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4-8 December, 2017 I New Delhi

MEDICAL DEVICE SINGLE AUDIT PROGRAM (MDSAP) EXPERIENCE

DOMINIK RETERSKI
VICE PRESIDENT QUALITY AND REGULATORY AFFAIRS,
ASIA PACIFIC

Medtronic
Further, Together

Agenda

- The Medical Device Single Audit Program
  - What is it/ What it is not & a brief history
  - Who can conduct, Audit Model, Audit Frequency & Audit Duration
  - Grading Nonconformances & Audit Response Timing
- Benefits & Lessons Learned
- Challenges of MDSAP
- What's on the Horizon:

MEDICAL DEVICE SINGLE AUDIT PROGRAM (MDSAP)

- ✓ What is it/ What it is not, and a brief history
- ✓ Who can conduct, Audit Model, Audit Frequency & Audit Duration
- ✓ Grading Nonconformances & Audit Response Timing

MDSAP – What is it?

Conceived by the International Medical Device Regulators Forum (IMDRF) at its inaugural meeting in Singapore in 2012, the IMDRF identified a working group to develop documents & implement the program. It is a global approach to auditing and monitoring the manufacturing of medical devices to improve their safety and oversight on an international scale.

Current MDSAP Participating Geographies:

- United States – U.S. Food and Drug Administration
- Canada – Health Canada
- Australia – Therapeutic Goods Administration of Australia (TGA)
- Brazil – Agência Nacional de Vigilância Sanitária (ANVISA)
- Japan – Ministry of Health, Labor & Welfare (MHLW)/ Pharmaceuticals and Medical Devices Agency (PMDA)

Indirect Participants:

- 'Affiliates': Russian Federation, Mexico, Asian Harmonization Working Party (AHWP)
- 'Official Observer': European Union and World Health Organization (WHO)

MDSAP – What is it?

MDSAP has several main goals:

- *Allow more timely execution of the routine Quality Systems audits*
  - *Some Medical Device manufactures had well over 2-3 years between FDA, TGA, ANVISA MHLW, Health Canada inspections. Other Medical Device manufactures have never had a visit from these Regulators*
- *Reduce the total number of audits to an organization, by leveraging of regulatory resources, globally, thus helping to minimize medical device manufacturing disruptions due to multiple regulatory audits*
- *Ultimately, to develop a standard set of requirements documents for auditing organizations performing regulatory audits of medical device manufacturers' Quality Management Systems*
- *An attempt to accelerate international medical device regulatory harmonization/ convergence*

AOs conduct MDSAP audits following the Companion Document (e.g. MDSAP AU G0002.1.004) to satisfy the requirements of **all** of the medical device regulatory authorities currently participating in the MDSAP program (*i.e. United States, Canada, Brazil, Japan & Australia*).

MDSAP – What it is Not

- The Medical Device Single Audit Program (MDSAP) will not replace a directed or '**For Cause**' audit for any of the five MDSAP geographies (United States, Canada, Brazil, Japan & Australia)

- The Medical Device Single Audit Program (MDSAP) is generally accepted for low and medium risk devices (e.g. US FDA Class I & Class II devices), however, it is not currently accepted for Biologics, Class III, Combination products, etc., solely, without additional supplemental inspections and/or activities, as determined by the geography

- MDSAP is not a Quality Program. It is a global approach to auditing and monitoring the manufacturing of medical devices to improve their safety and oversight on an international scale.

MDSAP – US FDA Website Note

United States: U.S. Food and Drug Administration's Center for Devices and Radiological Health

- FDA will accept the MDSAP audit reports as a substitute for FDA routine inspections. Inspections conducted "For Cause" or "Compliance Follow-up" by FDA will not be affected by this program. Moreover, this MDSAP program would not apply to any necessary pre-approval or post approval inspections for Premarket Approval (PMA) applications or to decisions under section 513(f)(5) of the Act (21 U.S.C. 360c(f)(5)) concerning the classification of a device.

