QIBA SWS PROFILE EFFECTS
CLINICAL, RESEARCH, REGULATORY

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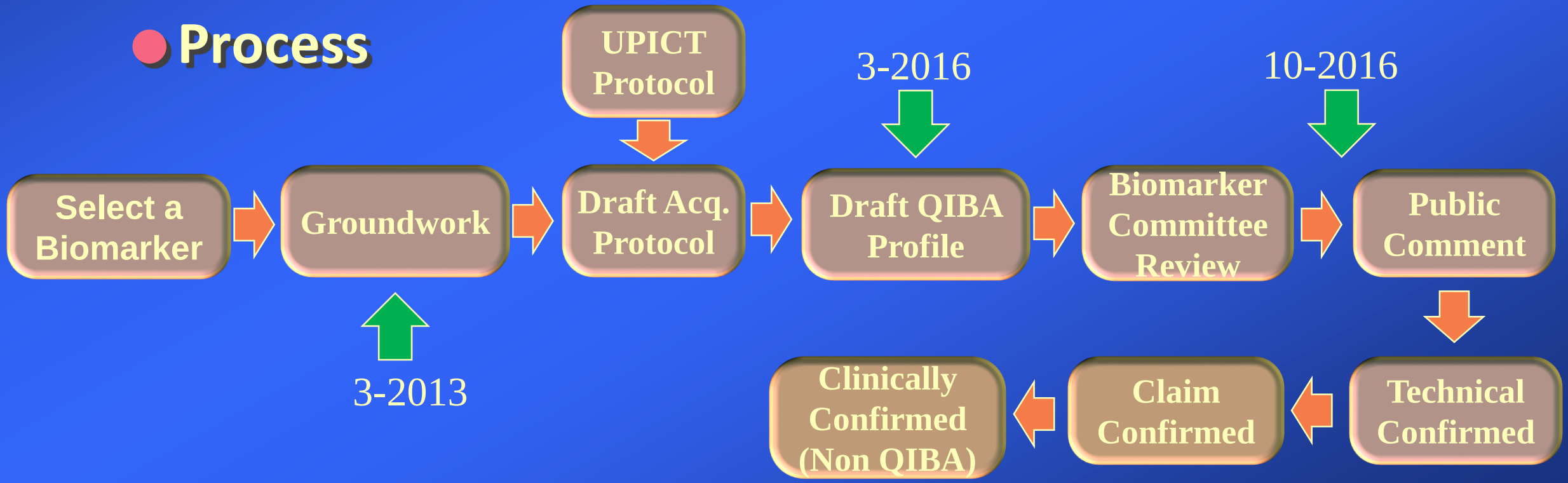
GOALS

- Review the Making of the QIBA US SWS Profile
- Review Current Status of US Shear Wave Speed Estimation
- Discuss Clinical Implications of SWS Profile
- Discuss Research and Development Implications of SWS Profile
- Discuss Regulatory Implications of SWS Profile

US SWS BIOMARKER COMMITTEE

- Organized Into Phantom/System Dependencies, and Clinical Working Groups
- Process



CLINICALLY CONFIRMED STATUS

- Means That the Relationship Between the Biomarker Metric and the Biomarker Has Been Developed and Confirmed in a Clinical Trial
- The Confirmed Biomarker Metric Could be Used for Diagnosis, Drug Testing, or Research
- The Large Clinical Trial Probably Needed to Reach This Status is Likely Beyond QIBA Resources

SWE-SWS LIVER FIBROSIS ASSESSMENT
CURRENT CLINICAL STATUS

- Measurement Devices
  - Fibroscan (non-imaging device)
  - Ultrasound b-mode Scanners (many manufacturers & implementations)
  - Magnetic Resonance Scanners (many manufacturers, one implementation)
- For US SWE-SWS: Good Performance Has Been Seen Across Systems

FIBROSCAN PERFORMANCE

- F ≥ 2: AUC ≈ 0.86
  - For Suggested cutoff > 7.0 kPa:
    - sensitivity 70%, specificity 81%
- F ≥ 3: AUC ≈ 0.95
  - For Suggested Cutoff > 9.5 kPa:
    - Sensitivity 80%, specificity 85%
- F = 4: AUC ≈ 0.97
  - For Suggested Cutoff > 12 kPa:
    - Sensitivity 86%, Specificity 88%

