Manufacturing Operations under Multiple Regulatory Requirements

Industry Perspective

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Quality Systems Advisor

Abbott Vascular

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Overview

- Background/History
  - Multiple requirements
  - Audit history
- Current Experience
  - Quality system organization
  - Employee training
- Future Plans/Recommendations

History with Multiple Systems

- Under FDA regulations, approvals and inspections since 1982
- Received ISO 9001 approval for California facilities in 1994 (BSi)
- Received ISO 9002 approval for Clonmel, Ireland facility in 1999 (BSi)
- Transitioned to ISO 13485:2003 in (2004 – 2006)
  Included Canadian CMDCAS

Various agency and certification body visits

- Australia TGA
- Hungary ORKI
- Japan PMDA
- Turkey TSE
- UK MDA (now MHRA)
- California FDB
- US FDA

- BSi
- MEDCERT
- KEMA
- TUV

Current Experience

Our path to certification

Lessons from our ISO13485:2003 upgrade

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Lessons from transition to ISO13485:2003

- Abbott Vascular Corporate Strategy
- Divisional execution
- Organizational resources
- Role of the notified body
- Early successes
- Current status
- Next Steps

Corporate Strategy

- Agreement on ISO13485:2003 and ISO 9000:2000 made in 2000
- Quality system design to parallel ISO 13485 in 2001-2002
- Agreement on eight key processes for all sites
  - Management Controls, CAPA, Design Control, Production and Process Controls, Document and Data Control, Product Approval, Materials Control, Post-Market Support
- Sub-processes and execution differ at the different sites
- Common training in 2003
- Core working group across all sites and divisions

Divisional execution

- Minor revisions to Quality System Manual
- Format changes for key process SOPs
- Few sub-process changes made
- Training of audit groups
- Training of process and sub-process owners
- Strategy made with BSi

Organizational resources

- Two quality system engineers – dedicated 50% for one year
- One Quality Manager – coordinating across different sites and divisions 20% for one year
- Conversion of non-quality process owners
- Training for employee base to 13485 completed as part of normal annual Quality System Training

The Role of the Notified Body

- Interaction began in late 2002
- Updates with each assessment visit (twice yearly)
- Used BSI's interview guides and turtle diagram
- June 2004: "low-risk interviews" with new process owners
- Agreement on transition: all at once
- Important: Certification is complete but open dialogue continues!

Early Successes

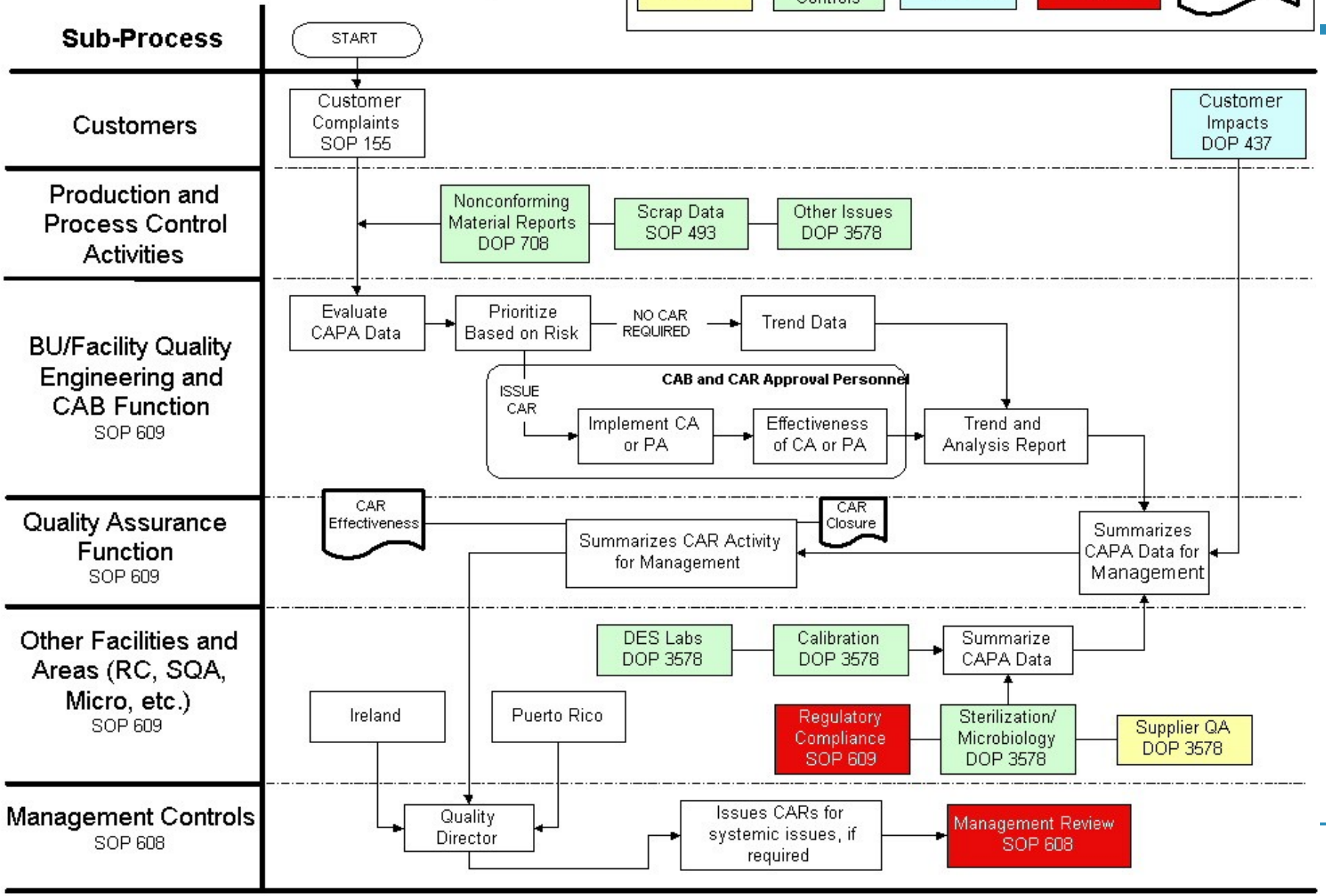
- Not a complete re-write for QSM
- Preparation for process approach revealed some gaps - links
- Acceptance of ownership by non-quality directors
- Communication with Notified Body – no surprises
- Process owners with process flow charts and metrics posted in their work areas