MDSAP – History

2012	• The IMDRF assigns a new Working Group to develop the MDSAP, 2012.
2014	• The MDSAP pilot was launched on January 1, 2014. Includes US, Brazil, Canada and Australia.
2015	• Health Canada notice dated January 16, 2015: HC intends to implement MDSAP as the sole mechanism for manufacturers to demonstrate compliance with the quality management system requirements.
2015	• Japan joins MDSAP, June 23rd, 2015.
2016	• Auditing Organizations completing required witness audits. Pilot winding down, concludes 31 December 2016.
2017	• MDSAP becomes official (no longer a pilot). 13 AOs now eligible to perform MDSAP audits (23-Aug-17).
2018	• Health Canada will accept certificates issued under both CMDCAS and MDSAP (01-Jan-17 to 31-Dec-18).
2019	• MDSAP replaces the Canadian Medical Devices Conformity Assessment System (CMDCAS) program. As of January 1, 2019, only MDSAP certificates will be accepted.

Who Can Conduct MDSAP Audits?

- 14 organizations are pursuing authorization
- 13 are authorized to conduct MDSAP audits (as of 23-Aug-17)

MDSAP – Companion Document

The Companion Document provides the detailed requirements & specific sequence followed, when performing MDSAP Audits

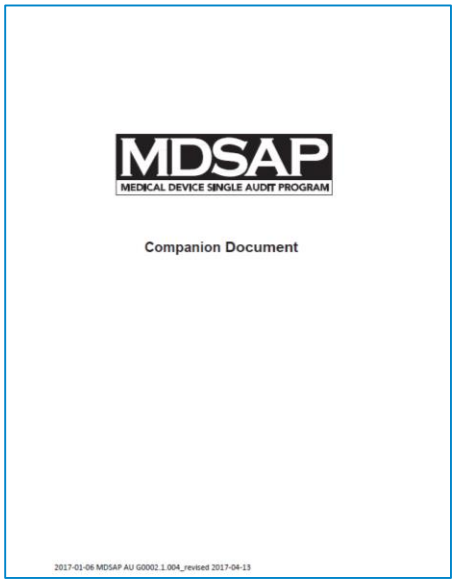
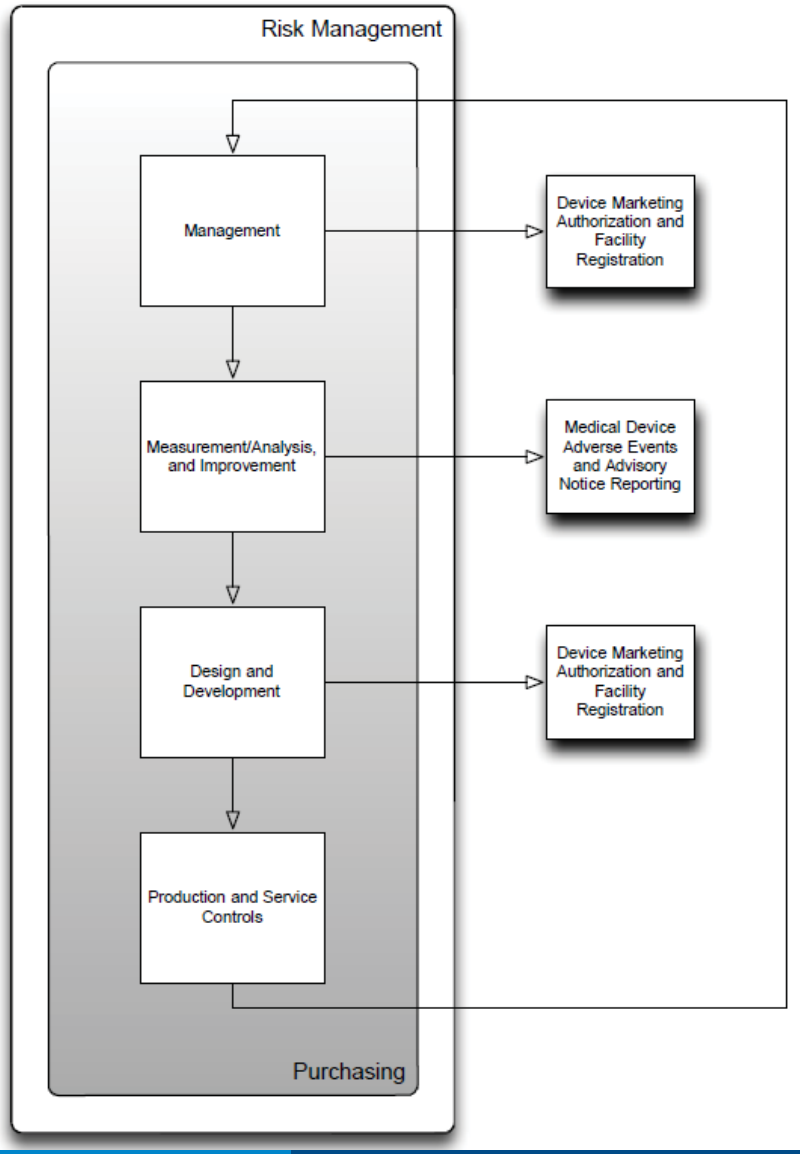