NEWER FIBROSCAN SYSTEMS INCLUDE ESTIMATION OF FAT CONTENT (ATTENUATION-BASED)

Ferraioli G et al. World Journal of Gastroenterology 2013

US SWE QUANTIFICATION VTTQ
COMPARISON WITH FIBROSCAN

PARAMETER	FIBROSCAN	SWE	P
Invalid Measure	6.5%	0%	<.03
AUROC ≥ F2	0.78	0.86	<.03
AUROC ≥ F3	0.83	0.94	<.003
AUROC = F4	0.80	0.89	=.09
Agree with BX	45.4%	54.7%	

Rizzo L et al. Am J Gastroenterol 2011

US SWE QUANTIFICATION SSI

COMPARISON WITH FIBROSCAN

Pathology	AUC Fibroscan	AUC SSI
F ≥ 2	0.84	0.92
F ≥ 3	0.98	0.96
F = 4	0.96	0.98

SSI Consistently Slightly Better Than Fibroscan
but Not Statistically Significant Except for F ≥ 2

MAGNETIC RESONANCE ELASTOGRAPHY

Comparison with Fibroscan & APRI

FIBROSIS LEVEL	AUC			
	APRI	FIBROSCAN	BOTH	MRE
F>2	.71	.84	.85	.994
F>3	.82	.91	.94	.985
F>4	.82	.93	.94	.998

Huwart et al Gastroenterology 2008;135:32-40

A COMMONLY RECOMMENDED DIAGNOSTIC APPROACH

- Fibroscan Performed in Hepatology for Patients Being Followed by Hepatologist
- US SWE Performed if Fibroscan Fails, Inconsistent Results are Achieved, or Patient Having US Anyway
- MRE Used if Fibroscan and US SWE Disagree or Results Inconsistent With Clinical Manifestations
- Patients in Primary Care May Be Referred for US SWE Prior to Hepatology Visit

LIVER SHEAR WAVE ELASTOGRAPHY (SWE) USEAGE

- Widespread - Especially Fibroscan by Hepatologists
- Much Larger Group Waiting to Fully Adopt
- Not Yet Adopted for Drug Trials
- Concern Regarding Variability of Results

US SHEAR WAVE ELASTOGRAPHY

SOURCES OF VARIABILITY

- Type of Liver Disease (Hep A-C, Acute vs. Chronic, Biliary Cirrhosis, Cholangitis etc.)
- Patient co-morbidities e.g. CHF
- Body Habitus, fasting, gender, breathing, body position
- Modality and System Factors e.g. Shear Wave Tracking Algorithm, Shear Wave Generation Method, Correction for focal depth, beam divergence
- Acquisition Factors: Variable location, depth.

VARIABILITY REDUCTION

- Medical Society Guidelines
- Manufacturer Guidelines
- Medical Literature
- System Enhancements
- QIBA Profiles

STANDARDS & GUIDELINES

- EFSUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography, Ultraschall Med 2013
- WFUMB Elastography Guidelines Presentation: 4 May 2013 Sao Paulo Brazil. Ultrasound Med Biol Fall 2014
- SRU Consensus Panel on Elastography for Liver Fibrosis, Oct 2014

QIBA PROFILE

ENHANCED CLINICAL PERFORMANCE & ADOPTION

- Ongoing Concerted Effort to Identify and Reduce All Sources of Bias and Variability
- Decreased AND Verified Bias and Variance – especially Machine to Machine variation.
- Manufacturer Specific Acquisition Variables but General Overall Conformance to Rules & Procedures (decreased training for operators)
- Mechanism for Reporting Performance Problems and Development of Solutions

QIBA PROFILE
TOWARDS MORE RELEVANT METRICS

- Pathologic Grading an Imperfect Indicator for Clinical Management
  - Sampling errors
  - Too Few Stages for Monitoring Change
  - Interpretation Subjectivity & Variability
- Truly Reliable SWS Estimates Able to Distinguish Smaller Changes in Stiffness Could Supplant Pathology for Treatment & Prognostication

