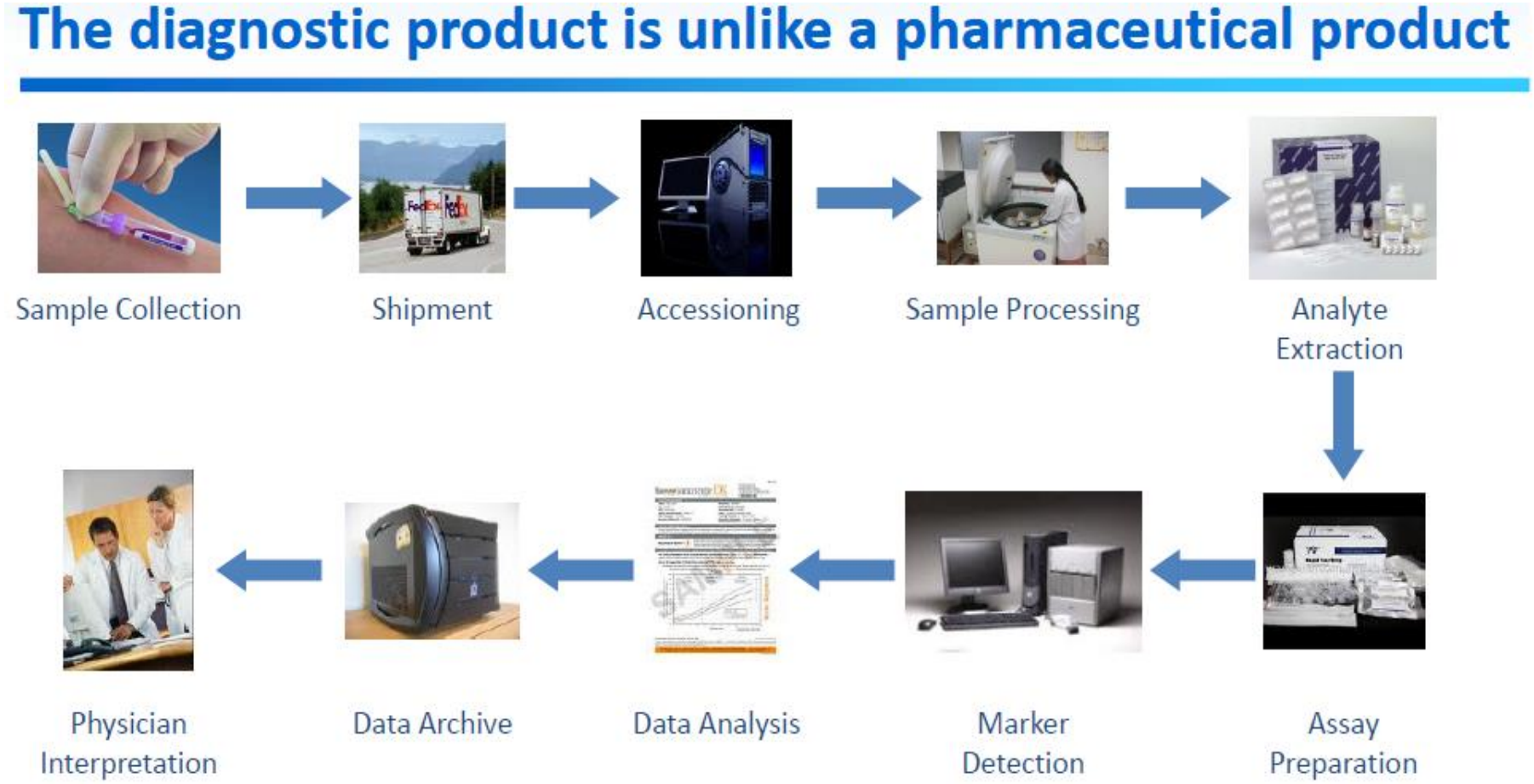
Sarah Parsons

Director Global Regulatory Affairs Diagnostics, Janssen R&D, October 2018

"Look, I don't want any funny business."

What is the product?