Table of Contents

MDSAP – How is it Implemented

- MDSAP audits are process based; focusing on seven (7) defined chapters, includes a defined method for linking these processes.
- Audits do not deviate from the chapter order (i.e. Chapter 1, Chapter 2, etc.).
- The audit model, inspired by the FDA's Quality System Inspection Technique document, is based on a "top-down" auditing approach
- Long term - reports DB will be created to track/ trend nonconformities



MDSAP – Frequency of Audits

Frequency is similar to that of the current Notified Body process driven by the European Union, and is based on a three (3) year audit cycle. There are two (2) initial certification audits, followed by annual 'surveillance audits', and the 'recertification audit', each third year (full QMS audit).

The initial audits consists of a Stage I and a Stage II audit:

- Stage I – The first audit consists of a documentation review and the evaluation of the readiness of the manufacturer to undergo a Stage 2 audit (*may be performed on or off-site*).
- Stage II – Determine if all applicable requirements from the five geographies have been effectively established/ implemented, and are being maintained.

MDSAP – Special Audits (Short Notice)

Special audits are unique audits, in that they are not part of the planned audit cycle. These audits will likely only be used when necessary, and will focus on specific elements of the QMS (e.g. CAPA, Design & Development, etc.), at the request of any of the geographies, based on poor performance, potentially significant complaints or for other reasons (much like 'For Cause' inspections).

Short-notice audits may be conducted at the request of any participating regulatory authority, or at the discretion of the auditing organization.

Other Examples:

- New or modified products made between regularly scheduled audits.
- A shortfall in oversight by the MDSAP recognized auditing organization (e.g. due to insufficient audit time, inappropriate audit team make-up, etc.).
- Follow up on specific post-market issues (e.g. potentially significant complaints).
- Follow up on significant findings from the previous MDSAP audit.

MDSAP –Audits Duration

Audit Duration is determined using MDSAP procedure AU P0008.005. An Audit Duration Calculation Form (MDSAP AU F0008.2.002) will be completed:

- The form utilizes formulas to determine the duration for each MDSAP Chapter/ Task and includes a tab for instructions for use & two (2) tabs for duration calculations:
  - Audit Duration Calculation #1 – Used for Witness Audits, by witnesses (e.g. United States, Canada, Brazil, Japan & Australia)
  - Audit Duration Calculation #2 – Used by the Auditing Organization to determine audit duration, in the development of the Audit Plan & Schedule

Note: *The formulas within the form are locked down & safeguarded from unauthorized changes.*

