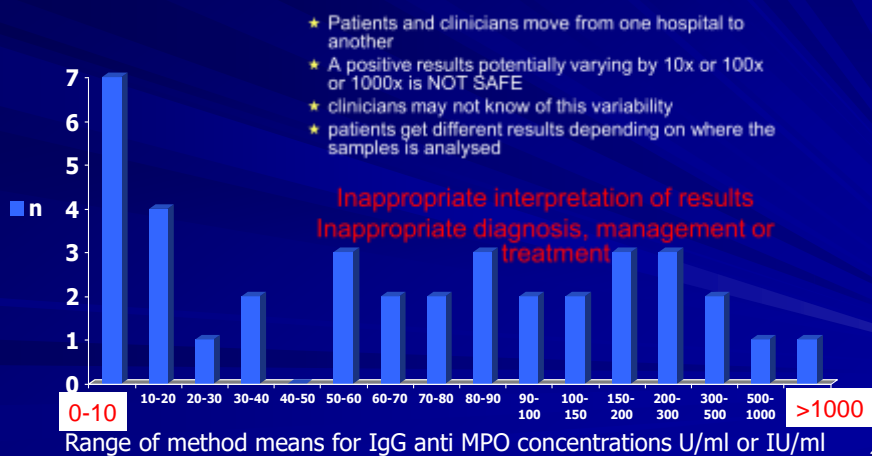


IFCC involvement in harmonisation or standardisation of autoimmune tests – challenges in a new field of investigation.

Joanna Sheldon
Protein Reference Unit,
St. George's Hospital

There is a problem!

Used with permission of UKNEQAS 2010
Antibodies to myeloperoxidase, known positive sample
– distribution of method means (n=38)

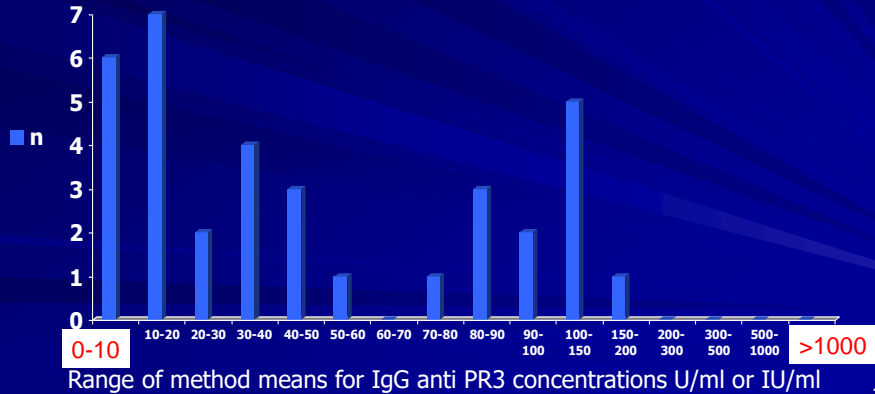


There is a still a problem!

Used with permission of UKNEQAS 2018

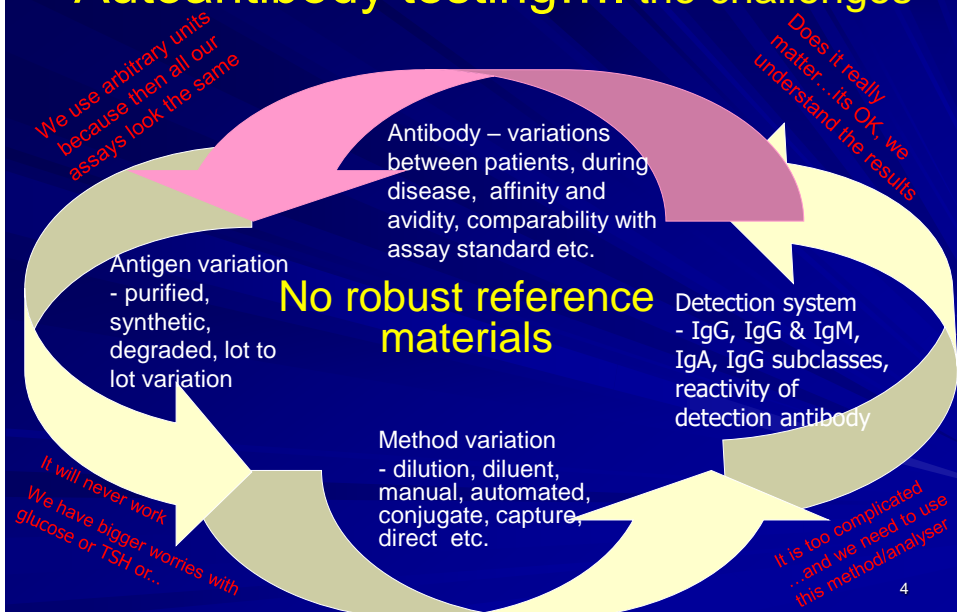
Antibodies to proteinase 3, known positive sample
– distribution of method means (n=35)