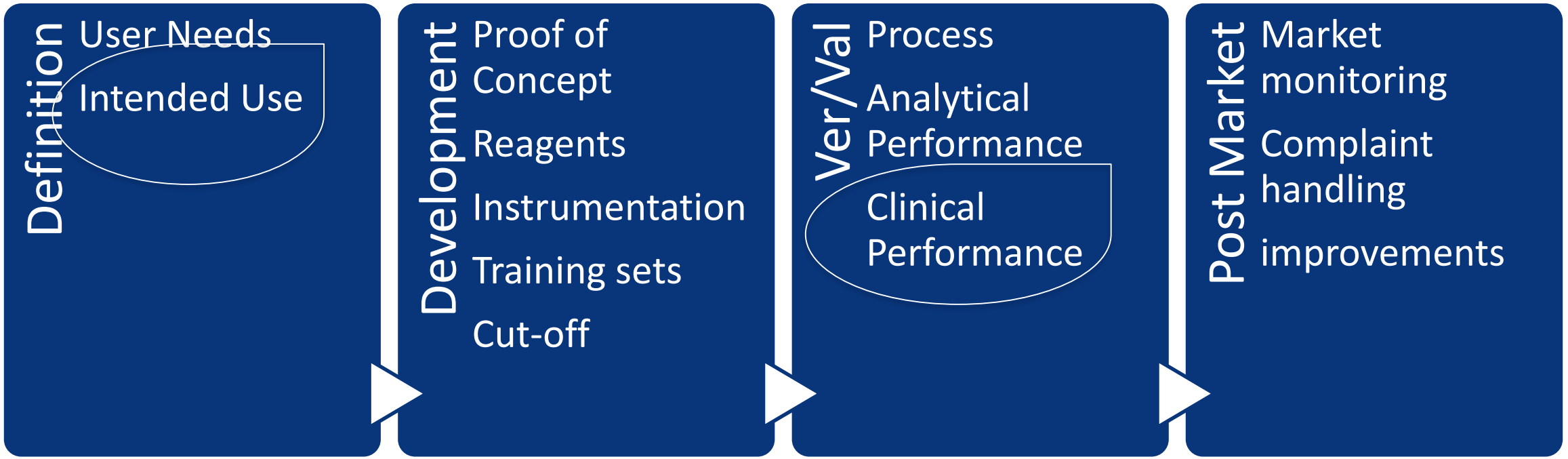
- The test,
- The sample
- The collection tube
- The system
- The software



Intended Use: Drives the class of the device based on risk

- AFP: Class II for measuring AFP and AFP-L3 sub-fraction in serum as a risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma with other laboratory findings.
- AFP Class III : for measurement of maternal serum or amniotic fluid as an aid in the detection of fetal open-neural tube defects.
- PSA: Class II for monitoring patients for disease progress or response to therapy or detection of recurrent or residual disease
- PSA: Class III Prostate Specific Antigen, as an aid in the detection of prostate cancer in men

IVD Development Process



Development Team Inputs into RA Strategy and Plan

- Strategy: the what
  - High level information
  - Early on (Proof of Concept?)
  - Basic Design Inputs and Intended Use
  - Marketing Strategy
- Plan: the how
  - Final Intended Use
  - Requirements by country
  - expected timeline based on experience
  - Reviewed by in country experts
  - Signed off
  - Part of DHF
- Clinical Plan
  - Aligns with clinical requirements
  - Details scope, objectives, timing and costs of trials.

Clinical Trials and Clinical Samples: Based on RA and Clinical Plan

Determine what samples will be needed:

- Input from HA interaction
- Does the test have Common Technical Specifications (EU)?
- Are there Special Controls (US)?
- Is there an expectation for prospective trial samples?
- Is the analyte stable for sample storage?
- Is there analyte free sample available?
- What is the clinically relevant concentration of the analyte?

