Trends in IVD Deficiencies – A Compliance Perspective

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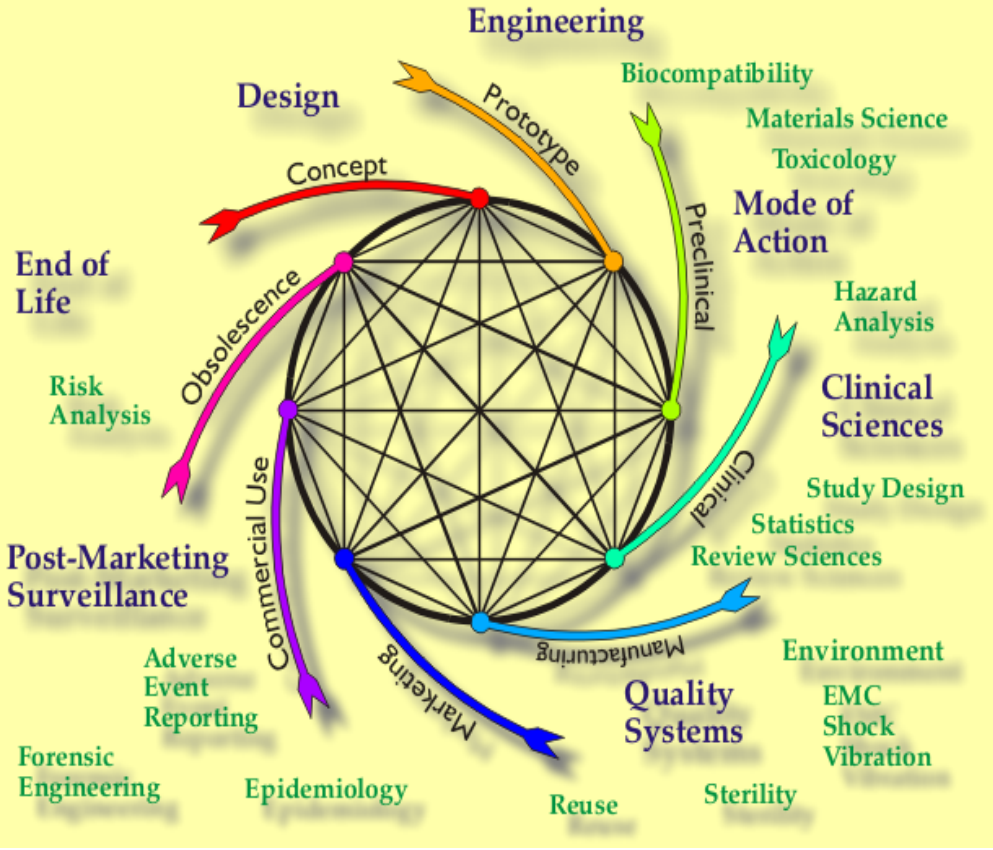
Outline of Presentation

- *The TPLC program in OIR*
- *Functions of the OIR postmarket group*
- *Postmarket and compliance related deficiencies*
  - *Complaint investigations*
    - *devices requiring a 510(k)*
  - *Manufacturing review deficiencies*
    - *Original PMA manufacturing section*
    - *PMA annual reports*
  - *Recall reporting deficiencies*