MDSAP – Grading Nonconformances

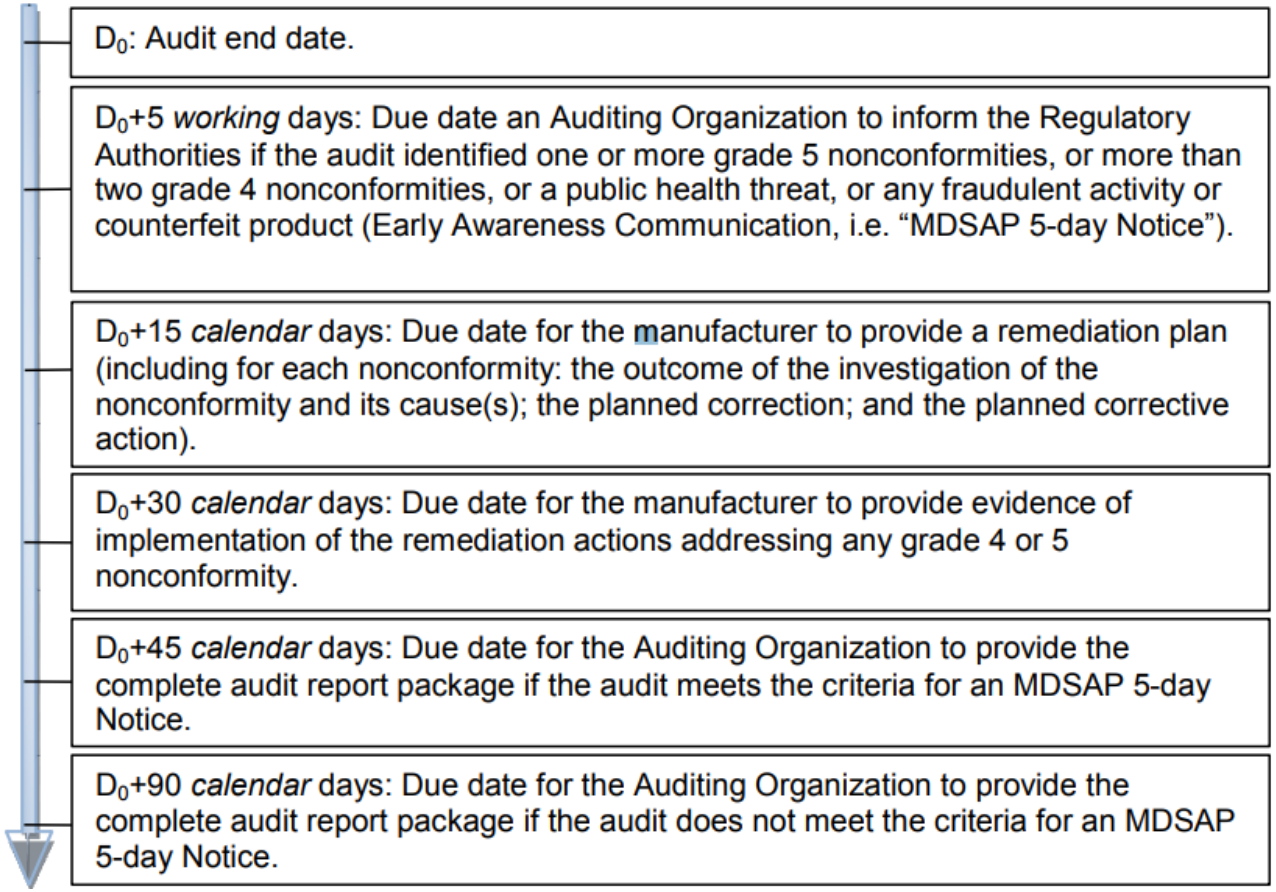
- Major and minor classification of nonconformities commonly used does not provide enough detail. Therefore the terms major and minor nonconformity are not defined nor utilized within the MDSAP. The intent of this new grading system for regulatory purposes is to support the exchange of audit results that go beyond the binary concept of major and minor to a 5 level grading system of nonconformities.

- The five (5) MDSAP regulatory authorities can determine how to use the audit information provided in the report. Regulatory authorities will also consider other data sources in addition to the outcome of the regulatory audits such as product evaluations, recalls, vigilance reports, etc. for regulatory oversight.

- Grade 4 & 5 nonconformances may trigger an unannounced audit within 3-6 months for follow up.