Interaction with Health Authorities

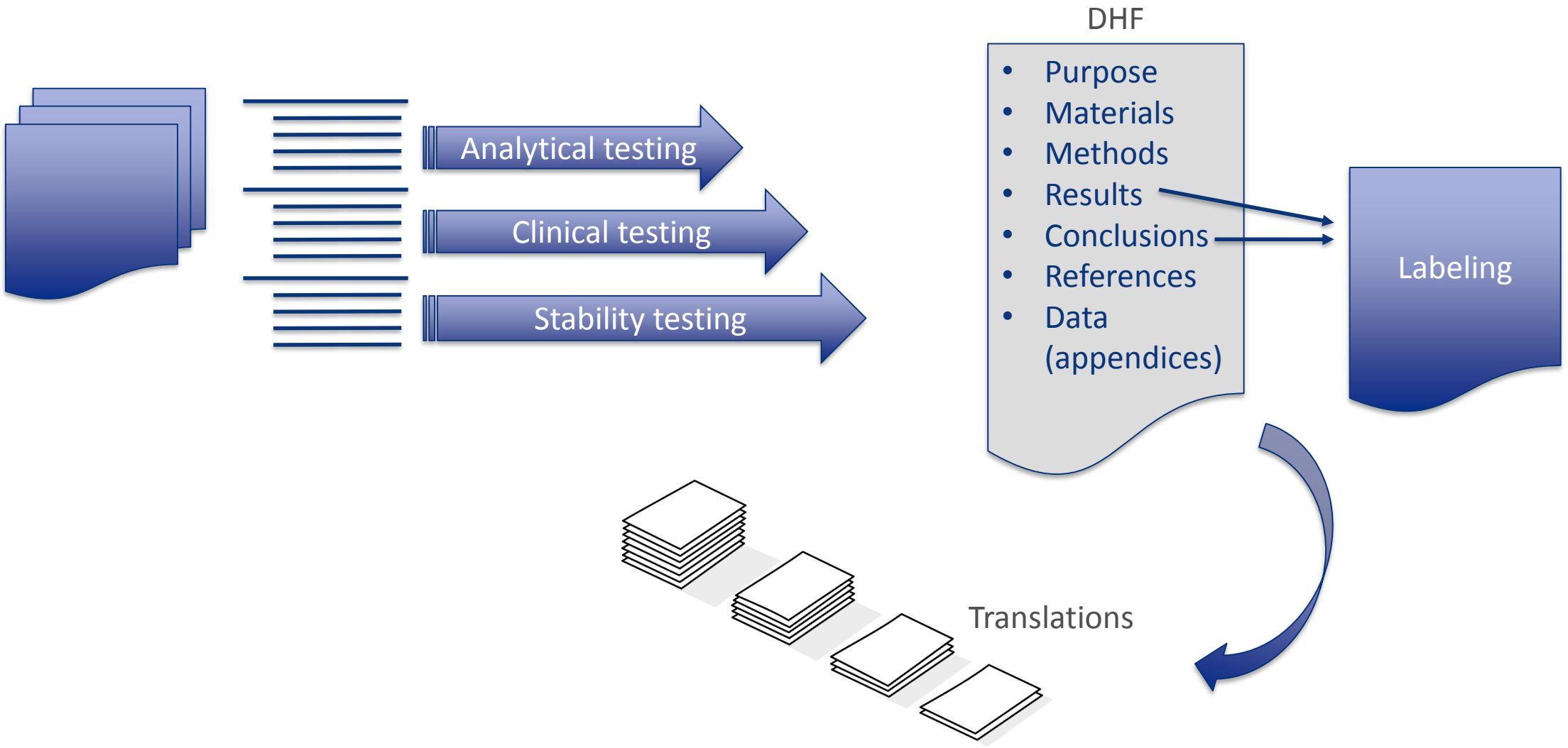
- How novel is the IVD?
  - One of a kind tests require more thought and planning
  - Companion Diagnostics have specific regulations
- Is interaction needed?
- Provide plans for analytical and clinical testing
- Plan interaction for each country:
  - US: presubmission meeting with OIR. 75 days after full package is submitted
  - EU: Notified Body (Competent Authority?) communication may be necessary to gain agreement on clinical studies
  - Japan: consultation with PMDA preliminary and formal meetings can take up to a year