SRU SUGGESTED REPORTING

- Report Study Results (Philips Epiq) as:

Fibrosis Group	METAVIR	Elasto Value (*EV*)
No Signif Fibrosis	≤ F2	< 5.7kPa (1.37 m/s
Moderate Fibrosis	F2, F3	5.7kPa ≤ *EV* ≤15kPa
Adv Fibr/Cirrhosis	F3, F4	> 15kPa (2.2 m/s)

- Give ROI Location in Liver and Depth
- Give Interquartile Ratio & Rating (< 0.30 is good) or Give % Std Dev (SD/Median x 100)

QIBA PROFILE
FUTURE CLINICAL VALIDATION

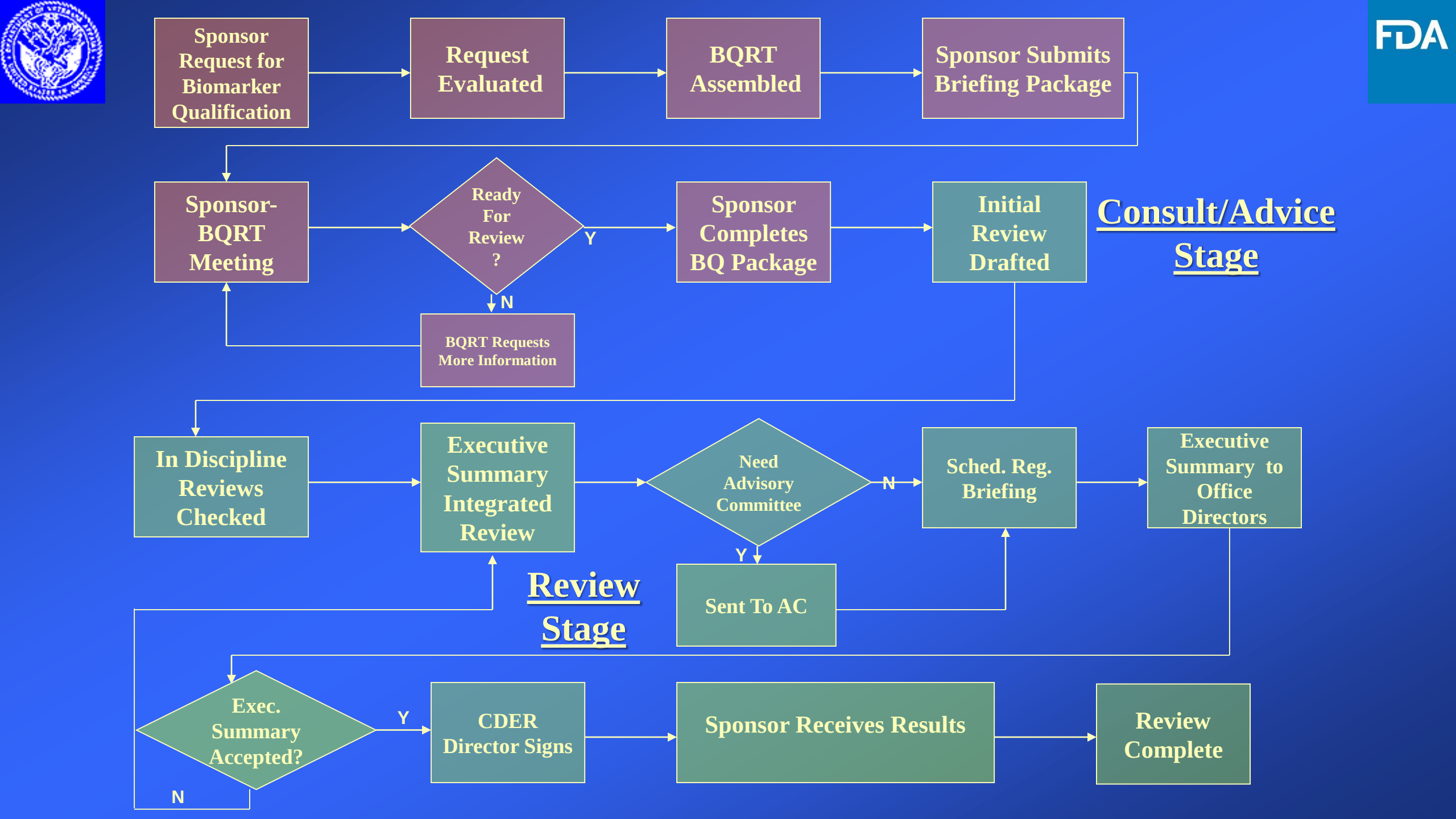
- Improved Performance May Make Validation Against Pathology Inappropriate in Upcoming Clinical Studies
- Direct Testing of SWS Defined Treatment Thresholds Against Outcomes Is More Logical