MDSAP – NC Responses

- Audited manufacturer will be responsible for timely development and implementation of action plans to address non-conformities identified during audits MDSAP AU P0027.004 Post Audit Activities and Timeline Policy.

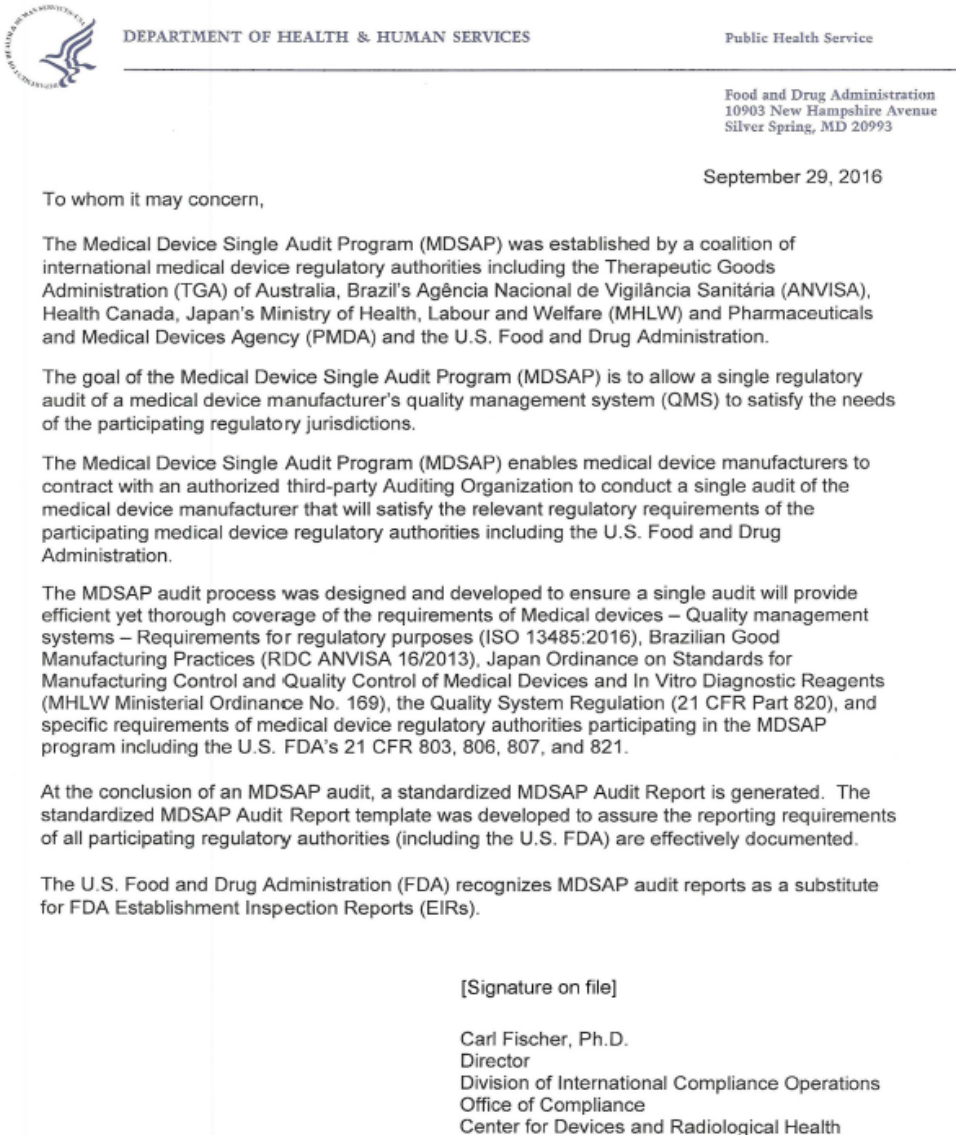


MEDICAL DEVICE SINGLE AUDIT PROGRAM (MDSAP)