Typical Process Flow

Simplified flow from Quality Manual

High Level

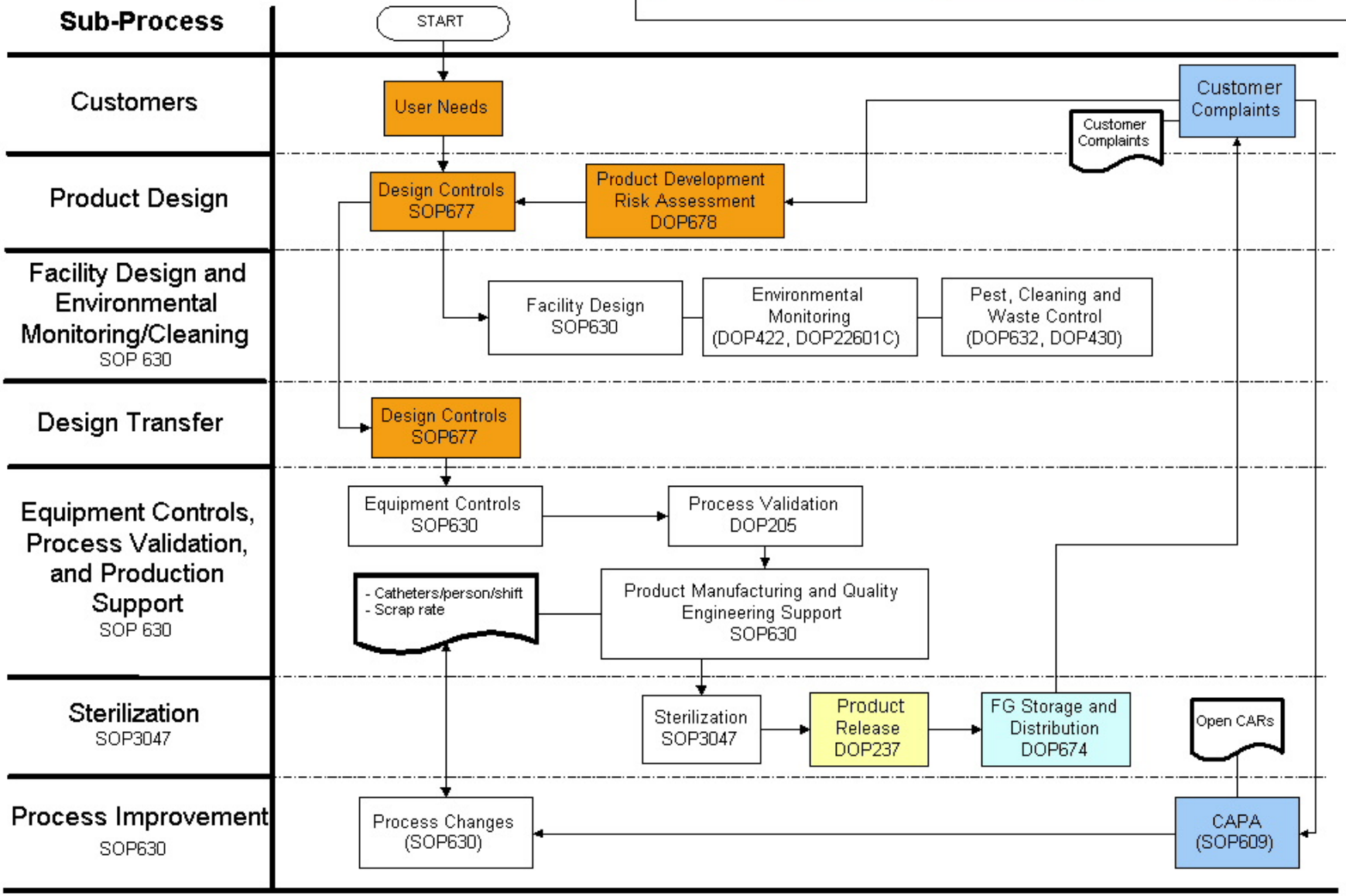
Key Process: CAPA
Process Owner: Connie Speck