TPLC – Total Product Lifecycle -

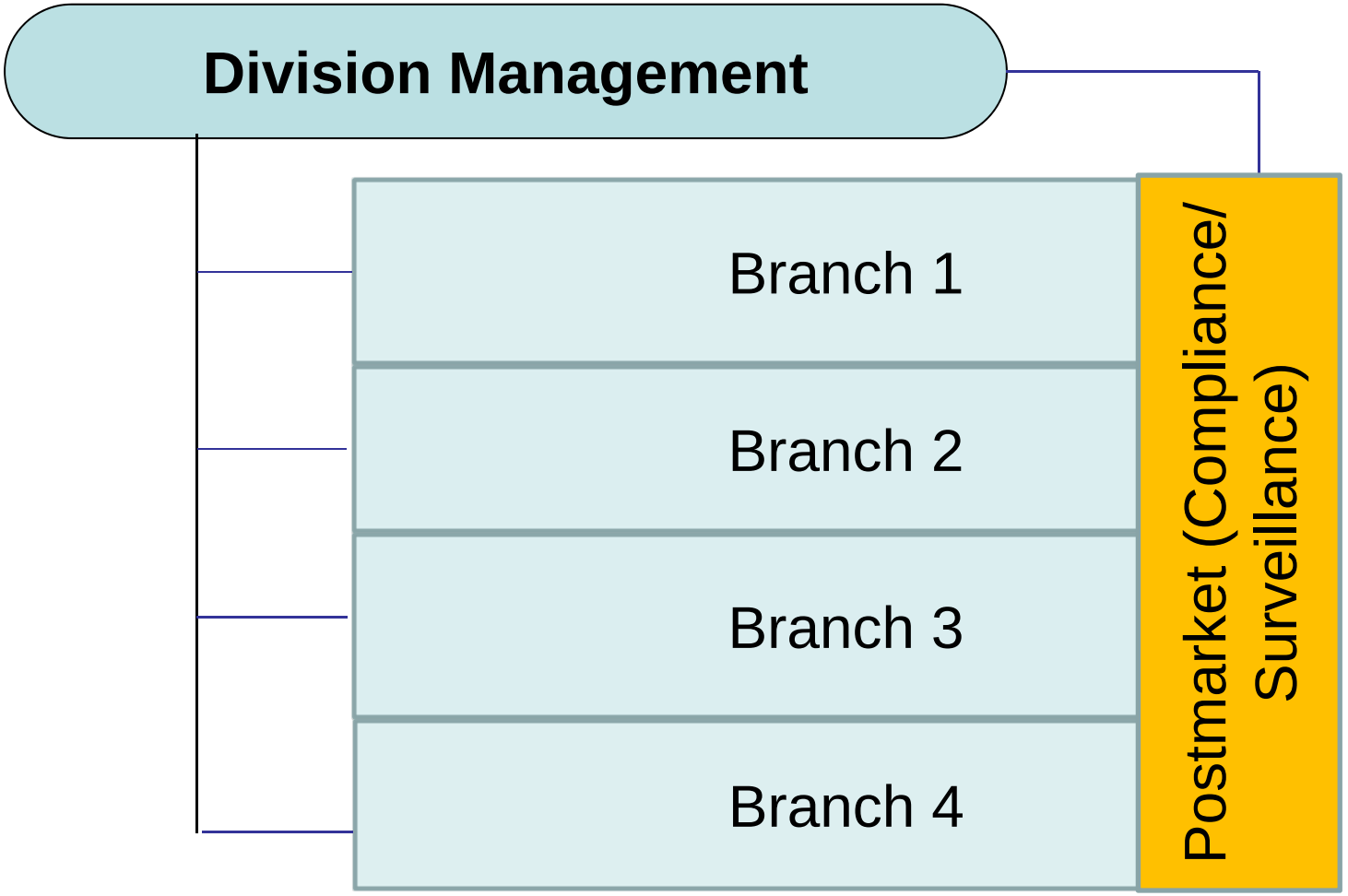
- *Product Design and Development*
- *Manufacturing/ Quality Systems*
- *Postmarket surveillance*



The TPLC process is unique to OIR

	IVDs and Rad Health products	Other Medical Devices
Premarket (Design/Development)	**OIR**	ODE
Compliance (Manufacturing/QS, Recalls)	**OIR**	OC
Surveillance (MDR Review)	**OIR**	OSB

Matrix Management of Compliance and Postmarket in OIR



What type of assignments do OIR Postmarket reviewers handle?

- *Manufacturing reviews*
  - *Original PMAs*
  - *30-Day Notices*
  - *PMA Annual Report Manufacturing Consults*
- *Review of Inspection Reports and drafting of Warning Letters*
- *Investigation of complaints*
- *Classification of recalls*
- *Review of adverse event reports*

Investigation of Complaints

- *Sources: industry, professional groups, concerned individuals*
- *Sometimes identified internally*
- *FDA cannot update the source on the status of the action*
- *FDA cannot share the source of the information with the target of the investigation*

Processing of Complaints

- *Acknowledgment letter sent to source*
- *FDA investigates & verifies information*
- *FDA initiates discussions with target firm*
  - *Email, phone, or "It Has Come to Our Attention" letter*
- *Frequently observed deficiencies:*
  - *Changes requiring a new 510(k)*
  - *Limitations on exemption for Class I devices*
- *Various modes of resolution depending on case*

When is a new 510(k) required?