Test to the highest requirements

Based on markets of interest.

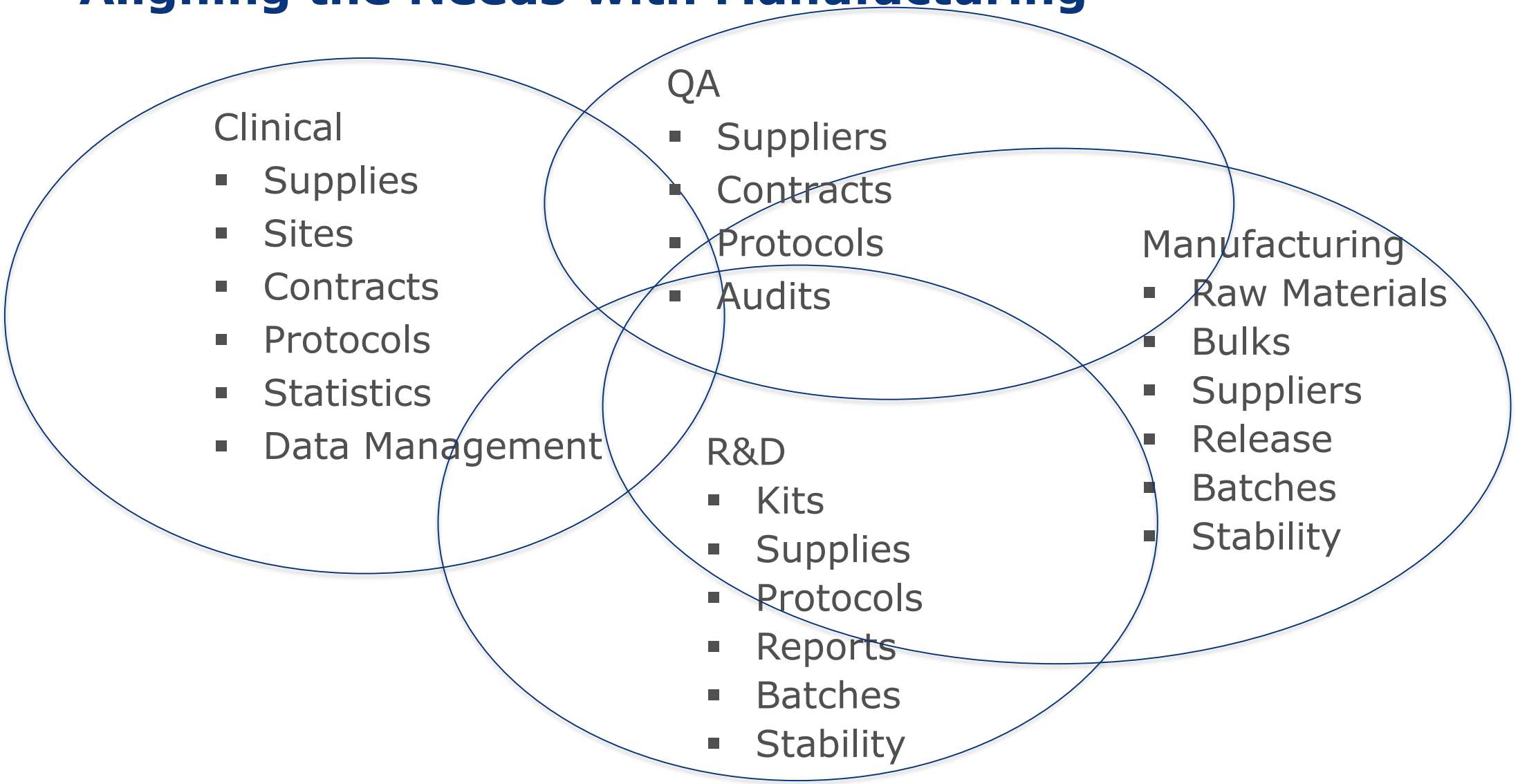
- Japan has significant stability requirements
  - 3 lots of test kits
  - Time 0, mid, end
  - Minimum of 3 replicated per testing time in order to calculate precision
  - Minimum of 2 positive and 2 negative samples tested to determine within test reproducibility
- US utilize CLSI as standards for performance
  - Adjust for clinically relevant levels of analyte in question
  - LOB, LOQ, LOD
  - Take Qualitative/ quantitative ranges into account

