Critical Connection

To Whom It May Concern:

As the medical director of CriticalConnection, a community-based and supported consortium of employers and physicians dedicated to improving the quality of healthcare in Austin, Texas, I would like to comment on the recent FDA draft guidance document ("DGD") on Analyte Specific Reagent testing.

The draft guidance FAQ document on analyte specific reagents (ASRs), issued 7 September, 2006 (http://www.fda.gov/cdrh/oivd/guidance/1590.pdf) purportedly to clarify the regulations and the roles and responsibilities of ASR manufacturers regarding commercially distributed ASRs (21 CFR 809.10(e), 809.30, and 864.4020) seems to be at odds with the FDA's mission and is likely to result in degradation in the quality of patient care.

I understand that the FDA originally had developed the ASR rule to clarify the agency's policy with regard to the status of in-house tests and to provide incremental controls to ensure the quality of the materials being used to create these tests. I agree with the intent to ensure that laboratories preparing these tests are able to establish and maintain performance and to assure that those laboratories understand their responsibility for accomplishing this. In addition, I understand that the intent is to provide appropriate labeling so that healthcare users will understand how these tests were being validated. The rule defines the active ingredients of in-house tests as analyte specific reagents and sets up a series of controls applicable to the manufacturers selling these devices and the laboratories using them. The agency has established polices on "home brew" tests and the regulation of laboratories that develop and offer such test. I must note that until recently, well-established FDA policy provided that such assays were exempt from regulation and that the agency had no intent to regulate them.

However, under the current draft of the FAQs, it seems that there has been a substantive policy change that would result in a condition wherein no product could qualify as an ASR. For example, in Section 8 of the DGD, it states that "*multiple moieties (e.g. antibodies, probes, primers) bundled together in a preconfigured or optimized way so that they are intended to identify and quantify more than one chemical substance or ligand*" are not ASR's. The very next sentence then states that "*such products are not ASRs because ASRs are defined as intended for use in "identification and quantification of an individual chemical substance or ligand in biological specimens*". The statements are internally inconsistent and technically not viable. For example, when using real time polymerase chain reaction (PCR) testing to identify "*an individual chemical substance*", one must use more than one primer to perform the PCR reaction. Based on the above cited statement, the use of more than one primer disqualifies the reaction as an ASR. It

seems unlikely that the HHS intends to drive all PCR tests into the in-vitro diagnostic (IVD) process, but the current language would mandate that result.

The draft goes on to state that "*FDA considers a product a test system rather than an ASR when it includes more than one ASR*". The concept that there may be only one ASR is inconsistent with how tests are performed and goes against the current regulations as 21 CFR 864.4020 states that "*ASR's are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents, which through specific binding or chemical reaction with substances in a specimen are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens*". The regulations say nothing about an ASR being singular. The draft FAQs imposition of "one ASR/one ligand" is a material change to 21 CFR 864.4020, and is therefore an expansion, rather than a clarification, of the existing regulation.

The real concern is that the outcome of this arbitrary expansion of the existing regulation could result in precluding from patient care many of the existing ASR testing procedures that are the main-stay of current medical diagnosis, including immunohistochemical assays (IHC), fluorescent in-situ hybridization (FISH) testing, real-time PCR assays, and or oligoligation assays.

Section 8 of the draft cites "reagents that are extensively processed (e.g., arrayed on beads) as examples of entities that the FDA does not consider to be ASRs. The term "extensively processed" is extremely confusing considering the world of reagents. All reagents that are to be used as an ingredient of a "home brew" test are "extensively processed". Such processing can include sterilization, pH calibration, manufacturing under cGMP conditions, etc.

To cite a specific example of this concern, on page 7 of the DGD, the FDA cites the use of "arrayed on beads" as an example of 'extensively processed'. The Luminex open platform is an example of an "arrayed on beads" assay. As each labeled microsphere 'bead' is in itself a single assay, there is no real difference between assaying for many analytes in many tubes vs. assaying for many analytes on many microspheres. If assaying for many analytes in many tubes, slides or microbeads is an example of 'extensively processed' then all fluorescent in-situ hybridization (FISH) testing, real-time PCR assays, and or oligoligation assays are likewise 'extensively processed'.

This arbitrary designation would certainly hamper the availability of certain testing procedures that have been developed by accredited institutions and have resulted in improved patient care in the disciplines of clinical oncology (e.g. neoplasm identification by IHC; Her2-neu testing, etc.), obstetrics and gynecology (e.g. HPV phenotyping; genetic testing, etc.) and infectious disease (e.g. HIV, HCV and HPV phenotyping; rapid infectious organism identification, etc.). Specifically, HIV, HCV and HPV phenotyping methodologies have no FDA-approved IVD against which to compare 'home brew' or ASR methods, precluding these clinically vital test results from the physicians' diagnostic armamentarium. One hundred and twelve physicians including the members of the Texas

Healthcare Quality Collaborative, Adult Care of Austin, Capitol Surgeons Group and the Austin Radiological Association (see attached signatures) agree with me and support this conclusion that…

These proposed changes would result in a lowered standard of care for all patients by depriving clinicians of well-tested and accepted modalities of diagnosis that are now the standard of care.