Key Process: Production and Process Controls
Process Owner: Dennis Lint

Related Key Processes:

- Design Controls
- CAPA
- Material Controls
- Post-Market Support
- Metric



Auditing Tool

- External Audits
  - Visual description of processes
  - Early commitment by Abbott years ago to encourage cross recognition of ISO 13485 audits
- Internal Audits
  - Check basic order
  - Check linkages
  - Check metrics

ISO13485:2003 Successes

- Assessment combined with upgrade Dec 1 – 10, 2004
- Passed with recommendation for certification
- Certificate received mid-January 2005
- Clonmel, Ireland audited Feb 2005
- Three more sites Q2 to Q4 2005

Unexpected Success
Kano Model: Quality Delighters

- AV – FDA visit
  - Full QSIT – 7 days
  - Process approached used to describe CAPA, Management Controls, Materials Controls, Process Controls
  - Genuine ownership displayed
  - Process owners *were* prepared
  - No 483 issued
- Guidant, (Johnson & Johnson), and Abbott acquisition
  - Key process framework used for quality system

Future Steps: Where do we go from here?

- Map out sub-processes
- Continued improvement of our quality systems manual
- Monitor, evaluate and update metrics
- Add new major processes
  - ISO 14001 EMS – environmental group used similar approach
  - Information Systems – recently added
  - Laboratory Controls

2008 Quality Systems Training

How to train 5000+ employees to multiple requirements

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Abbott Quality System Orientation

Imagine…

You or someone you love – a child, parent, spouse, close relative or friend – is using one of Abbott's products to treat a health condition.

What are your expectations of the products being used? Do you demand certain characteristics in a health care solution to meet these medical needs?

Minimally, you would want these products to be…

High Quality, Safe and Effective

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AHWP
ASIAN HARMONIZATION WORKING PARTY

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Excerpt of AV Quality System Training

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Abbott Vascular Quality Systems Manual

FOREWORD

Quality Policy

Quality: "Built as if intended for my family", sums up Abbott Vascular's policy on Quality.

Abbott Vascular provides innovative products that improve patients' lives. We are dedicated to meeting or exceeding our customers' expectations by providing the highest quality products and services. Abbott Vascular will meet all applicable regulations, standards, and laws in the design, manufacture, and sale of its products. We will accomplish this policy through continuous improvement in our operations, ongoing training of our personnel, and a complete and thorough understanding and communication of all applicable requirements to Abbott Vascular personnel.

