MDSAP AUDIT PROCESS

A Manufacturer’s Perspective

Connie Hoy
EVP Regulatory Affairs
Cynosure, Inc.
Cynosure

- Located in Westford, MA
  - Largest manufacturer of Medical Lasers
- Second location in Hicksville, NY
  - Manufacturer RF devices for surgery and aesthetic procedures
- Recently Acquired by Hologic
KEEP CALM AND LET THE MADNESS BEGIN
AUDITS!

• In 2014 we had the following audits:
  • ISO Certification
  • Japan
  • Korea
  • 3 Brazil GMP (our site + 2 OEM manufacturers)
  • 2 FDA audits of IDEs
  • 1 QSIT Audit

• Prompting Cynosure to decide to enroll into the MDSAP Pilot program – We applied in early 2015

• Notified Body is Intertek SEMKO AB (Swedish)
Agenda

• Why?

• The Audit Experience

• How we prepared for the Audit

• How we should have prepared for the Audit

• 450 vs 41 employee facility
Who is affected and when?

- Any device firm that distributes in USA, Canada, Brazil, Australia or Japan should understand the program and contemplate participation.
- FDA went live with MDSAP on 1 JAN 2017 – acceptable replacement for routine inspections.
- Health Canada / CMDCAS makes MDSAP mandatory effective 1 JAN 2019!
  - MDSAP participation will soon be mandatory in Canada
  - May be heading that way in other participant markets
- Important for all to understand MDSAP program mechanics, benefits, risks and challenges to facilitate timely decisions, and timely preparation.
• FDA will accept MDSAP in lieu of routine inspection, but not for initial visits or “for cause inspections.”

• Health Canada will use MDSAP to satisfy CMDCAS, and is planning to replace CMDCAS with MDSAP in **January 2019**. Therefore, medical device manufacturers currently selling in Canada will have to obtain MDSAP certification.

• ANVISA will accept MDSAP for initial audits. This will help with the country’s current backlog of inspections, but the agency will still require its auditors to conduct ANVISA audits for higher-risk devices.

• TGA will use MDSAP to satisfy TGA requirements, considering MDSAP certificates as equivalent CE certificates.

• MHLW will accept MDSAP in lieu of an on-site Japanese Quality Management System (J-QMS) audit.
What happens in the EU?

- Europe (EU) has been participating in MDSAP as an official observer
  - Concerns is that it would be difficult to obtain agreement among all member states
  - Participation of European notified bodies in the program shows a strong link between EU and MDSAP
- There is optimism the EU will join the program
  - MDSAP’s aim to harmonize quality system compliance (ultimately increasing the safety and efficacy of medical devices)
  - Serve as a way for EU to increase quality consistency across its member states
What happens in the EU?

• Given EU focus on updating MDR regulations, this may not be soon

• But: registrars auditing to MDSAP already have 13485 and MDD baked into the current audit process!!!
What MDSAP is NOT

• Replacement for CDRH audits for Radiation emitting devices

• Replacement of “for cause” audits

• Replacement for INMETRO (electrical safety) audits for Brazil
MDSAP Audit

- Can currently audit to ISO 13485:2003 or 2016
  - 2016 is mandatory February 28, 2019
- Based on 3 year cycle (similar to ISO 13485:2003)
  - Initial Certification Audit of entire quality management system (QMS)
    - Stage 1: preparation review
    - Stage 2: registration audit
  - Annual Surveillance Audits – partial coverage
  - Recertification audit in 3rd year
- Non-conformance findings are graded for severity
  - No more Major / Minor findings
## Grading System

- Based on GHTF/SG3/N19:2012

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Repeat</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
What does that mean?

- Indirect impact clauses 4.1-6
  - Administrative requirements
- Direct impact clauses 6.4-8.5
  - Process that relate to safety and effectiveness of product

- Escalation factors include:
  - Repeat occurrence
  - Lack of documented procedure
  - Release of nonconforming material caused by lack of process

- It is possible to end with a Grade 6 finding, which requires immediate intervention
MDSAP Audit Elements (In Order)

- Number of audit tasks:
  - Management (11)
  - Device Marketing Authorization and Facility Registration (3)
  - Measurement, Analysis and Improvement (16)
  - Medical Device Adverse Events and Advisory Notices Reporting (2)
  - Design and Development (17)
  - Production and Service Controls (29)
  - Purchasing (16)
MDSAP Audit