We further believe that these proposed changes are contrary to the mission of the FDA:

> The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. *The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.*

If the FAQs are passed as currently drafted, many tests will no longer be available to patients. Companies will have to decide if it is feasible to take so many tests through the very expensive and lengthy IVD process. Ultimately, many tests will not be submitted for IVD processing, and will be taken off the market all together.

It is difficult to ascertain how sweeping the market of many useful tests is protecting or advancing the public health but it is not difficult to see who will suffer most…the patient.

Recommendation to the FDA

We believe that the existing regulatory framework provides sufficient oversight, and can be bolstered by augmenting the CLIA regulations to address any specific safety concerns of the FDA.

Comments:
We believe that the proposed changes violate the Administrative Procedures Act as the FDA and HHS must comply with that Act if they seek to change the agency's practices and established polices on "home brew" tests. Until recently, well-established FDA policy provided that such assays were exempt from regulation and that the agency had no intent to regulate them. FDA cannot depart from the precedent without providing some explanation for the change.

In addition, the FDA must properly allow public comment and review for such extensive changes. Under the APA, before the FDA may implement a new policy, it must explain the reasoning behind the change and open the new policy to public comment. Use of FAQ's as a mechanism for changing policy is not appropriate.

The APA requires notice-and-comment rulemaking whenever a federal agency wants to act in a way that materially changes established burdens and benefits, "*by which rights or obligations have been determined, or from which legal consequences will flow.*" Clearly,

FDA is now acting to substantively change the "*rights and obligations*" of ASR manufacturers. And the "*legal consequences*" that will flow from not meeting the FDA's demands are known and already occurring such as warning letters, seizures, injunction, civil penalties and prosecution.

Finally, we believe that the FAQs are inconsistent with current technology and create more ambiguity that will result in a lower standard of care for all patients throughout the country.

Sincerely,

Paul A. LeBourgeois, MD, FCAP, FASCP
CriticalConnection Medical Director

CriticalConnection, Inc. 6225 US 290 East Austin, Texas 78723 P.O. Box 15584 Austin, Texas 78761-5584 512-236-1887

Texas Healthcare

P.O. Box 15584
Austin, Texas 78761-5584

MD
PETER A. RUFF MD.

PhD
Steven H. Pickett, M.D., Ph.D.

MD
David Fleeger, MD
Austin Colorectal Surgeons

D. Berger, DPM

Tom R. Green MD
3708 Timmie St
Houston Tx. 77049
General Practice - Board Certified

Donald P. Ward m.d.

Adult Care of Austin, PA
7201 Manchaca Road, Suite B
Austin, Texas 78745.5259
512.443.3577

Amy Arrant - Internal Medicine

Lee Johannsen, MD Emergency Medicine

Jeff Rhodes - Emergency Medicine

Neil Mendelsohn - Emergency Medicine

B. Duke Kimbrough MD - Emergency Medicine
Col (Ret.)

Robert Stroud MD - Internal Medicine

MICHAEL B. MARTIN RADIOLOGY

Allen Sonstein, MD

Steven Dobberfuhl, MD

Homar Bartra, MD

Adult Care of Austin, PA
7201 Manchaca Road, Suite B
Austin, Texas 78745.5259
512.443.3577

S. Venkatesh, MD Internal Medicine

V. Nguyen. MD Internal Medicine

R. Markus, MD General Surgery

Casey Mulcihy MD Pediatrics

S. Asfouri, MD Obstetrics & Gynecology

J. Myers, MD Hematology/oncology

Plant Claudia MD Hematology/Oncology

T.N. Tracey MD - Cardiology

Lewis King, MD CV Surgery

ER

ER

INTERNAL MEDICINE
Homar Bartra, MD FACP
Steven Dobberfuhl, MD
Allen Sonstein, MD

Barbara Carson, RN C-FNP
Linda Hargrove, RN C-FNP
Kaye Kendall, RN C-FNP

AUDIOLOGY
Daniel Harris, PhD CCC-A

SOCIAL SERVICES
John Pratt, LCSW

PHYSICAL THERAPY
Debra McDowell, PT MSHP

CHIROPRACTIC MEDICINE
Jeff Fluitt, DC

Texas Healthcare [redacted]

P.O. Box 15584
Austin, Texas 78761-5584

Board of Trustees

W. Thomas Cotten
Chairman
CEO, Texas Medical Liability Trust

Richard Bettis
Vice-Chairman
CEO, Texas Hospital Association

Phil Dunne
Secretary/Treasurer
Healthcare Consultant
Former CEO,
Texas Medical Foundation

Jim Martin, R.Ph
Executive Director/CEO
Texas Pharmacy Association

David R Woerner 9-11-2006

DAVID R. WOERNER, M.D.
4310 JAMES CASEY ST., #1-A
AUSTIN, TEXAS 78745
TEL: (512) 442-2611
FAX (512) 442-4906

Mark Wallace, MD.