Excerpt of AV Quality System Training

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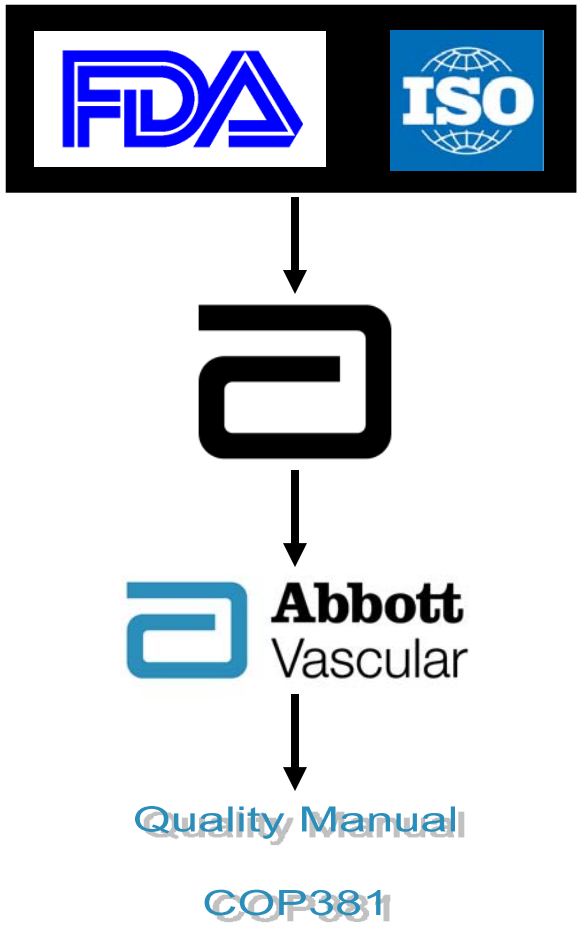
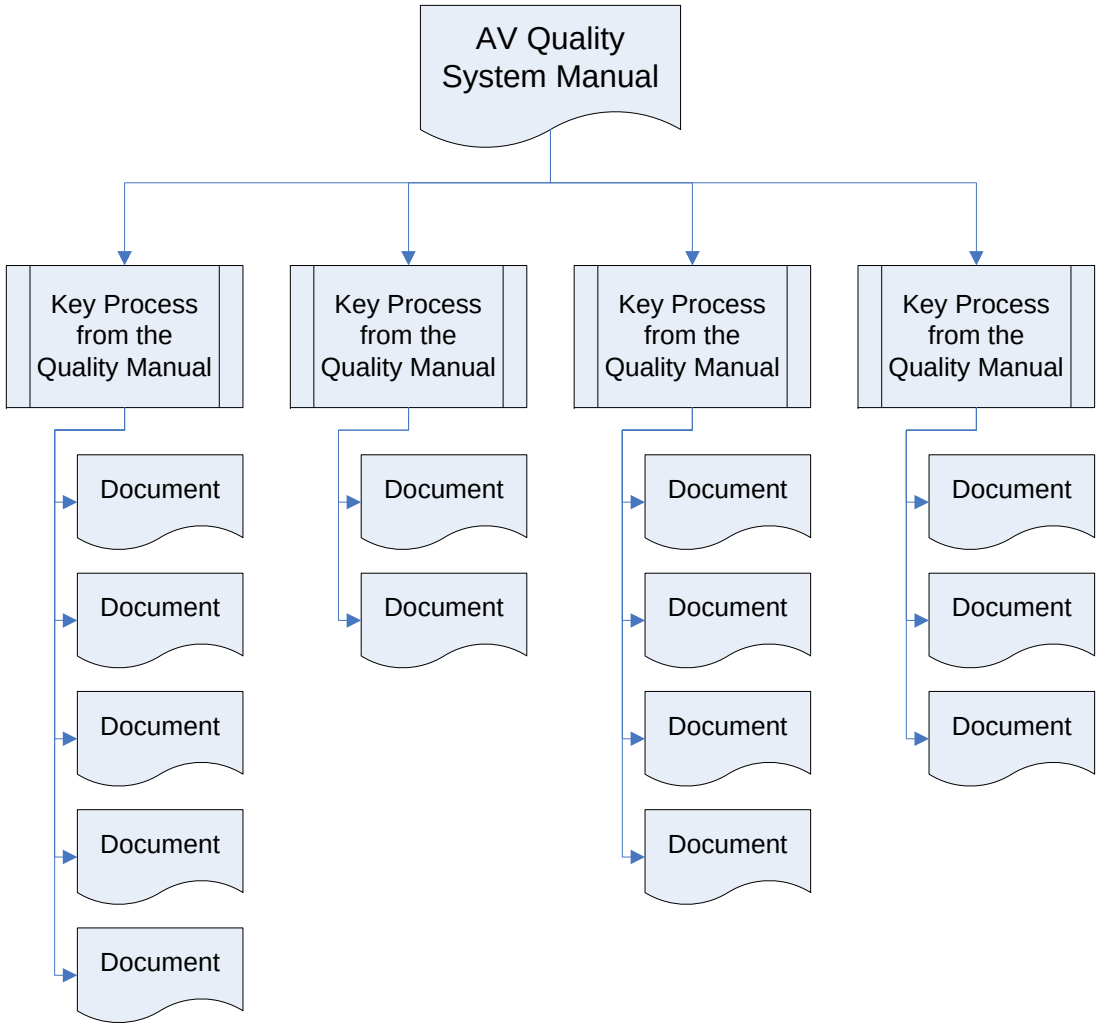
Quality System Structure





Our Key Processes and Owners

Our Business has identified nine key processes and the corresponding process owners for affected sites