- Audit duration is based on the elements to be covered in the audit (up to 94), not on number of employees (as in ISO 13485)
  - A pre-determined amount of time is allocated to each task (range: 15 – 44 minutes)
    - reduced for no sterilization, service, installation or implants (¾ hr. each), or design (5 hrs)
    - increased for critical supplier visits (4 hours each), outstanding NCRs (15 min. each)
Audit Duration Range examples

<table>
<thead>
<tr>
<th>Stage 1 Audit</th>
<th>Stage 2 Audit &amp; Recertification</th>
<th>Annual Surveillance Audits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typically 1 day</td>
<td>6 ½ on-site man-days:</td>
<td>3 ½ – 5 on-site man-days:</td>
</tr>
<tr>
<td></td>
<td>Including design, sterilization,</td>
<td>Including design, sterilization,</td>
</tr>
<tr>
<td></td>
<td>service, installation &amp; implants in scope</td>
<td>service, installation &amp; implants in scope</td>
</tr>
<tr>
<td></td>
<td>5 ½ on-site man-days:</td>
<td>3 – 4 ½ on-site man-days:</td>
</tr>
<tr>
<td></td>
<td>Not including the above</td>
<td>Not including the above</td>
</tr>
</tbody>
</table>
MDSAP Audit Style

• 100% Prescriptive

  • Follows a Step by Step series of questions that are asked in order
  
  • Questions are in an Audit Checklist and does not vary from the flow of the checklist

  • Does link to other processes during each section
<table>
<thead>
<tr>
<th></th>
<th>Process: Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Verify that a quality manual, management review, and quality management system procedures and instructions have been defined and documented.</td>
</tr>
<tr>
<td>1</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>Confirm the organization has established a quality plan which defines the quality practices, resources, and activities relevant to devices that are designed and manufactured.</td>
</tr>
<tr>
<td>2</td>
<td>Confirm top management has documented the appointment of a management representative. Verify the responsibilities of the management representative include ensuring that quality management system requirements are effectively established and maintained, reporting to top management on the performance of the quality management system, and ensuring the promotion of awareness of regulatory requirements throughout the organization.</td>
</tr>
<tr>
<td>3</td>
<td>Verify that a quality policy and objectives have been set at relevant functions and levels within the organization. Ensure the quality objectives are measurable and consistent with the quality policy. Confirm appropriate measures are taken to achieve the quality objectives.</td>
</tr>
</tbody>
</table>
## Second – Country Specific

<table>
<thead>
<tr>
<th>5</th>
<th>Canada</th>
<th>Verify that the roles and responsibilities of any regulatory correspondents, importers, distributors, or providers of a service are clearly documented in the organization’s quality management system and are qualified as suppliers and controlled.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>EU</td>
<td>Has the manufacturer changed their EU Authorized Representative? Do they have process to advise us, their Notified Body, of this substantial</td>
</tr>
</tbody>
</table>


Third – Links to other processes

| Link | During audit of the firm’s Purchasing process, ensure that management has assured the appropriate level of control over suppliers, including an assessment of the relationship between supplied products and product risk. |
Risk assessment

- Focus on Risk related to the processes
- For example:
  - Verify that the system for monitoring and measure of product characteristic is capable of demonstrating conformity. Confirm that product risk is considered in the type and extent of product monitoring activities.

- Confirm that the manufacturer has established and maintained a file for each type of device (DMR) Confirm that the manufacturer determined the extent of traceability based on the risk posed by the device.
Outsourced Processes

- OEM manufacturers
- Vendors (components)
- Outsourced processes (sterilization, PCB manufacturers)
- Engineering services
- Regulatory services (auditors and third party registrars)
- Storage Facilities
- Consultants

Focus on Supplier agreements and Supplier Controls especially as it relates to RISK
Non-conformities

- Nonconformities identified during an audit will be grade on a scale from 1 (least critical) to 5 (most critical)

- Major / Minor terminology no longer exists

Companion Document
Companion Document

http://www.fda.gov/downloads/MedicalDevices/InternationalPrograms/MDSAPPilot/UCM375697.pdf
What is the Companion Document?