A >10x difference in results is STILL not safe



3

Autoantibody testing... the challenges



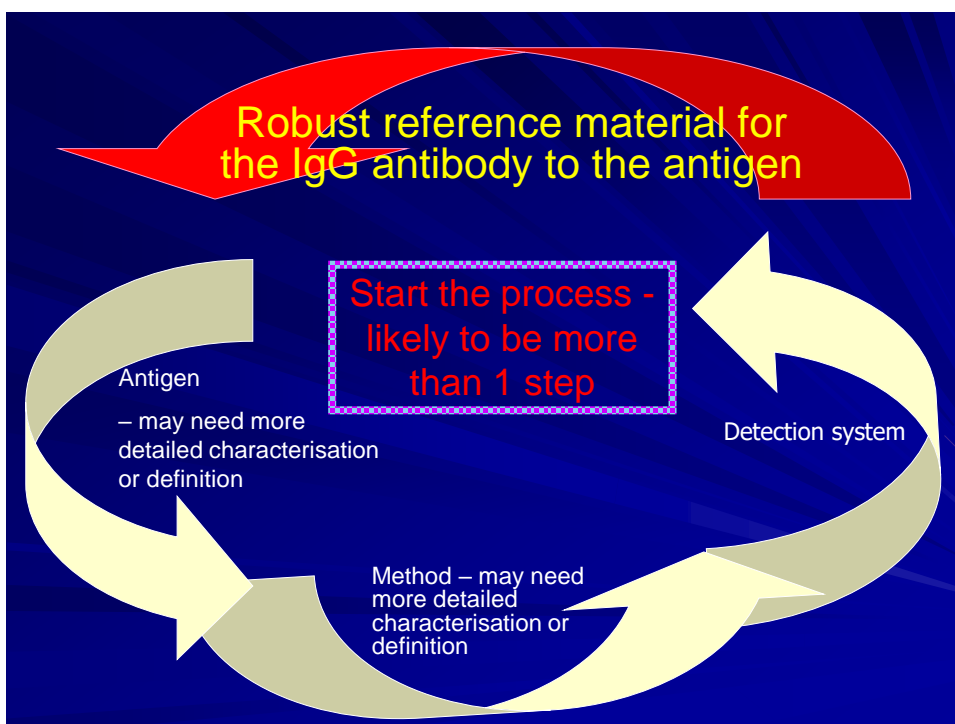
4

IFCC Committee on Harmonisation of Autoantibody Testing - aims

- ★ Identify which autoantibodies would be suitable for standardisation

★ Prepare and evaluate reference materials

- ★ Identify the sources of variation in autoantibody testing
- ★ Introduce reference materials and assess their impact



Certified materials for IgG anti MPO and IgG anti PR3

NOTE – values assigned in mg/L NOT in arbitrary units



ERM-DA476/IFCC

- ★ IgG anti Myeloperoxidase
- ★ Certified value 84mg/L
- ★ Uncertainty 9mg/L

ERM-DA483/IFCC

- ★ IgG anti Proteinase 3
- ★ Certified value 270mg/L
- ★ Uncertainty 29mg/L

We have certified materials for IgG anti MPO and IgG anti PR3

Why aren't we using them?