Translate the RA requirements into actions (in theory)

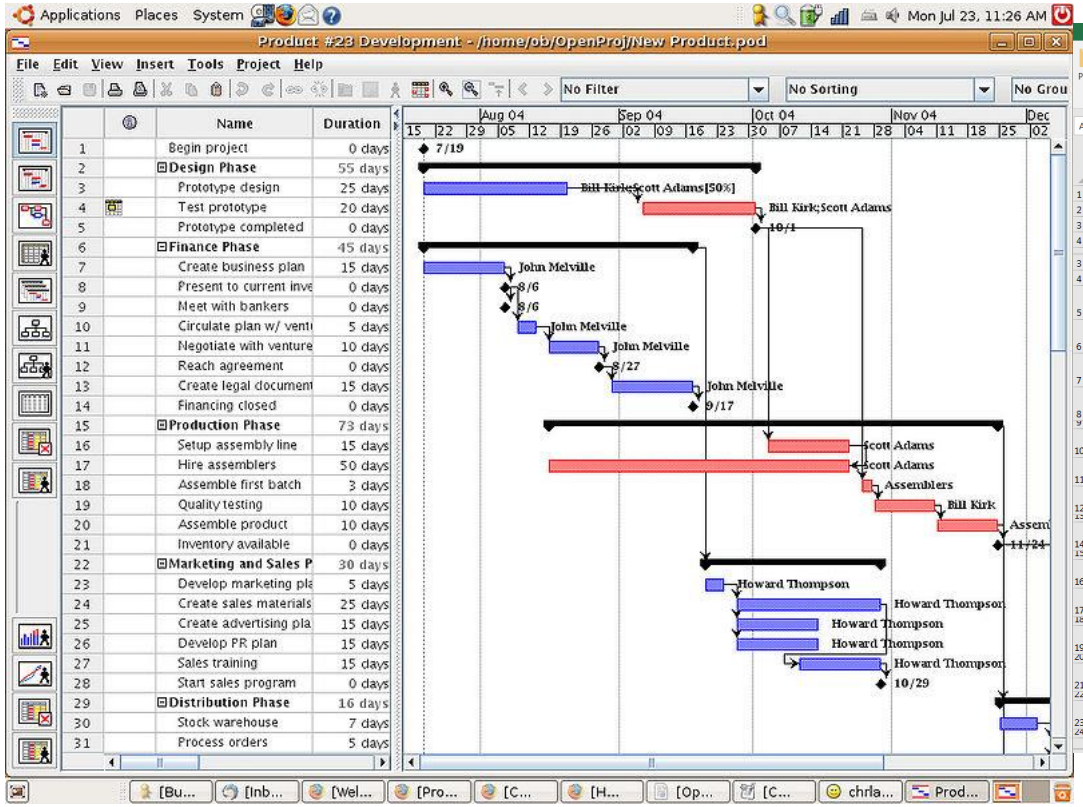


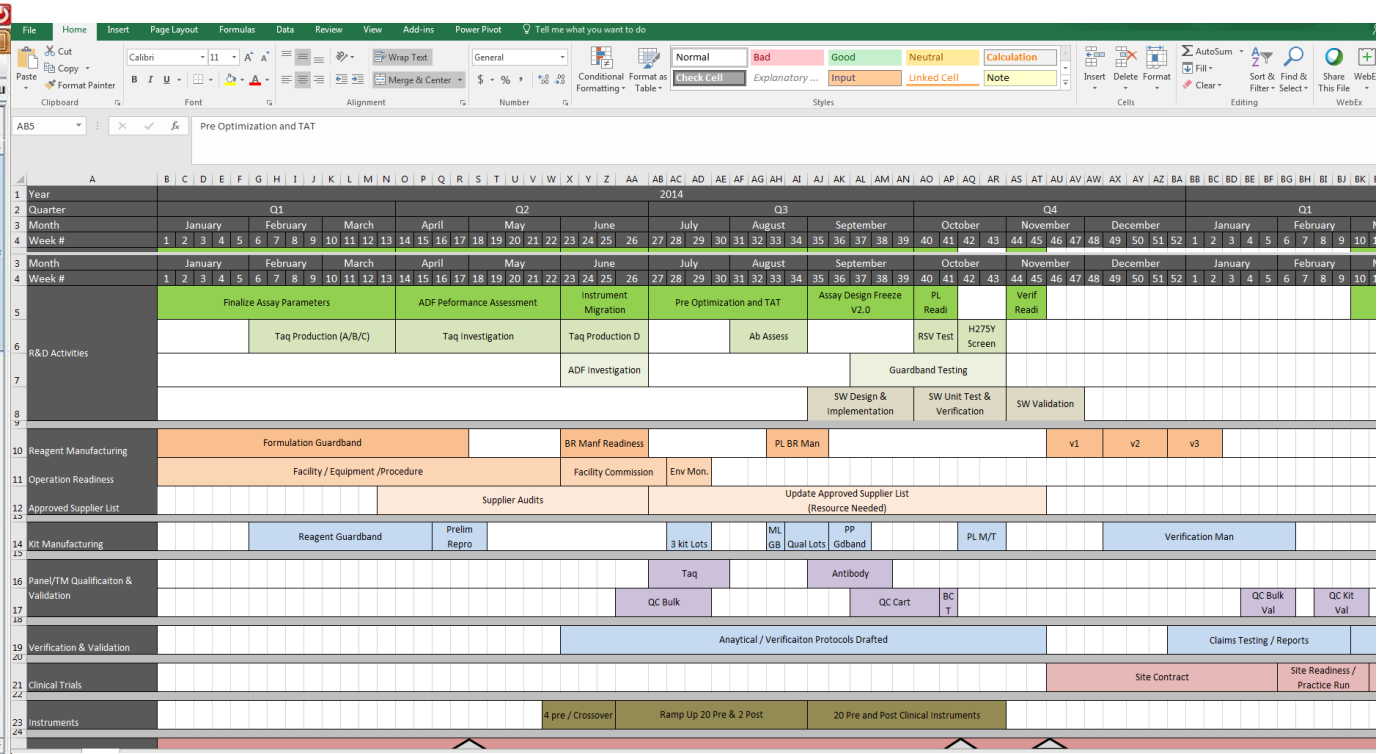
Creating the Road Map: Brainstorming Helps