QIBA SWS PROFILE
IMPACT ON DRUG EVALUATION

- Pharma Interest for at Least Four Years
- Relevance of SWS to a Specific Treatment Remains the Responsibility of the Drug or Therapy Sponsor.
- Validated SWS Profile Lessens the Burden on the Sponsor to Find a Validated Monitoring Tool
- May be Proposed as a FDA Qualified Biomarker for Regulatory Purposes

CDER BIOMARKER QUALIFICATION

- Biomarker Qualification Program
  - Supports Groups Attempting to Establish a Biomarker for Use in Drug Development for Multiple Companies
  - Provides Consistent Review Structure While Minimizing Burdens
  - Established Process for Interactions With Biomarker Sponsors
- Co-development of a Drug and a Test
  - Older "traditional" Method
  - Takes a Long Time to Generalize


Sponsor Request for Biomarker Qualification
Request Evaluated
BQRT Assembled
Sponsor Submits Briefing Package
Sponsor-BQRT Meeting
Ready For Review ?
Y
N
BQRT Requests More Information
Sponsor Completes BQ Package
Initial Review Drafted
Consult/Advice Stage
In Discipline Reviews Checked
Executive Summary Integrated Review
Need Advisory Committee
N
Y
Sent To AC
Sched. Reg. Briefing
Executive Summary to Office Directors
Review Stage
Exec. Summary Accepted?
Y
N
CDER Director Signs
Sponsor Receives Results
Review Complete

QUALIFICATION

- A conclusion that within a carefully and specifically stated "context of use" the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in decision-making
- Utility in drug development, particularly regulatory decisions, is very important
- Assay Methods Needed to Measure the Biomarker Are Also Qualified

CONTEXT OF USE

- Comprehensive Statement of Manner & Purpose of Use of the Biomarker
- May Include:
  - Range of Disorders
  - Range of Drug Classes
  - Range of Species
  - Procedures & Criteria for Obtaining Samples
    - Sample Handling May Be Part of Assay Method
  - How Results are Interpreted
    - Limitations on Interpretation / Application
- May be Expanded Over Time With New Evidence

QUALIFICATION SUBMISSIONS

- 18+ Submitted Since 2007 – One Sponsored by QIBA (PET SUV)
- Three Qualified, No Disqualifications
- Time Interval to Qualification 1-4 Years
- Most All Still in Advice/Consultation Phase

QIBA SWS PROFILE
IMPACT ON RESEARCH

- A Validated Tool for Investigations Into Liver Disease and Fibrosis: Diagnosis; Staging; Treatment; Causes
- Validated Tool to Begin Studies of Stiffness in Other Organs and Diseases
- Study Further Improvements in Biomarker Accuracy & Biomarker Profile Development Methods

ADDITIONAL AREAS OF IMPACT

- QA Methods can be Applied to Other Imaging Tasks
- Compliance Methods can be Used for Other Types of Clinical and Research Tasks
- Profile Can be Adapted to Future Elasticity Methods Such as Quantitative Strain Elastography
- Stimulation of Phantom and Other Tool Development for System Enhancements, QA and Regulatory