This is your GUIDEBOOK

If you don’t have a highlighted, redlined, dog-eared, coffee stained copy of this in your possession, then you are not ready for your MDSAP Audit.
Format

- Each process has a chapter that includes:
  - Purpose
  - Expected outcomes for the auditor
  - Audit Tasks and Links to other processes

- Audit Tasks are numbered and correspond to the audit checklist

- Section to explain what should be assessed during each audit task

- Country specific requirements
Example: Task 8 of Management

8. Verify that procedures have been defined, documented, and implemented for the control of documents and records required by the quality management system. Confirm the organization retains records and at least one obsolete copy of controlled documents for a period of time at least equivalent to the lifetime of the device, but not less than two years from the date of product release.

Clause and Regulation: [ISO 13485:2003: 4.2.1, 4.2.3, 4.2.4; RDC ANVISA 16/2013: 3.1; 21 CFR 820.40, 820.180]

Additional country-specific requirements:

Australia (TGA):

Confirm that Quality Management System documentation and records in relation to a device are retained by the manufacturer for at least 5 years [TG(MD)R Sch3 P1 1.9].

Brazil (ANVISA):

Verify that change records include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective [RDC ANVISA 16/2013: 3.1.5].

Confirm that the manufacturer maintains a master list of the approved and effective documents [RDC ANVISA 16/2013: 3.1.5].

Verify that electronic records and documents have backups [RDC ANVISA 16/2013: 3.1.6].
Preparation is the key
What to do!

• Read the Companion Document cover to cover
  • ALL 96 pages!
  • This will help you understand the overall flavor of the audit
  • Look for Risk related activities

• Highlight all the Audit tasks in each section
  • I did it first in the hard copy
  • Then in the e-Copy

• Ask your notified body if they will provide you with the audit checklist
MEETING NOTICE!
Explain!

• Meet with the appropriate dept. heads to explain the new audit style – you need to prep your organization

• Focus:
  • Audit “Tasks” that you have highlighted in the eCopy
    • I didn’t hand the entire document….I selected the pertinent sections for each department head
  • Risk related activities

• QA may need to hold some hands on this especially for “old-timers” who have been through lots of audits
Pre-Audit???

- Located a few consultants who can do an audit to MDSAP
- May be more prudent to use the Companion document and/or the audit checklist and perform internal audit(s)
- There is some training available from consulting firms
The Cynosure Audit

• 0.5 day of desk audit (1 auditor)
  • Quality Manual
  • Top Level procedures (I sent 37 total SOPs)

• 4.5 days of on-site audit (2 auditors)

• Total of 9.5 (audit days)

• This is based on number of employees. Cynosure has 400 employees at their corporate office

• Scope was MDSAP, ISO 13485(surveillance) and Medical Device Directive (MDD)
The Cynosure Desk Audit

• After the Desk Audit, I received a list of “things missing” from the SOPs

• Example:

  7.3.7 Control of design and development changes - Additional Country requirement: Australia

  Verify that the manufacturer has a process or procedure for notifying the auditing organization of a substantial change to the design process or the range of products to be manufactured [TG(MD)R Sch3 Cl1.5].
The Cynosure Desk Audit

- We have a substantial change process in place, but we did not specifically indicate how we would deal with notifying Australia.

- We updated all the SOPs that had “missing things” prior to the site audit

- The updates were verified during the audit
The Cynosure Site Audit

- Audited separately
  - You need 2 conference rooms
  - Subject matter experts queued up

- There is NO changing of the audit flow
  - For example, we asked to have Purchasing moved to earlier in the week which was a no-go

- The audit moves at a fast pace

PRE-GAME
Pre-game

• All procedures queued up electronically or paper (ask the auditor before he/she arrives for preference)

• Matrix of all your registrations by product / country (with registration number in the matrix)
  • Objective evidence to show that your products are registered
    • Copies or electronic

• Copies of your establishment registrations by country
Pre-Game

• Documentation like you would support an ISO or QSIT

• Distributor / Subsidiary agreements
  • Considered an outsourced process
  • Quality Agreements
    • We were asked to show agreements with our Sub office in Australia

• Supplier Agreements
  • Qualifications per your Vendor List
  • Supplier / Quality Agreements
Pre-Game

• Change Control
  • Risk Assessment for significant changes
  • Decisions on when to notify a government agency of a change
    • For example, a change to a critical component will require notification to INMETRO and ultimately ANVISA

• Other
  • Translated Manuals / Labeling
  • Translated GUI
War Room?