- ★ We need to reduce the risk to patients of ANCA testing
- ★ We need to reduce the variability of ANCA testing
- ★ We need to better understand the sources of variation in autoimmune tests



- ★ Who knows what is right?
- ★ It will be expensive to re-write all the kit inserts
- ★ It will be complicated
- ★ We understand what we are doing now
- ★ We need to get FDA approval and that is difficult, expensive, complicated etc.

We need to get FDA approval and that is difficult, expensive, complicated etc.

1

The US Food and Drug Administration - responsible for **protecting the public** health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices.

2

IF something has been through an FDA evaluation process and retains FDA approval, it is satisfactory. Anything that is comparable in the future will be compared to this **PREDICATE** device.

Comparison to Predicate device.

510 submission (for IgG anti PR3, MPO and GBM) - sections

A-G – names, type of test etc.

H - intended use

I – device description

J – Substantial Equivalence Information – to PREDICATE

- predicate device names and 510K number(s)

- table of comparison of new test to predicate - intended use, assay type, quantitation, assay characteristics: temp, cal frequency etc., cut off values, similarities and differences to predicate

K – standard/Guidance documents referenced

L – test principle

M – performance characteristics – precision, linearity, detection limit, analytical specificity, assay cut off

Traceability, Stability, Expected values

Comparison – with predicate

Clinical studies – if good comparison with predicate, none needed

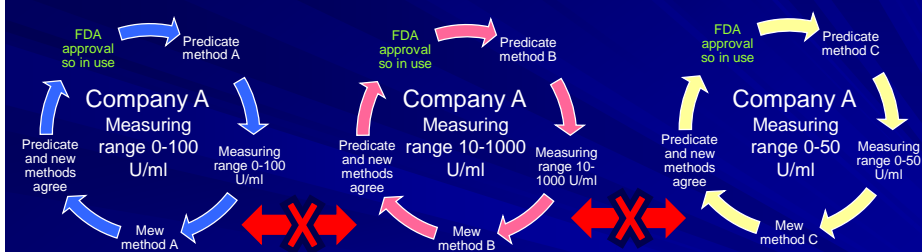
N – Proposed labelling

O - Conclusions



TRACEABILITY is 1 line in 13 pages

Comparison to Predicate device hypothetical analyte protein X



No FDA expectation of traceability
No expectation of comparability between different manufacturers

This explains (in part) some of the issues we have

- ★ Samples from some patients do not behave consistently in all methods
 - ★ In terms of positivity or negativity
 - ★ In terms of value
- ★ IgG anti proteinase 3

Sample	A IU/ml	B IU/ml	C IU/ml	D U/ml
958971	13.6	5.3	>200	
960223	4.1	15.2	70.5	
958651	21.4	22.0	114.0	
958228	4.7	6.0	28.7	
955695	2.3	10.8	<5	
99261	95.2	<4	<5	
952420	9.1	12.0	<5	
952501	2.3	9.1	<5	
953548	10.7	43.4	>200	
926188	3.5	29.7	>200	
937548	10.7		>200	
926188	3.5		>200	
81305			8.0	0.4
81906			6.2	0.3
81670			3.8	>200
58376	<2			99.0
KJ	<2			15.0
94483	<2			30.0
984687	<2			7.1
923406	9.1			190.0

This explains (in part) some of the issues we have e.g.

- ★ Samples from some patients do not behave consistently in all methods

- ★ In terms of positivity or negativity
- ★ In terms of value

- ★ IgG anti proteinase 3

Sample	A U/ml	B U/ml	C U/ml	D U/ml
95899	13.5	3.3	>200	
96022	4	15.2	70.5	
95861	21.4	22.0	114.0	
95828	4.7	6.0	28.7	
955695	2.3	10.8	<5	
99261	35.0	3.4	<5	
952400	9.5	12.0	<5	
902501	2.3	9.1	<5	
933548	10.7	43.4	>200	
926188	3.5	29.7	>200	
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13