– 21 CFR 807.81(b)(3)(i): A new 510(k) is required when:

"*A change or modification in the device that* ***could significantly affect*** *the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process*."

Examples of "significant change"

- *New antibody*
- *Change in antigen composition*
- *New primers or probes*
- *Change in cut-off*
- *Change in assay range*
- *Change in reference standard*
- *Change in software diagnostic algorithm*

Failure to submit a 510(k) – limitations of exemption

21 CFR 862.9, 864.9, 866.9 – Limitations of exemption on Class I IVD devices:

- *Different intended use*
- *Different fundamental scientific technology*
- *Other limitations (next slide)*

*Limitations of exemption on Class I IVD devices**

- *diagnosis, monitoring, or screening of*
  - *neoplastic diseases*
  - *familial or acquired genetic disorders*
  - *life-threatening diseases , e.g. AIDS, hepatitis, tuberculosis, or myocardial infarction;*
- *assessing the risk of cardiovascular diseases;*
- *diabetes management;*
- *identifying a microorganism directly from clinical material;*
- *for detection of antibodies to microorganisms*
- *point of care (includes OTC)*

- **21 CFR 862.9, 864.9, 866.9*

Examples: limitations of exemption

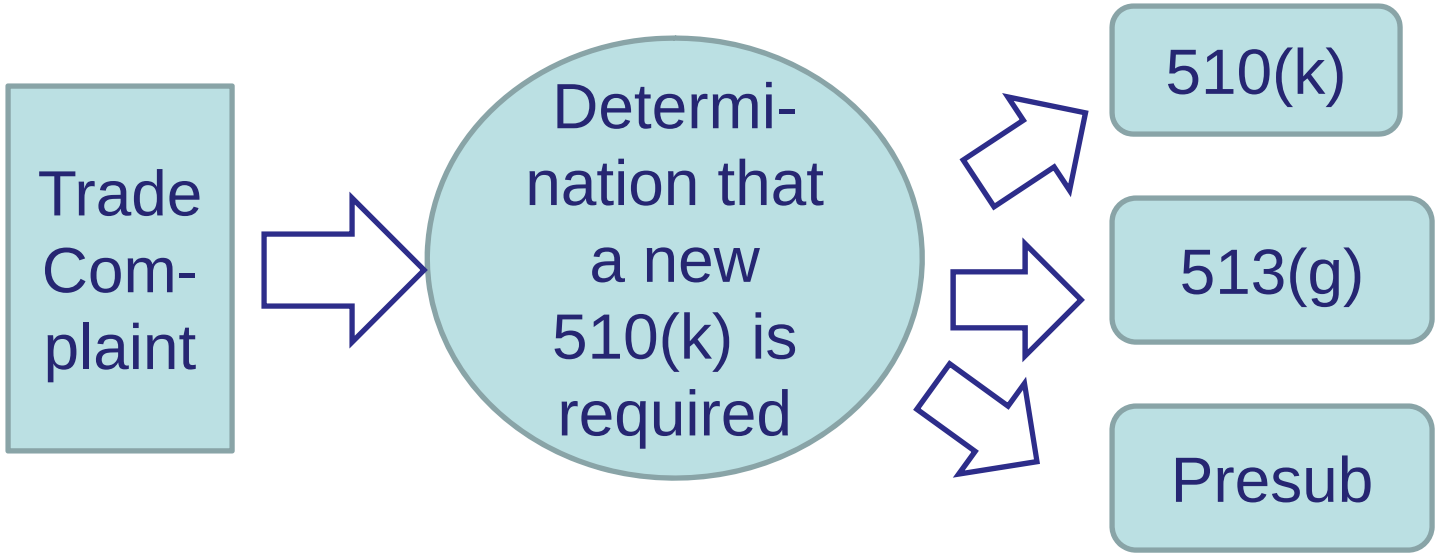
- *Class I cholesterol test system (21 CFR 862.1175) when used in as an aid in the diagnosis of cardiovascular disease: → Class II*