Site: / Key Process	Process Owner		
	California (excluding Redwood City)	**Clonmel**	**Puerto Rico**
Management Controls	Director, Regulatory Compliance	Director, Quality Assurance and Regulatory Compliance	Manager, Quality Assurance and Regulatory Compliance
Production and Process Controls	Director, Operations	Manager, Manufacturing Engineering	Director, Operations
Corrective and Preventive Action (CAPA)	Director, Quality Systems	Manager, Quality Assurance and Compliance	Manager, Quality Assurance and Regulatory Compliance
Product Approval	Director, Regulatory Affairs	N/A	N/A
Change Management and Document Control	Director, Quality Services	Manager, Regulatory Compliance	Manager, Quality Assurance and Regulatory Compliance
Material Controls	Director, Engineering Services	Manager, Supply Chain	Director, Operations
Design Controls	Director, Research and Development	N/A	N/A
Post Market Support	Director, Customer Service	N/A	N/A
Information Technology (IT)	Director, IT	Director, IT (TEM)	Director, IT (TEM)

- Each Process has defined metrics for the purpose of measuring the effectiveness of that system

Process Approach to Quality Management

- Any activity that receives inputs and converts them to outputs can be considered a process
- For an organization to function effectively, it has to identify and manage numerous linked processes
- Often the output from one process directly forms the input to the next

ISO 13485:2003,

Medical devices –

Quality management systems-

Requirements for regulatory purposes

What is a Process? (ISO13485)

Details of resources used - machines, materials, equipment.

Details of personnel involved- required skills and competence criteria, safety equipment etc.

What?

Who?

Input

PROCESS

Output

How?

Key Criteria?

Linked processes and controls, support processes, procedures and methods.

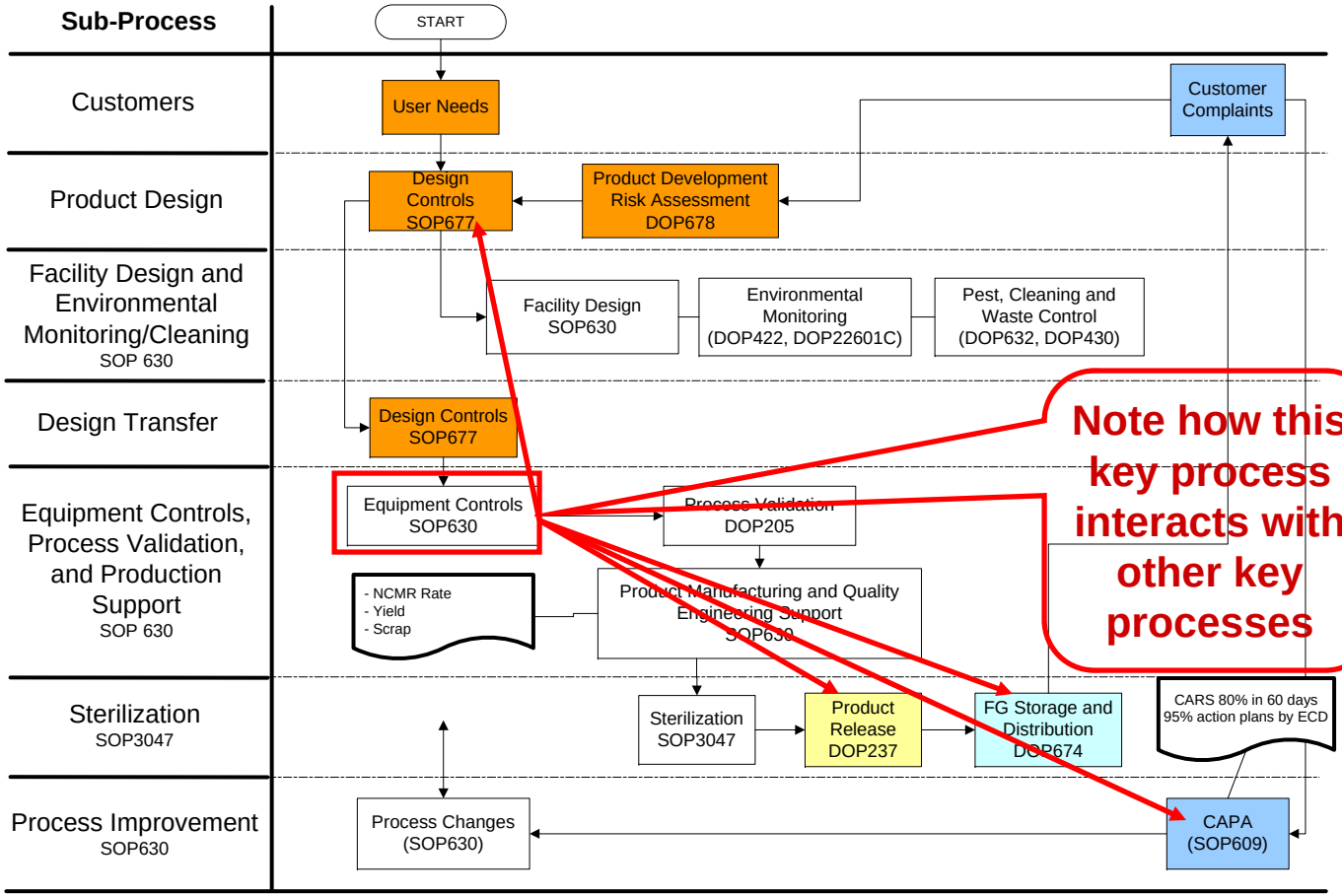
Measures of the process effectiveness, targets and results.