• We decided not to have a war room

• We did set up a IM communication tool (SLACK) and a Dropbox for documents

• Didn’t miss the War room but REALLY happy we had SLACK set up

• Learn to use expanded desktop to present items to auditors to avoid IM messages popping up during audit!!!
DON’T FEAR THE AUDIT.
The Audit

• Very promptly started and sticks to a strict schedule

• Followed Audit Task Checklist to the letter and typed into the checklist during the audit
  • If you understand the Audit Tasks this is very direct

• Seemed to be some overlap between the two auditors
  • For example, metrics were reviewed in Management Review and also reviewed in Monitoring and Measurement

• Did spend time on the production floor
  • Process Control
  • Calibration
The Audit

- Focus on Risk Activities as it relates to ALL processes
- Focus on outsourced processes including risk mitigation for outsources processes
- Focus on Validation
  - Design
  - Process
- Focus on Change management and associated risks
- Found multiple times where the subject matter expert for particular topics was required in both rooms
  - Had to improvise!
• We did bring in lunch and spent that time chatting with the Auditors
Cynosure Westford Outcome

• **Finding:** (Grade 3)
  - Could not determine that records of installation are maintained when installation activities are carried out by distributors.

• **Requirement:**
  - 7.5.1.2.2 Installation activities
    If appropriate, the organization shall establish documented requirements which contain acceptance criteria for installing and verifying the installation of the medical device. If the agreed customer requirements allow installation to be performed other than by the organization or its authorized agent, the organization shall provide documented requirements for installation and verification. Records of installation and verification performed by the organization or its authorized agent shall be maintained.
Certificate of Registration

Intertek

This is to certify that the quality management system of

Cynosure, Inc.

Main Site: 5 Carlisle Road, Westford, Massachusetts 01886 United States
(DUNS# 780318028)

has been assessed and registered by Intertek, an MDSAP authorised auditing organisation, as conforming to the requirements of

ISO 13485:2003

Applicable regulatory requirements:

Brazil: Federal Law n. 8080/78; RDC ANVISA n. 16/2013; RDC ANVISA n. 23/2012; RDC ANVISA n. 87/2006; RDC ANVISA n. 58/2001
Canada: Medical Devices Regulations Part 1 - SOR 98/292
Japan: MHLW Ministerial Ordinance 108, Article 4 to Article 68, PMD Act

The quality management system is applicable to:

The Design and Development, Manufacturing, Installation and Service of Medical, Dermatological and Surgical Lasers, Rf Generators and Accessories.

Certificate Number: 0056163-00
Initial Certification Date: 18-Nov-2016
Certificate Effective Date: 18-Nov-2016
Certificate Expiry Date: 28-Feb-2019

Călin Moldovean, President
Intertek Testing Services NA, Inc. – 930 Cheimsford Street, Lowell, MA 01851 USA

Validity of this certificate may be verified at http://www.intertek.com/business-sureace/certificate-validation/
Cynosure Hickville

- Much smaller facility
  - 41 employees vs. 450 at Westford
- No Design Control
- Top level QMS activities managed through Westford
  - Management Review / CAPA
  - Internal Audits / complaints
  - Supplier control
- Revisited QMS Activities from Westford as related to Hicksville products
- Duration: 7 man days
Cynosure Hicksville Outcome

• **Finding: (Grade 3)**
  • Process for documenting nonconforming product is not effectively implemented

• **Requirement:**
  • 8.3 Control of nonconforming product
  • The organization shall ensure that product which does not conform to product requirements is identified and controlled to prevent its unintended use or delivery
Cynosure Hicksville Outcome

• Finding: (Grade 3)
  Process is not effective/Use of Obsolete Document

• Requirement:
  • 4.2.3 Control of documents
  • Documents required by the quality management system shall be controlled. Records are a special type of document and shall be controlled according to the requirements given in 4.2.4.
THEN WHAT?

- Grade 4-5 findings
  - 15 days to respond with corrective action plan
  - 30 days to correct
  - Expect unannounced audit to follow up

- Grade 1-3 findings
  - 15 days to respond with corrective action plan
  - Implementation with in 90 days
How Should we have prepared?

Take more time

- We had only 5 weeks from the time we got into the schedule until the first audit in October. We did not know about the companion document until this time!

- Become familiar with the Companion Document long before the audit
  - We update procedures all the time – we should have been considering the MDSAP in updates for the entire year

- Conduct Internal Audits against the Audit Task Checklist
MY BEST ADVICE...

START NOW.