- *Class I microscope (21 CFR 864.3600) with associated software that is used to assist with identification abnormal cells on a slide: → May be Class II or Class III depending on the analyte*

Device must be cleared for each sample type and IU

	Sample Type A	**Sample Type B**
Intended Use X	Cleared	Cleared
Intended Use Y	Cleared	Not cleared – can't be marketed for this IU

Compliance work feeds into premarket



Original PMA Manufacturing Review – Examples of Deficiencies

- *Failure to provide device-specific Design Control documentation (DDP, design inputs, transfer, verification, validation)*
- *Failure to provide device-specific acceptance procedures*
- *Inadequate process validation information (need specific protocols)*
- *Failure to adequately tie CAPA system to NCR, complaint handling systems*

Original PMA Manufacturing Reviews – Suggestions for Improvement

- *Utilize guidance document* as a checklist*
- *For companion diagnostics, timing is critical*
  - *Co-approval constraints (must pass inspection prior to drug approval)*
  - *Use of modular PMA highly recommended*
  - *Interactive review*

**Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff*

PMA Annual Reports

21 CFR 864.39(b): An applicant may make a change in a device after FDA's approval of a PMA for the device without submitting a PMA supplement **if the change does not affect** the device's safety or effectiveness and the change is reported to FDA in postapproval periodic reports required as a condition to approval of the device, e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device.

Changes requiring PMA Supplements – stricter standard than changes requiring a new 510(k)

New 510(k) required when:	**PMA supplement required when:**
*A change or modification in the device **could significantly affect** the safety or effectiveness of the device*	*A change **affects** the device's safety or effectiveness*

Examples of PMA Annual Report deficiencies

- *Failure to provide sufficient information for OIR evaluation*
- *Use of firm-specific jargon in the presentation of annual reportable changes*
- *Note: if FDA needs to review data to ensure the change does not affect safety and effectiveness, the change typically requires a supplement.*

Examples of changes requiring a PMA supplement

- *Changing from manual to automated vialing or assembly*
- *Changes to a reagent vial, where the changed region **contacts the solution***
- *New supplier for a critical component*
- *Changes to incoming or final QC procedures*
- *Software changes that can impact S&E*

Types of PMA Supplements

Type of PMA Supplement	Design Changes	Manufacturing Changes	FDA review clock	User Fee?
Panel-Track Supplement	Significant (or new IU), needs clinical data		180 days	Yes
180-Day Supplement	Significant change, needs analytical data		180 days	Yes
Real-Time Supplement	Minor change		90 days	Yes
Site Change Supplement		Change in mfg facility	180 days	No
30-Day Notice		Changes affecting S&E	30 days*	Yes
Special PMA Supplement – CBE		Changes enhancing safety	30 days	No

Submission of correction and removal reports to FDA

- *Per 21 CFR 806.10, a report must be submitted to FDA if the correction/removal (i.e. a recall)*
  - *Reduces a risk to health posed by the device*
  - *Remedy a violation of the Act*

Classification of recalls – goes in the opposite direction from device classification!

Class	Risk level	Risk to health	Probability
I	High	Serious adverse consequences or death	Reasonable probability
II	Medium	Serious adverse consequences or death	Remote
		Temporary/ medically reversible conditions	May cause
III	Low	Any health consequences	Not likely

How does OIR classify recalls?

- *By precedent*
- *By Health Hazard Evaluation*
- *By policy*
  - *Marketed without a 510(k) – Class II*
  - *Others under development in OIR*

- *Requires Medical Officer sign-off*

Challenges for firms in reporting recalls

- *Class III recalls = no risk to health -> do not need to be reported*
- ***Note that FDA considers delay of results a potential risk to health in some instances (e.g. coag, troponin)***
- *Firm should be conservative in preparing their HHE*
- ***When in doubt, report it!***

Guidance documents – 510(k) related

Deciding When to Submit a 510(k) for a Change to an Existing Device

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm

Guidance for Industry and FDA Staff; Replacement Reagent and Instrument Family Policy

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079185.htm

Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems - Guidance for Industry and FDA Staff

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077819.htm

Guidance documents – PMA Manufacturing Reviews

Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf

Guidance for Industry and FDA Staff - 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080192.htm

Questions?

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