Production and Process Flow Map

- Cross functional interaction with other processes

In this example Production & Process Controls interact with:

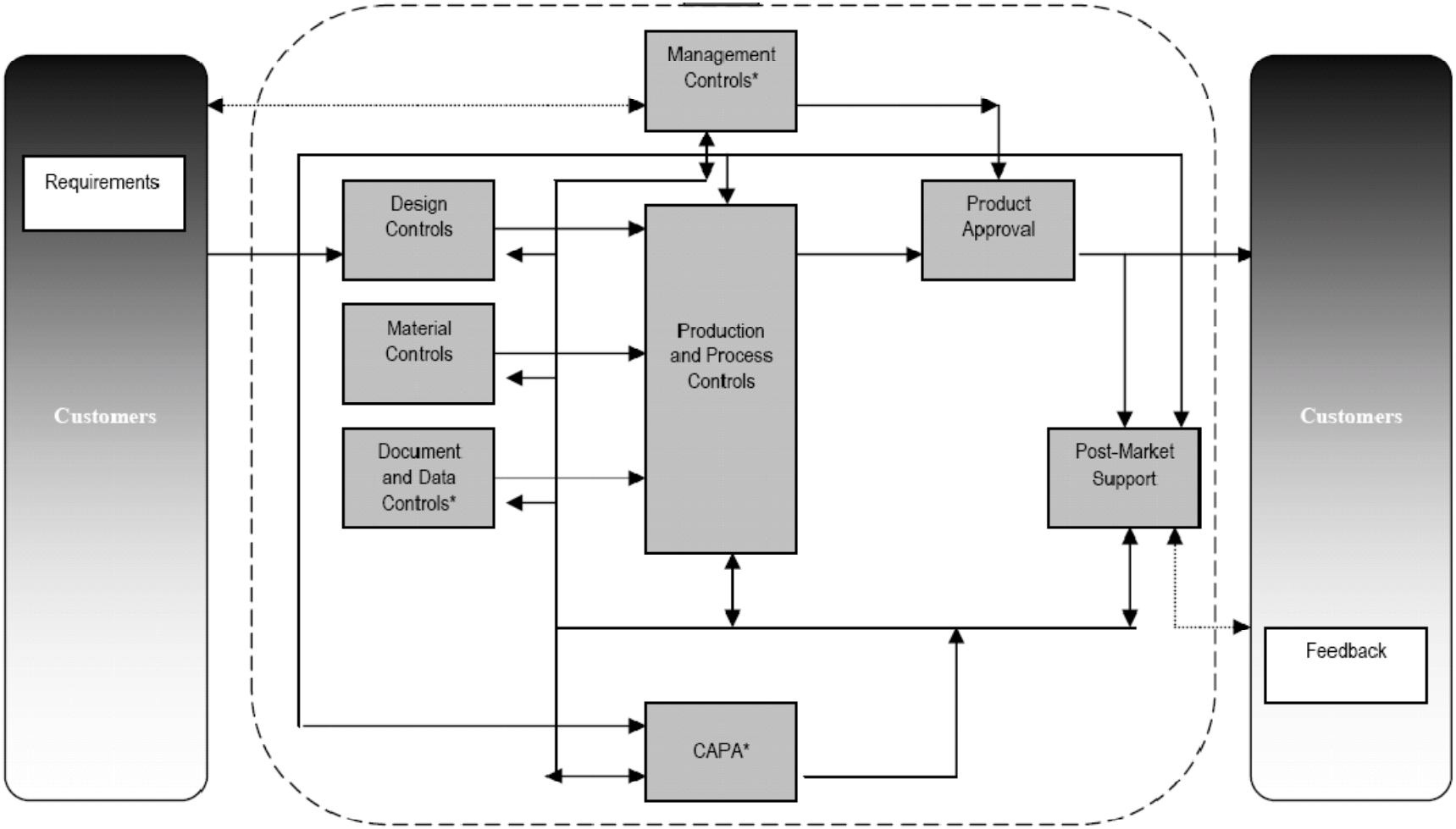
- Design Controls
- Material Controls
- CAPA
- Post-Market Support