ADVANCED PAIN CARE
6818 Austin Center Blvd., Ste. 205
Austin, TX 78731

Reg C Martin, MD

ADVANCED PAIN CARE
6000 S. Mopac, 2nd Floor
Austin, TX 78749

Paul Tucker M.D.

Texas Cardiovascular Consultants

CAPITAL SURGEONS GROUP

Capital Surgeons Group, PLLC
Comprehensive, Compassionate General Surgery Care

Stephen S. Clark, M.D., FACS
Tim L. Faulkenberry, M.D., FACS
Mark R. Sherrod, M.D., FACS
Nancy G. Marquez, M.D., FACS
Paula S. Oliver, M.D., FACS
Patrick C. Dillawn, M.D., FACS
Steven M. Fass, M.D., FACS
Rob A. Fuller, M.D., FACS
Moya M. Griffin, M.D., FACS
Bridget M. Brady, M.D.

Capital Surgeons Group

Texas Healthcare [redacted]

P.O. Box 15584
Austin, Texas 78761-5584

James R Eskew, MD

Michael J. Yaum, MD

Harish Gogneja, MD
Austin, Tx

Chia-wen Hsu, MD, MPH
Austin, Tx

Scott Becker, MD
Austin, Tx

Robert E. Butler, MD

Pradeep Ramamurthy, MD
Austin, Tx

Stephen Letts, MD
Austin, Tx

Dan Rice, MD
Austin, Tx

Texas Healthcare [redacted]

P.O. Box 15584
Austin, Texas 78761-5584

J.D. Hudson MD

J.D. Hudson, MD
Neurology
sleep

E. Ortiz, MD
Neurology
sleep

Rhonda Boles RN FNP-C

M Edmond MD

M. Edmond, MD
Neurology

Peter Miller MD

Peter Miller, MD
Internal Medicine
Nephrology

C. Cipley, MD

K. Simpson, MD

B. Welch, MD

S. Beathard, MD

W. Moore, MD

AUSTIN RADIOLOGICAL ASSOCIATION

10900 Stonelake Blvd. • Suite 250 • Austin, Texas 78759 • P 512.795.5100 • F 512.795.5122

Signature
Greg Karnaze
Printed Name

Signature
Printed Name

Signature
Printed Name

Signature
Connie Hsu
Printed Name

Signature
DAVID GOLDBLATT
Printed Name

Signature
David Feldman
Printed Name

Signature
Jeffrey S. Lava
Printed Name

Signature
Hillel Ben-Avi
Printed Name

Signature
NEAL RUTLEDGE
Printed Name

Signature
Anthony K. Trevino
Printed Name

Signature
KONRAD L. HOELSCHER
Printed Name

Signature
Andrew Renfroe
Printed Name

Signature
Marc McLellan M.D.
Printed Name

Signature
Eugene Tong
Printed Name

AUSTIN RADIOLOGICAL ASSOCIATION

10900 Stonelake Blvd. • Suite 250 • Austin, Texas 78759 • P 512.795.5100 • F 512.795.5122

Signature
Vince Wiseman
Printed Name

Signature
Curtis A. McClure
Printed Name

Signature
Mary Z. Wincott
Printed Name

Signature
Thomas Fletcher
Printed Name

Signature
Robert Milman
Printed Name

Signature
Michael Aronoff
Printed Name

Signature
Binh Truong
Printed Name

Signature
Kent E Ibanez
Printed Name

Signature
Chris Butschek
Printed Name

Signature
William Rodriguez
Printed Name

Signature
John E Manning
Printed Name

Signature
Joshua Abramowitz
Printed Name

Signature
Gael Donegan
Printed Name

Signature

Printed Name

AUSTIN RADIOLOGICAL ASSOCIATION

10900 Stonelake Blvd. • Suite 250 • Austin, Texas 78759 • P 512.795.5100 • F 512.795.5122

Signature G Trevian lt Printed Name	Signature Printed Name
Signature Debra J Pennington Printed Name	Signature Printed Name
Signature F. Michael Pfeifer Printed Name	Signature Printed Name
Signature Elizabeth Moorehead Printed Name	Signature Printed Name
Signature JOHN HOLT MD Printed Name	Signature Printed Name
Signature JOHN R LEARY Printed Name	Signature Printed Name
Signature ANTHONY M MASARIK MD Printed Name	Signature Printed Name