Aligning the Needs with Manufacturing



Gantt the project

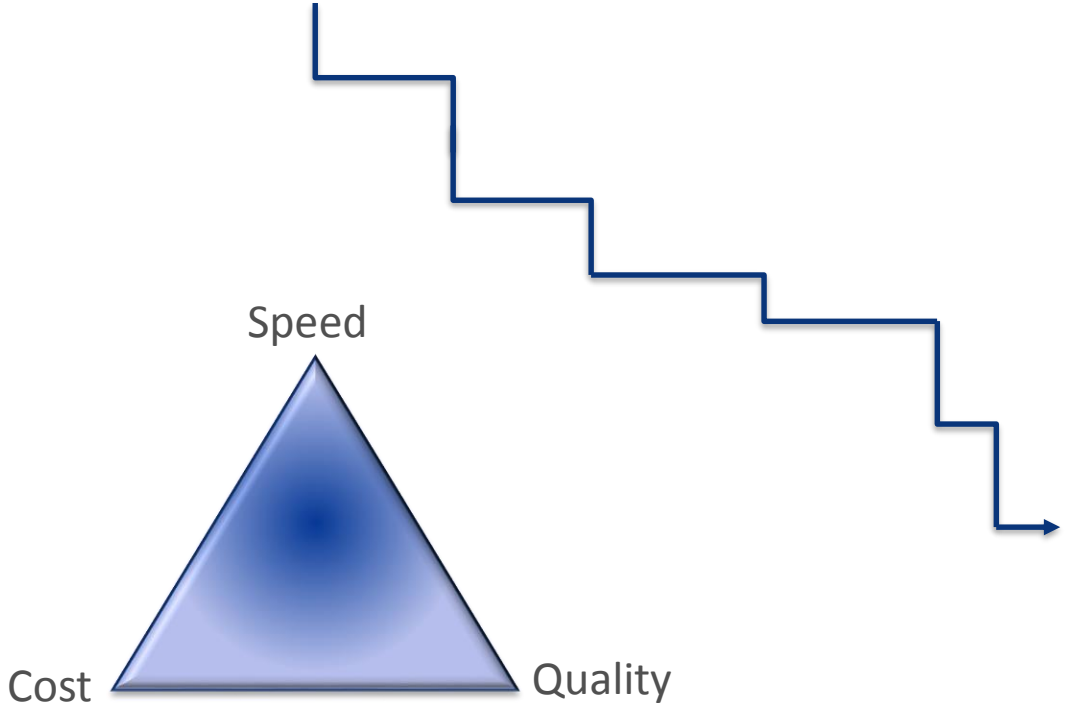


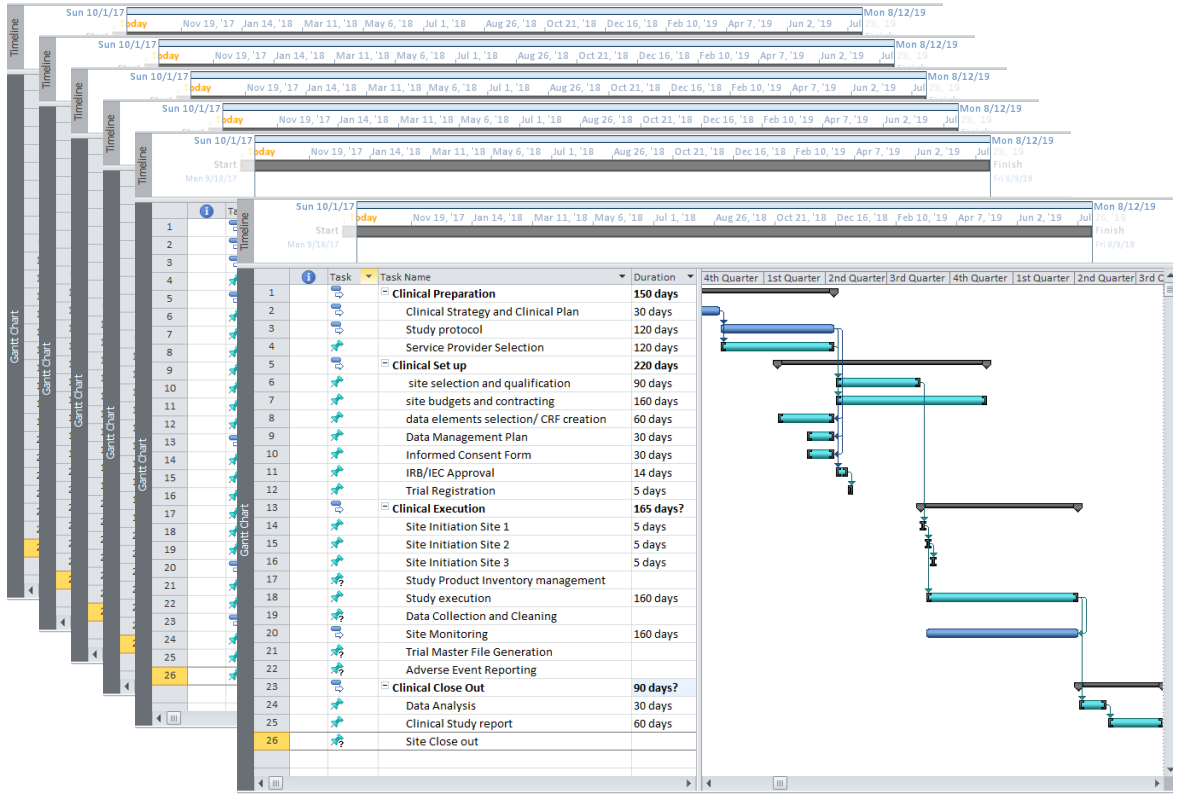


Regardless of the tool used, be sure everyone understands and agrees with it.

Track the Critical Path: Role for Project Management

- Each function will have their own critical path
- The project will have a critical path





Clinical and Regulatory Touch-points

- Labeling (Investigational): needed for trial and compliance
- Protocols: submitted to IRBs
- Risk Determinations: requested by IRBs (sometimes)
- Informed Consent
- IDE (if needed)
- Clinical Study Report
- Submission

Significant Risk Testing/ IDE

- Most IVDs are exempt from IDE requirements-812.2(c)
- Sampling procedures that are invasive (21CFR812.3(k)) remove the exemption and require the filing of an IDE.
- Venipuncture is not considered invasive (lumbar puncture: routine)
- IDEs need to be filed at least 30 days before the start of the clinical trial, FDA will notify of approval, approval with modifications or disapproval.
- The contents include:
  - General Information on Device
  - Investigational Plan
  - Manufacturing (Methods/ facilities/ controls)
  - Prior experience (clinical and analytical)
  - Investigators/ IRB/ Informed Consent
  - Device labeling
  - References

Aligning the Support

Clinical scientists
Data management
Writers
QA

- The process of the data transfer, cleaning may not be well understood by all.
  - Be sure hand-offs are clear
- Challenge what is necessary in order to maintain quality and expediency
- Monitor the data as it comes in to meet % agreement or target.
  - Blinding can be assured at the site and still monitor results

