use monitor.

ONLY IF there is a temperature excursion:

11. Right click the icon with the "S" symbol or squares, file name ending in "ttx." Email this file by repeating steps 6 through 10.

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Handling Temperature Excursions

What are the steps RC's need to take when they receive the monitors in a shipment?

- Open the shipper and stop the monitor-Red button
- Download the temperature information following the instruction sheet enclosed with shipment
- Email the temperature results to the contacts listed
- Store the IP in a locked, temperature controlled area if not alarmed. If alarmed, store in a quarantined controlled area.
- Immediately call or email and notify which carton numbers received that are damaged or had been in a shipper which alarmed with a temperature excursion
- Any non-useable cartons will be replaced in a new shipment

Used Ring Bags

Research Centres will be receiving pre-labeled Used Ring Bags

- To be used if ring is expelled and not re-inserted
- To be used to store returned rings at the RC
- Each bag will be pre-printed with all needed information. For every ring dispensed, the participant will be sent home with a bag.

IP Storage Conditions

- Secure location with access restricted
- Temperature maintained between **15°C to 30°C** (59°F to 86°F)
- Temperature monitored on daily basis
- If temperature excursion
  - Quarantine IP – DO NOT DISPENSE
  - Notify Cindy Jacobson-MTN and Laura Lappine-IPM immediately
  - Await IPM approval to use or not
- Follow RC SOP

IP Dispensing

- One ring dispensed every 4 weeks from enrolment.
- Label has a tear-off portion – affix to source documents
- Complete IP Inventory and Accountability Log
- Dispense ring, return bag and instructions for use

ASPIRE STUDY

Identifying and Managing Product Complaints

Handling of complaints is part of Good Manufacturing Practice (GMP) therefore any GMP complaint should be taken seriously.

Sponsor should have a well-designed GMP complaint handling system that can be readily implemented to tackle the issue (CAPA), and if necessary, recall the entire batch of that product from the market.

Theory

- Product Complaint:
  A Complaint means that something might not be right with the product or the product is defective. For pharmaceutical companies, the GMP complaints are mainly confined to quality of product, but it may also mean improper packaging, such as, smeared labels, tear off panel missing, wrong labeling.

- It could also reflect poor quality bulk drug, such as, un-sealed pouches, ring discoloration, pitting, rough edges, etc.

Definition

- Product Complaint:
- Any written or oral communication that questions the safety, efficacy, identity, quality, durability, reliability or performance of a Clinical Trial Material. Complaints may come from any source (e.g., telephone contact, letter, conversation, e-mail, report from a Clinical Monitor, etc.).

Documenting the Incident

- Upon becoming aware of a complaint, all (sponsor) employees, contractors and temporary employees are responsible for gathering all the required information possible and promptly reporting complaints to IPM Regulatory Affairs (RA) group.
- Which Department handles complaints is an organizational decision—larger companies would have this done by a dedicated complaint unit or Customer Service Center.
- Regulatory Affairs acts as a triage, gathering all of the information onto the complaint form and delegating further investigation to the functional areas directly responsible and maintaining complaint files (as outlined in an official SOP procedure), such as, Product manufacturing, Medical Safety, etc.

RC's Contact IPM for Complaint

- Promptly report a complaint received from any source to RA by calling or emailing detailed information. When possible, include the reporter's name, date and time, contact information and nature of complaint.
- Regulatory Affairs would fill out the complaint form on behalf of the RC, identifying any written documentation and/or returned product (with associated packaging) relating to the complaint as part of the complaint.

IPM Regulatory Affairs would:

- Assign the next complaint number for the given year, following the format PC-YY-XXX; where YY is the last two digits of the current year and XXX are the sequentially-assigned number of complaints received in the current year
- Enter the complaint number and date received in the Complaint Log

IPM RA: Assigning Responsible Party

- Complete the Complaint Form by entering the complaint number and evaluating if an investigation is necessary and what functional area should conduct it.
- Inform the appropriate functional area of the complaint
- Issue an acknowledgement letter to the complainant to confirm receipt, request additional information and inform the complainant that evaluation is underway.

IPM RA: Complaint Verification

- If an investigation is deemed unnecessary, document the deciding person's name and justification in the complaint file.
- When deemed necessary, conduct the complaint investigation and compile documentation thereof into a written report
- Inform and consult with the appropriate (sponsor) Team when necessary
- Upon completion, forward the investigation documentation to RA

IPM Regulatory Affairs-Close Out

- Review the complaint investigation and any testing results
- When appropriate, approve the complaint file for closure when all required elements are completed.
- **Note:** A complaint file may be re-opened for further investigation at any time if a complaint sample becomes available or additional relevant information prompts such action.
- Generate a final response letter to the complainant and complete the Complaint Form.
- Update the Complaint Log and file the complaint file.
- Monitor the frequency of complaints and report any trends to the appropriate functional area of (sponsor).

RC Steps to Take

- 1. Identify product and place in Quarantine.
- 2. Contact IPM RA, Cindy Jacobson via email or phone describing complaint, including participant #.
- 3. IPM RA will fill out Complaint Form.
- 4.IPM/Cindy will respond with next action to take, order replacement product, returning product as directed.
- 5. IPM/MTN would evaluate any trending in manufacturing.

Sample IPM RA Complaint Form

Complaint Form

Date Received: _____ **Received by:**_____

Final Pkg. Batch #(s): _____ **Pkg. Desc.:** _____

Clinical Trial Number: _____ **Participant No.:** _____

Investigator Name & Address:_____

_____

_____

Complainant Name: _____ **Tel.#:** _____

Address:_____

_____

_____

Nature of Complaint:_____

_____

_____

_____

Request Complaint Sample: ☐ **Quantity (units):** _____

****RA Use Only****

RA Assessment:

☐ Investigation required ☐ Complaint resolved ☐ No action required

Investigation Outcome:_____

_____

_____

Sample IPM RA Complaint Form

RA Follow-up:

1. Acknowledgement Letter sent by: _____ Date: _____

Airbill tracking # - Letter to Complainant: _____ Return Spl Pkg: _____

*(**Note:** Complete and enclose airbill for product being returned with complaint number and RA Contact as recipient)*

2. Complaint sample received by: _____ Date: _____

3. Response letter to complainant sent by: _____ Date: _____

Closure Date: _____ **RA Signature:** _____

Closing

- Any Questions?

- Thank you very much for your attention!