FDA PHANTOM EFFORTS

NEW MATERIALS DEVELOPMENT

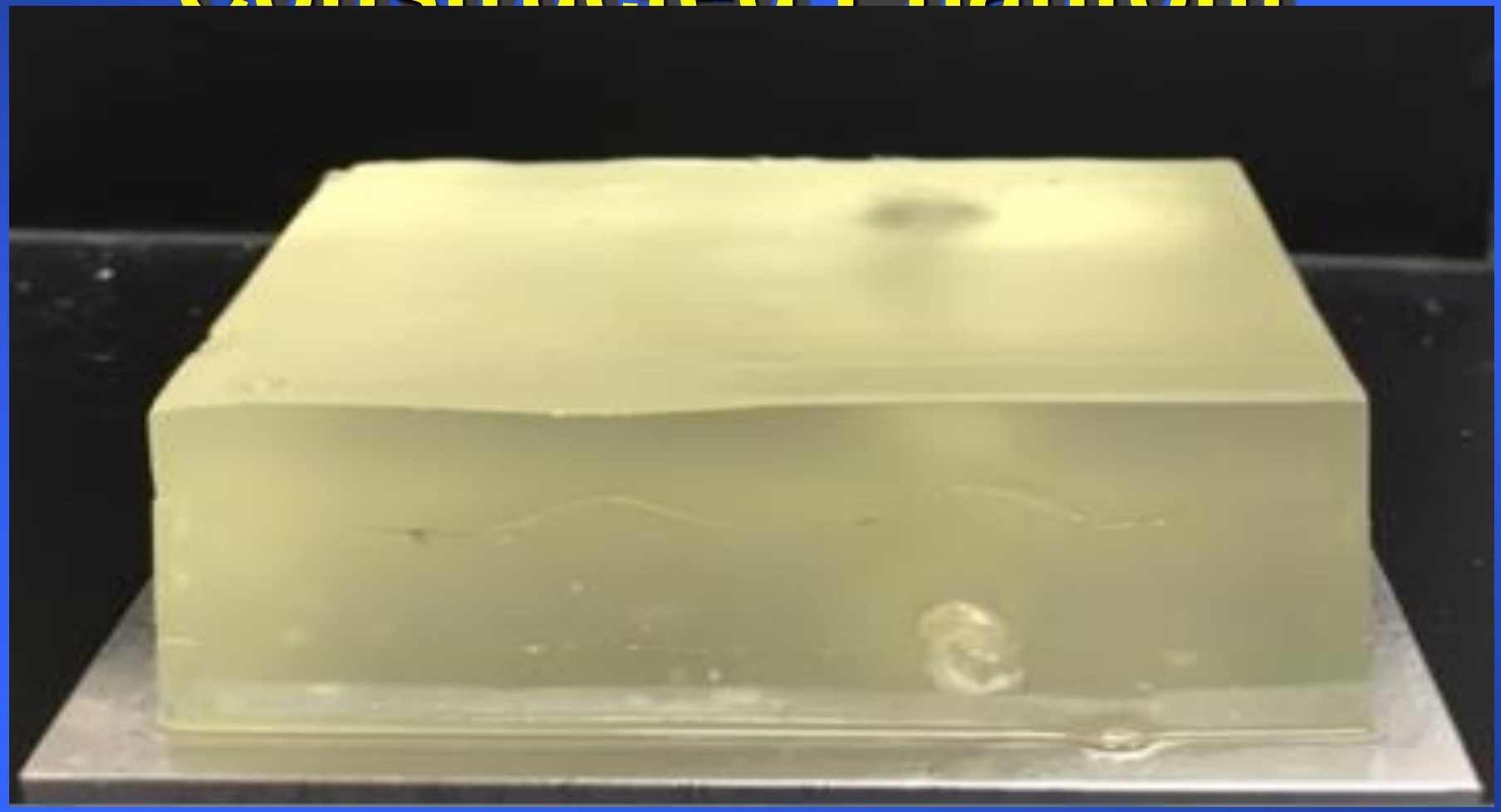
- Tunable Polyvinyl Chloride Plastisol
  - Adjustable Acoustic and Stiffness Properties
  - Ingredients:
    - Polyvinyl Chloride Resin
    - Plasticizers : Benzyl Butyl Phthalate (BBP); diethylhexyl adipate (DEHA)
    - Glass Beads for Backscattering