Process Owner

- The process owner is responsible for reviewing and approving any corrections, updates, or improvements to his/her process
- The process owner maintains, and reports on metrics and goals for his/her process
- Metrics and goals may change over time at the discretion of the process owner as approved by senior management
- Metrics reported to senior management during formal management review
- Receives organized training from Quality Systems group

How does your function link with the rest of the Quality System? Refer to COP 381



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The employee's guide to meeting regulations

Excerpts from employee QSM training

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Abbott Vascular CT Quality Systems Manual - Overview, Continued

References

21 CFR Part 7(c) - Recalls (Including Product Corrections) - Guidelines on Policy, Procedures, and Industry Responsibilities
21 CFR - Part 11: Electronic Records: Electronic Signatures
21 CFR – Part 58 – Good Laboratory Practices for Nonclinical Laboratory Studies
21 CFR - Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs
21 CFR Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals
21 CFR - Part 312. Investigational new drug application
21 CFR - Part 801: Labeling, Regulatory Requirements for Medical Devices
21 CFR Part 803: Medical Device Reporting (MDR)
21 CFR Part 807: Manufacturers and Distributors of Medical Devices
21 CFR - Part 810: Medical Device Recall Authority
21 CFR - Part 812. Investigational device exemptions
21 CFR - Part 814: Premarket Approval of Medical Devices
21 CFR - Part 820: 1996 FDA Quality System Regulation
21 CFR – Part 822: Post Market Surveillance
Pre-Market Approval; Investigational Device Exemption and Pre-Market Notification Guidelines
ICH Q7A GMP Guidance for Active Pharmaceutical Ingredients
Federal Food, Drug and Cosmetic Act
Safe Medical Device Act, 1990 and 1992
ISO 13485: 2003 Medical Devices-Quality Management Systems-Requirements for Regulatory Purposes
ISO 14971 – Medical Devices-Application of Risk Management to Medical Devices
ISO 14155-1,-2 – Clinical Investigation of Medical Devices-for Human Subjects
EN 14299:2004 Non active surgical implants – Particular requirements for cardiac and vascular implants – Specific requirements for arterial stents
BS 5295: Environmental Cleanliness in Enclosed Spaces
MEDDEV 2.12/1, April 2001, Guidelines on a Medical Device Vigilance System
MEDDEV 2.1/3, Guidelines relating to the demarcation between: Directive 90/385/EEC on Active Implantable Medical Devices; Directive 93/42/EEC on Medical Devices and Directive 65/65/EEC relating to medicinal products and related directives (rev.5)
Medical Device Directive (MDD) 93/42/EEC, 14 June 1993

We just have to follow these regulations

Using COP 381: Example 1 – Table of Contents

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Contents

Introduction In this section, you will find a listing of the various requirements sections and the pages where they can be found.

Next, look up the table of contents

Using COP 381: Example 1 – Look up a section

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SECTION 6

Document Control

Doc Control

Look up section for that system

Policy

Abbott Vascular CT will have written procedures to ensure control of the creation, approval, maintenance, distribution, revision, inactivation of and deviation from Quality System documents, and to ensure that an assessment of the impact of changes that have the potential to affect product safety and effectiveness is considered and documented. The Document Control department is responsible for monitoring, distributing, controlling, and maintaining procedures and documents within Abbott Vascular CT. To maintain control of documents and changes, the latest and/or correct revision status of documents will be available to persons performing activities.

Where electronic signatures or hand written signatures executed to electronic records are used to fulfill requirements of the Quality System, Abbott Vascular CT certifies that these electronic signatures are the legally binding equivalent of traditional hand written signatures.

In addition to Abbott Vascular CT's Quality System documents, relevant external documents such as federal and international standards and specifications are controlled by the Document Control department's External Document System.

Governing Specifications

FDA Quality System Regulation 1996: 21 CFR § 820.40
21 CFR Part 11: Electronic Records: Electronic Signatures
FDA Current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals 1996: 21 CFR § 211.22, 211.100
Medical Devices-Quality Management Systems-Requirements for Regulatory Purposes ISO 13485 § 4.2.3
GMP Guidance for Active Pharmaceutical Ingredients ICH Q7A §6.1, 13

Regs. For Doc.Control

Using COP 381: Example 1 – Doc. Control cont'd.