Align the Clinical Studies with Regulatory Requirements Example: aHAV

- Marketing Countries: US, EU, Japan, China, Canada

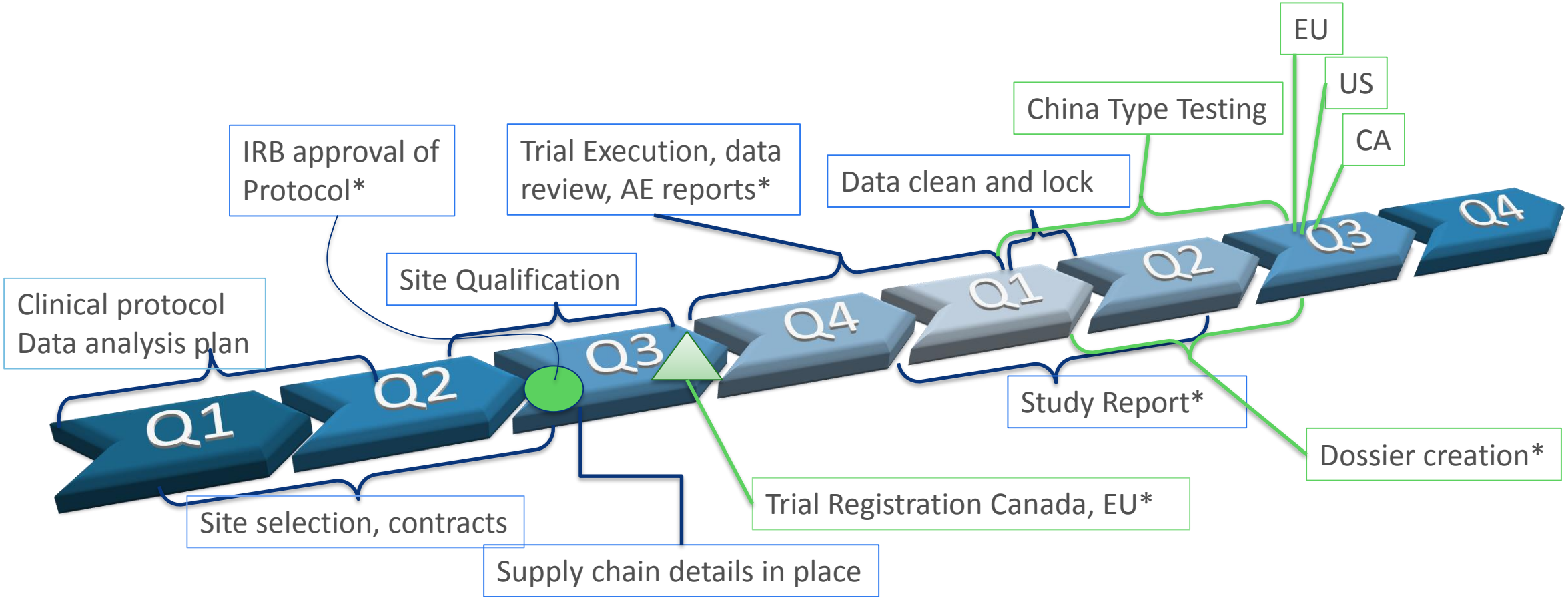
	US	EU	Japan	China	Canada
Class	II	Self/C	III	III	II
In country trials?	Yes, prospective	Justify population	No, but need 2 comparators	Yes, CFDA approved comparator, 3 sites	No
Predetermined number of samples?	Special controls/CLSI	No CTS	Minimum # of + (100) and – (200) samples	Minimum # of + (300) and – samples (1000 total)	No

Determine:

- Total materials needed to support trials, including control testing, repro
- Sites and locations to meet greatest expectations (collection/ testing)