YOUNG'S MODULUS OF MATERIAL

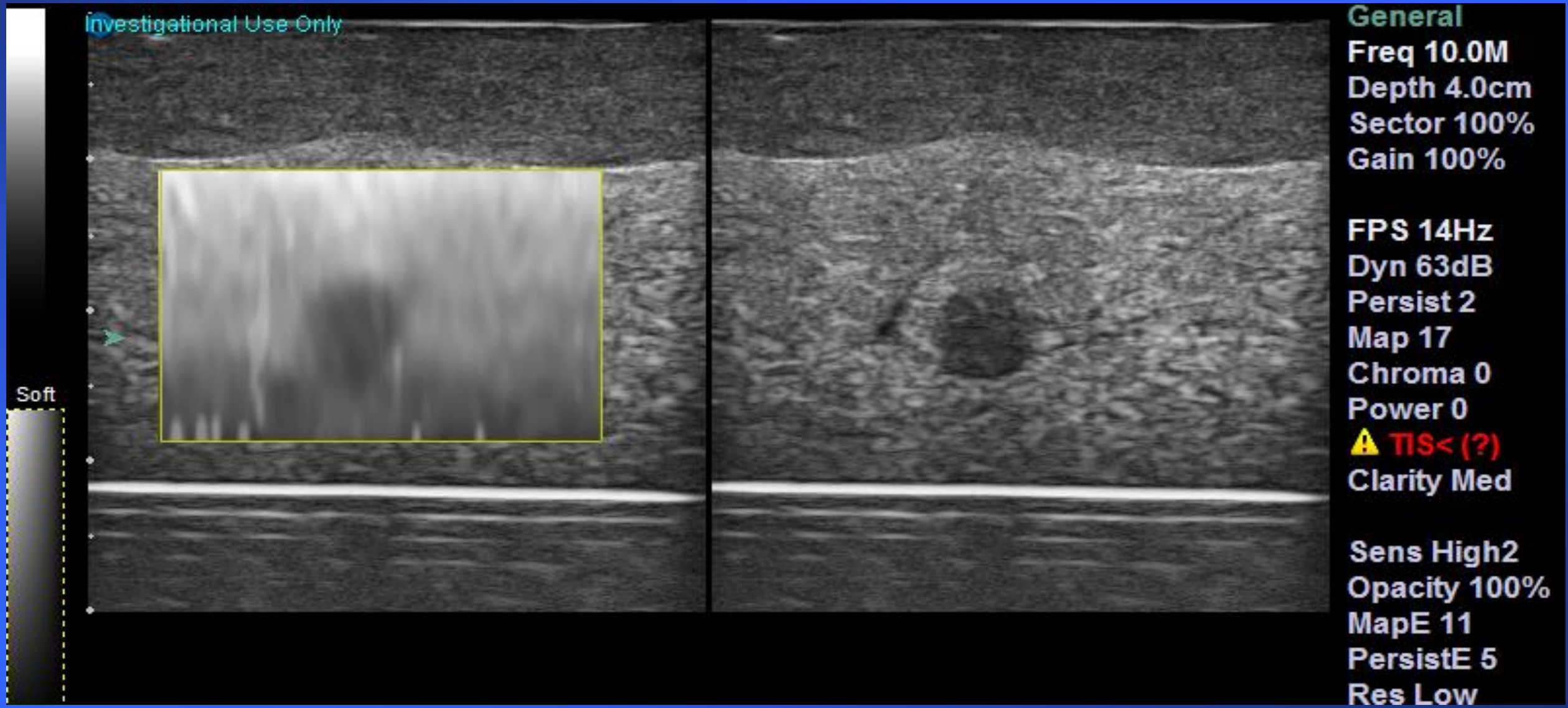
Tissue type	Pf (kPa)	Pg (kPa)	Lesion (kPa)
Young's modulus	6.4	9.4	32.6

Young's modulus values were set to match published work by Krouskop et al, 1998

Constructed Phantom



ELASTOGRAM + B-MODE IMAGES



CONCLUSIONS

- By Providing Documented Performance Improvements Over Current Measurements, the QIBA US SWS Profile can Significantly Enhance the Use & Popularity of Shear Wave Ultrasound in all Areas
- Components of the Profile Can be Reused in Other Profiles and in Other Types of Imaging QA
- Provides a Framework for Additional Profiles and Development of Quality Monitoring Tools

DISCLAIMER

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