- Some of the Benefits and Lessons Learned - of the new Program

MDSAP Certification is Equivalent

- Various geographies would not accept a verbal commitment of MDSAP equivalency.
- US FDA posted to FDA.gov to communicate that MDSAP certification would be equivalent to a successful outcome of a FDA Inspection (i.e. replace an Establishment Inspection Report (EIR))



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

September 29, 2016

To whom it may concern,

The Medical Device Single Audit Program (MDSAP) was established by a coalition of international medical device regulatory authorities including the Therapeutic Goods Administration (TGA) of Australia, Brazil's Agência Nacional de Vigilância Sanitária (ANVISA), Health Canada, Japan's Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) and the U.S. Food and Drug Administration.

The goal of the Medical Device Single Audit Program (MDSAP) is to allow a single regulatory audit of a medical device manufacturer's quality management system (QMS) to satisfy the needs of the participating regulatory jurisdictions.

The Medical Device Single Audit Program (MDSAP) enables medical device manufacturers to contract with an authorized third-party Auditing Organization to conduct a single audit of the medical device manufacturer that will satisfy the relevant regulatory requirements of the participating medical device regulatory authorities including the U.S. Food and Drug Administration.

The MDSAP audit process was designed and developed to ensure a single audit will provide efficient yet thorough coverage of the requirements of Medical devices – Quality management systems – Requirements for regulatory purposes (ISO 13485:2016), Brazilian Good Manufacturing Practices (RDC ANVISA 16/2013), Japan Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and In Vitro Diagnostic Reagents (MHLW Ministerial Ordinance No. 169), the Quality System Regulation (21 CFR Part 820), and specific requirements of medical device regulatory authorities participating in the MDSAP program including the U.S. FDA's 21 CFR 803, 806, 807, and 821.

At the conclusion of an MDSAP audit, a standardized MDSAP Audit Report is generated. The standardized MDSAP Audit Report template was developed to assure the reporting requirements of all participating regulatory authorities (including the U.S. FDA) are effectively documented.

The U.S. Food and Drug Administration (FDA) recognizes MDSAP audit reports as a substitute for FDA Establishment Inspection Reports (EIRs).

[Signature on file]

Carl Fischer, Ph.D.
Director
Division of International Compliance Operations
Office of Compliance
Center for Devices and Radiological Health

MDSAP Benefits & Lessons Learned

- Medical Device Manufactures may obtain all the procedures and documentation at no cost (www.fda.gov)
- Ability for any Medical Device Manufacturer to fully understand the audit model, path and more importantly the specific audit focus, as it relates to which products and processes will likely be reviewed during the MDSAP audit.
- MDSAP Audits are very structured and do not deviate from the Chapter order, allowing for a significant amount of pre-staged procedures, records, etc.
- Companion Document is detailed and clearly written as compared to some regulations and standards (*easy to understand/ follow*)

MDSAP Benefits & Lessons Learned

- MDSAP Certificate = FDA Establishment Inspection Report (EIR)
- Internal Audit programs can relatively easily be modeled after the MDSAP process
- If a medical device manufacturer is currently shipping to the five (5) MDSAP geographies, then it is likely the organization is already complying with the MDSAP regulations – limiting the scope of the change to the new MDSAP process and methodology vs. the content of the regulations
- It is beneficial to complete the Stage I audit on-site, this allows for more interaction, allowing for limited questions to the AO, better understanding of all deliverables

MDSAP Benefits & Lessons Learned

- Typically results are favorable, when sites perform a thorough self-assessment (gap-assessment), with sufficient time to react to any/ all identified issues and concerns
- A very detailed FAQ with ~ 100 questions/ answers is available on-line
- Use caution when retrieving MDSAP documents off the Web. Multiple versions are available - by design (aligned with ISO13485:2003 and a different version aligned with ISO13485:2016. There are currently 2 Companion Documents - be mindful of the alignment to 13485:2003 or 2016
- Consider developing a Charter for your organization (avoid the lone firefighter methodology)