Japan

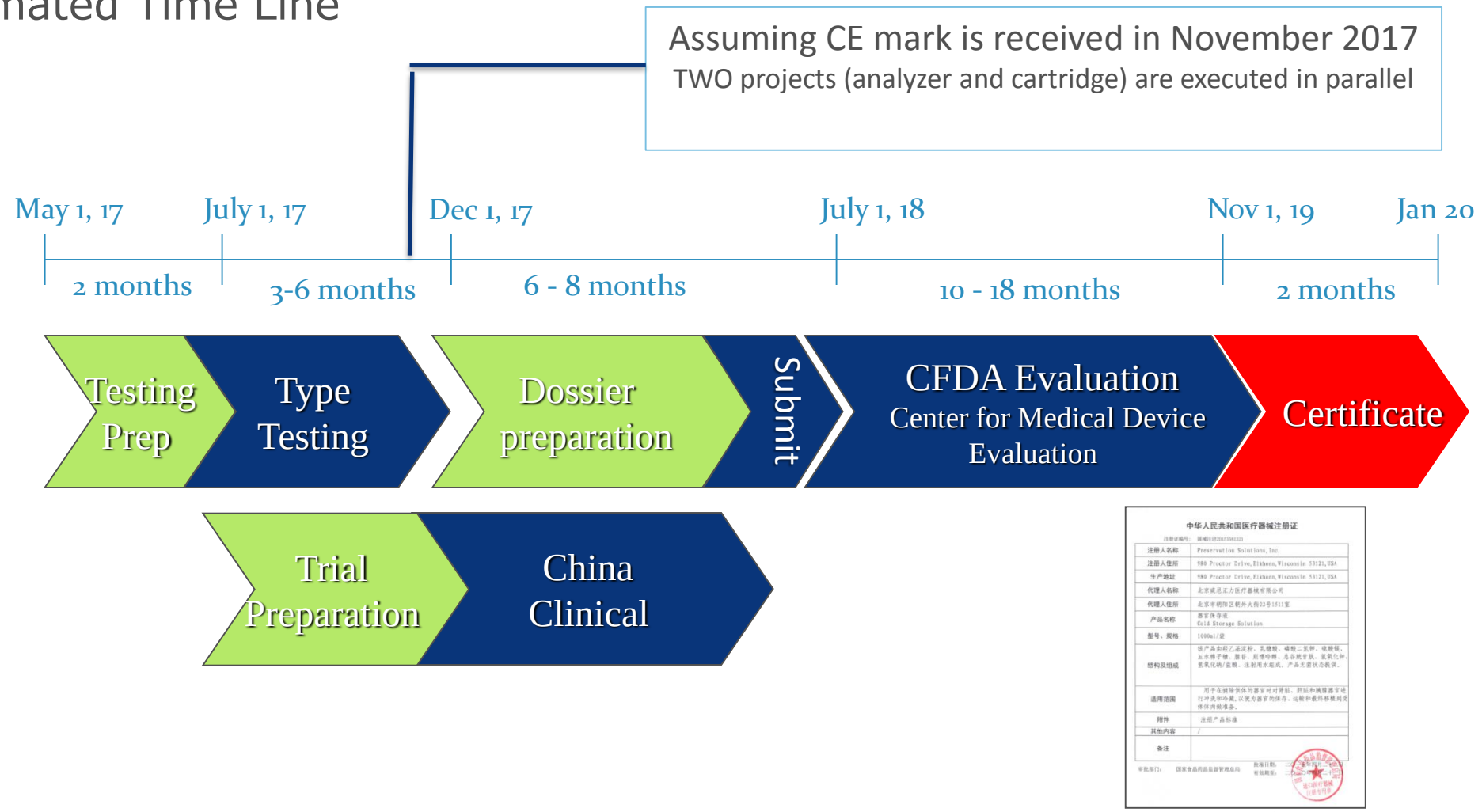
- Premarket approval (Shonin)
- Do you have in Country presence? Do you need a Foreign Manufacturers Registration? This must be complete before you register your IVD.
- Consider experienced consultant if this is new.



* Areas where CA and RA touch

China Timing with Program

- Estimated Time Line



中华人民共和国医疗器械注册证

注册人名称	Preservation Solutions, Inc.
注册人住所	980 Proctor Drive, Elkhorn, Wisconsin 53121, USA
生产地址	980 Proctor Drive, Elkhorn, Wisconsin 53121, USA
代理人名称	北京威尼汇力医疗器械有限公司
代理人住所	北京市朝阳区朝外大街22号1511室
产品名称	器官保存液 Cold Storage Solution
型号、规格	1000ml/袋
结构及组成	该产品由羟乙基淀粉、乳糖酸、磷酸二氢钾、硫酸镁、五水棒子糖、腺苷、别嘌呤醇、总谷胱甘肽、氢氧化钾、氢氧化钠/盐酸、注射用水组成。产品无菌状态提供。
适用范围	用于在摘除供体的器官时对肾脏、肝脏和胰腺器官进行冲洗和冷藏，以便为器官的保存，运输和最终移植到受体体内做准备。
附件	注册产品标准
其他内容	/
备注	

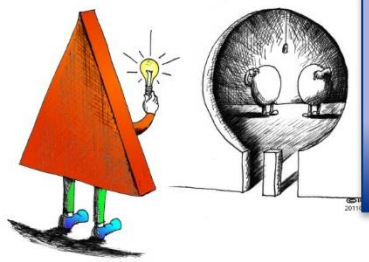
审批部门：国家食品药品监督管理总局　　批准日期：　　有效期至：

What can go wrong

Decision to add to the multiplexed test

Sept '11 | Dec '11 | April '14 | Oct '14 | Mar '15 | Nov '15

Phase 0 → Phase 1 → Phase 2A → Phase 2B → Phase 3 → Launch (CE) → Launch (US)



May '13
9 month delay in instrument availability, missed season in US.

July '14
Manufacturing issues of pilot lot and verification lots: missed season in US

Clinical Trials US, 510k submission and clearance

- Test development in parallel with instrument development: expect rework
- Seasonal analytes (Flu): timing is important, follow the disease
- It takes longer than you think

Thank you

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