Procedures (continued)

Area	Requirements	Procedures
Change Control	• Changes and modifications to documents must be controlled. Changes to documents will receive at least the same functional level of scrutiny by the same organization as the original document unless specifically designated otherwise, and shall include the approval date and the date the change becomes effective. • People who review and approve documents will have access to the appropriate change information so as to make the review meaningful. • Changes to documents will be identified to make their review easier, e.g., by circulating "red lined" documents or identifying changes in the margins. • Changes will be qualified by stating the reason for the change and the justification for the change, including process validation information, where indicated. • Approved changes will be communicated to affected personnel. • Master Lists of Quality System and External documents will be maintained so that the current revision can always be determined.	3000 570-VI
Obsolete Documents	• Obsolete documents will be electronically inaccessible when new revisions are released, so that an incorrect revision cannot be mistakenly used.	3000 570-VI
Electronic Signatures	• Before the use of Electronic Signatures written certification will be submitted to FDA indicating that such signatures are the legally binding equivalent of traditional hand written signatures. • Electronic signatures shall employ appropriate controls to ensure that they can only be used by the genuine owner.	638

Find other procedures related to that system

OP Titles

SOP 638 – Software Controls
SOP 3000 – Abbott Vascular ViewPoint Change Order Process
DOP 570-VI - Change Order Procedure
DOP 667 - Document Format

Looking for other requirements in our Quality Manual? Check out Appendix A of COP381

FICCI
Federation of Indian Chambers of Commerce and Industry

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Appendix A – FDA, ISO, and ICH Section Cross Reference

COP 381 Section	*QSR(1)*	*13485(2)*	*cGMP(3)*	*ICH(4)*
1	820.5 Quality System	4.1, 4.2.1, 4.2.2, 5.3, 5.4.2, 7.1	210.1, 211.22, 211.42c	2.1
2	820.20 Management Responsibility	5.1-5.6, 6.1	211.22, 211.180f	2.1-2.3, 2.5
3	820.22 Quality Audit	8.2.2, 8.2.3	211.22	2.2, 2.4
4	820.25 Personnel; training	6.2	211.25	3.1, 3.3
5	820.30 Design Control	5.2, 7.1- 7.3, 8.2.1	211.94, 211.137, 211.166	6.1, 8.3, 12.1, 12.5, 19.1, 19.3, 19.6, 19.7, 19.9
6	820.40 Document Controls	4.2.3	211.22, 211.100	6.1, 13
7, 8	820.50 Purchasing Controls	7.2, 7.4, 7.5.4	211.34, 211.80, 211.82, 211.84	3.3, 7.1, 16, 17
9	820.60, 820.65 ID and Traceability	7.5.3	211.80, 211.84, 211.101, 211.105, 211.122, 211.130, 211.142, 211.184, 211.186, 211.188, 211.192, 211.196	6.4-6.7, 7.2, 7.3

er requirements in our Quality M[illegible]k out Appendix A of COP381

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QSR: FDA Quality System Regulation

cGMP: FDA current Good Manufacturing Practice

13485: International Quality System Regulation for Medical Devices

ICH: International Committee on Harmonization GMP Guidance for Active Pharm. Ingredients

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Appendix [illegible] – FDA, ISO, and ICH Section C[illegible]

COP 381 Section	*QSR(1)*	*13485(2)*	*cGMP(3)*	*ICH(4)*
1	820.5 Quality System	4 [illegible] 2.1, 4.2.2, [illegible] 2, 7.1	210.1, 211.22, 211.42c	[illegible]
2	820.20 Management Responsibility	[illegible] 1	211.22, 211.180f	
			[illegible].22	
			[illegible].25	
			[illegible].94, 211.137, 211.166	
6	820.40 Document Controls	4.2.3	211.22, 211.100	6.1, 13
7, 8	820.50 Purchasing Controls	7.2, 7.4, 7.5.4	211.34, 211.80, 211.82, 211.84	3.3, 7.1, 16, 17
9	820.60, 820.65 ID and Traceability	7.5.3	211.80, 211.84, 211.101, 211.105, 211.122, 211.130, 211.142, 211.184, 211.186, 211.188, 211.192, 211.196	6.4-6.7, 7.2, 7.3

Audits and the Quality System

- Regular auditing of our processes and procedures is an important element of our quality system
- Internal and External audits:
  - FDA audits pre- and post-approval
  - MedCert and BSi (for Europe and other international markets)
    - Results often very similar for FDA and ISO 13485 audits
  - Abbott corporate audit
  - On-going internal audits
- Organizational expectations for all audit activities

Concluding remarks

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Future Plans/Recommendations

- Abbott Vascular – over twenty years of highly regulated quality management systems
- Successful in adopting process approach of ISO 13485
- ISO 13485 template for training process owners and employees
- Process approach has helped with compliance, certification and business success – even with US FDA
- Strong recommendation for expanded acceptance of ISO 13485 as the quality management system standard

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AHWP
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