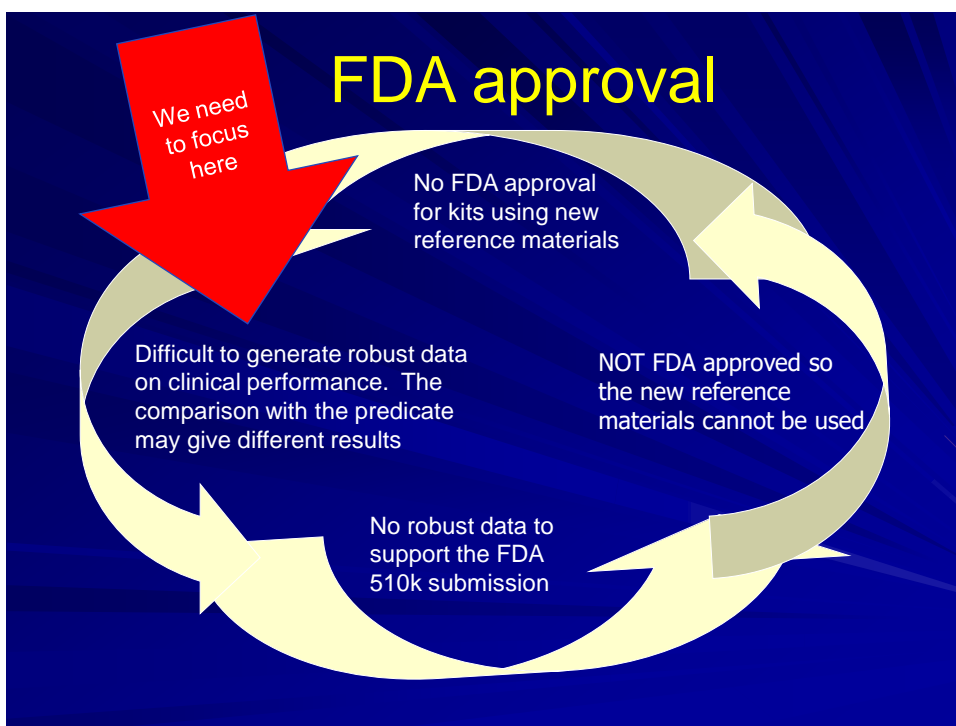
FDA approval

No FDA approval for kits using new reference materials

Difficult to generate robust data on clinical performance. The comparison with the predicate may give different results

NOT FDA approved so the new reference materials cannot be used

No robust data to support the FDA 510k submission



What should we be doing? - 1

IFCC C-HAT and users needs to

- ★ encourage companies to calibrate their assays w.r.t. ERM-DA476/IFCC and ERM-DA483/IFCC
 - ★ This could be as an option
 - ★ Labs could continue to report in their usual units but data traceable to the reference materials could be generated

- ★ Ultimately, this should generate robust data on clinical performance w.r.t. the IRPs to populate the FDA 510k submissions

What should we be doing? - 2

IFCC C-HAT and users needs to

- ★ encourage EQA providers to accept results in mg/L calibrated w.r.t. ERM-DA476/IFCC and ERM-DA483/IFCC
- ★ Ultimately, this should generate robust data on whether the methods, when measuring w.r.t. a common reference preparation give comparable results.

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What should we be doing? - 3

IFCC C-HAT and users needs to

- ★ Understand better the sources of variation in autoantibody testing
- ★ This is in progress for the IgG anti myeloperoxidase and IgG anti proteinase 3 testing
 - ★ Collaborating with Prof Speck to map the epitope reactivity of the reference materials
- ★ This will be invaluable in determining how to proceed with autoantibody standardisation from an EVIDENCE BASE
- ★ This will provide supporting evidence and explanation for any FDA submission

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We can improve the numbers....

- ★ The IFCC committee on harmonisation of autoantibody testing have made huge advances – there are now traceable commutable reference materials for IgG anti MPO and IgG anti PR3
- ★ Significant work is needed to get these materials widely adopted
- ★ Collaborative work is necessary
 - ★ IFCC C-HAT
 - ★ Companies
 - ★ EQA providers
 - ★ Laboratories
 - ★ Patient groups
 - ★ FDA, CE, Device validation groups
 - ★ Professional bodies
 - ★ Service users