MDSAP Benefits & Lessons Learned

- Additional scrutiny on areas not as often in the forefront of Quality Management Systems audits (e.g. Regulatory Affairs)
- Additional scrutiny to the process of evaluation and consideration for inclusion onto an organizations list of Suppliers (e.g. Translation Service providers, Regulatory Partners for the five geographies, Internal or External, Australian Sponsor, Agents, etc.)
- Additional scrutiny for Management Representatives and the Internal Audit core (*must have objective evidence of training to the five geographies regulations*)
- D & B Number - while those involved in Purchasing/ Supplier Controls will be used to obtaining any businesses D & B number (and associated information), this will be new to some. Why D&B, What is D&B

MDSAP Benefits & Lessons Learned

- Record/ Procedure retrieval timing may need to be accelerated. Nonconformances have been written for exceeding the allotted time on the schedule for a Task.
- To meet the requirements described in the MDSAP AU P0029 Initial Manufacturer Audit and MDSAP Manufacturer Withdrawal Notification Procedure, medical device manufacturers will have to submit a D-U-N-S number(s) which may take time to obtain

The site-specific D-U-N-S number is a widely recognized business identification tool and serves as a useful resource for MDSAP in identifying and verifying certain business information submitted by a user.

MEDICAL DEVICE SINGLE AUDIT PROGRAM (MDSAP)

- Challenges of MDSAP

MDSAP Challenges

- The MDSAP 5 day notice. If there is a grade 5 nonconformance, or two or more grade 4 nonconformances, all five geographies will be notified by the AO within 5 days.
- It may be cost prohibitive for some of the smaller Registrars and Notified Bodies to pursue MDSAP Certification as an AO
- Limiting therapies in specific geographies. The cost of transitioning to MDSAP may be a factor to smaller medical device manufacturers that ship very limited products into Canada, and may choose not pursue MDSAP

MDSAP Challenges

- Some organizations may misidentify the program as a Quality Initiative, diminishing the chances of success in obtaining MDSAP certification
- Grade 4 & 5 nonconformances trigger an unannounced audit, further burdening the organization
- Rapid exposure across the 5 geographies of nonconformances – if significant issues arise, potentially jeopardizing certificates/ registration - if egregious
- Auditing Organizations for MDSAP are much more disciplined to the schedule and MDSAP Task timing. Nonconformances have been identified and included in the report, if the allotted time is exceeded
- Witness Audits typically result in higher number of nonconformances

MEDICAL DEVICE SINGLE AUDIT PROGRAM (MDSAP)

- What's on the Horizon

MDSAP – What's on the Horizon

- CMDCAS going into sundown, replaced by MDSAP
- Potentially continued global Regulatory Convergence

MRA: FDA now recognizes EU Inspectorates in 8 of 28 countries

With 1 November, the EU-FDA Mutual Recognition Agreement (MRA) of GMP inspections of human manufacturers came into operation. This starts with the recognition of the FDA and the first 8 EU Member States. In a press release, the U.S. Food and Drug Administration states that the agency "will recognize eight European drug regulatory authorities as capable of conducting inspections of manufacturing facilities that meet FDA requirements": Austria, Croatia, France, Italy, Malta, Spain, Sweden, and United Kingdom...

Link: FDA now recognizes EU Inspectorates in 8 of 28 countries

MDSAP References & Links

http://www.imdrf.org/

•MDSAP Policies, Procedures, Templates and Forms
(Policies, procedures and other related documents supporting MDSAP)

•MDSAP Audit Procedures and Forms
(Procedures and forms supporting Auditing Organization Audits)

•MDSAP Assessment Procedures and Forms
(Procedures and forms supporting Regulatory Authority assessments)

•MDSAP QMS Procedures and Forms
(Procedures and forms supporting the MDSAP Quality Management System)

•MDSAP QMS Concern Resolution Report Form (PDF - 702KB)

•IMDRF/MDSAP WG and GHTF Documents
(IMDRF MDSAP WG and GHTF documents supporting the program)

•MDSAP International Regulations [English] (Australia, Brazil, Canada, Japan, and USA)

THANK YOU

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