
Scheppingsverhaal


Scheppingsverhaal
Medisch Laboratorium


Op de Eerste Dag


Op de Eerste Dag
Schiep Roche een IgX Bepaling


Op de Eerste Dag
Schiep Roche een IgX Bepaling
……Referentiewaarden 6 – 14 g/L


Op de Tweede Dag


Op de Tweede Dag
Schiep Beckman een IgX Bepaling


Op de Tweede Dag
Schiep Beckman een IgX Bepaling
……Referentiewaarden 4 – 11 g/L


Op de Derde Dag


Op de Derde Dag
Schiep Abbott een IgX Bepaling


Op de Derde Dag
Schiep Abbott een IgX Bepaling
……Referentiewaarden 8 – 20 g/L


Op de Zevende Dag


Op de Zevende Dag
Zag het Medisch Laboratorium


Op de Zevende Dag
Zag het Medisch Laboratorium
Dat het niet goed was


Want wat was het Probleem?

Eén IgX Bepaling

Verschillende Referentie Waarden

Roche 6-14 g/L
Beckman 4 – 11 g/L
Abbott 8 – 20 g/L

Verwarring

…..Elkaar tegensprekende Richtlijnen
……Andere Beslisgrenzen
…….Gevaar Foute Beslissingen Patiënten

Algemeen Probleem

1. Ontdekking Nieuw Analiet
2. Alle Fabrikanten willen erbij zijn
3. Ontwikkelen een eigen Test
4. Niet vergelijkbare resultaten
5. Verwarring

Daar moet wat aan gedaan worden

En dat gebeurt ook……..

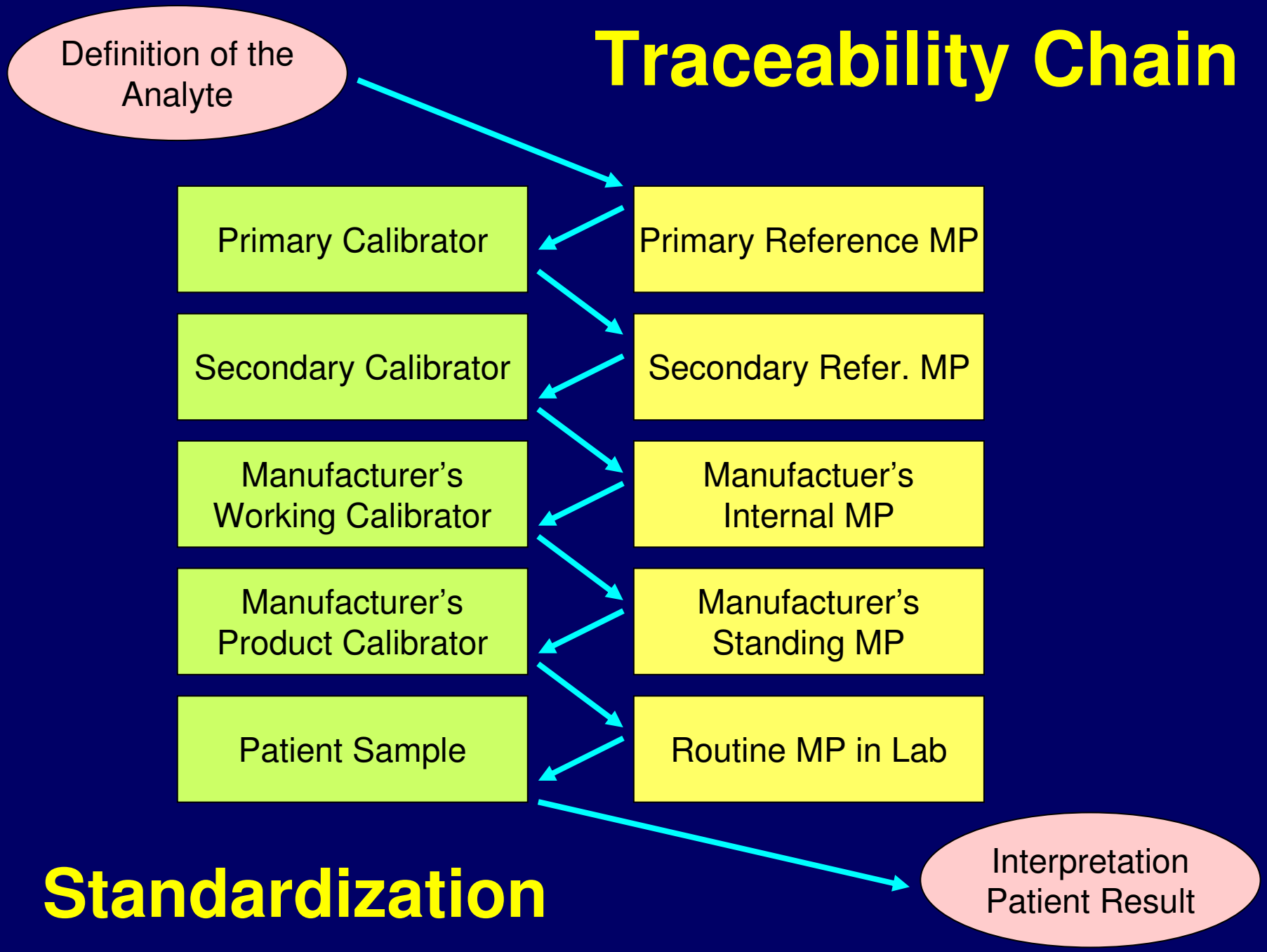
……..Op wereldschaal

Equivalence, Why?

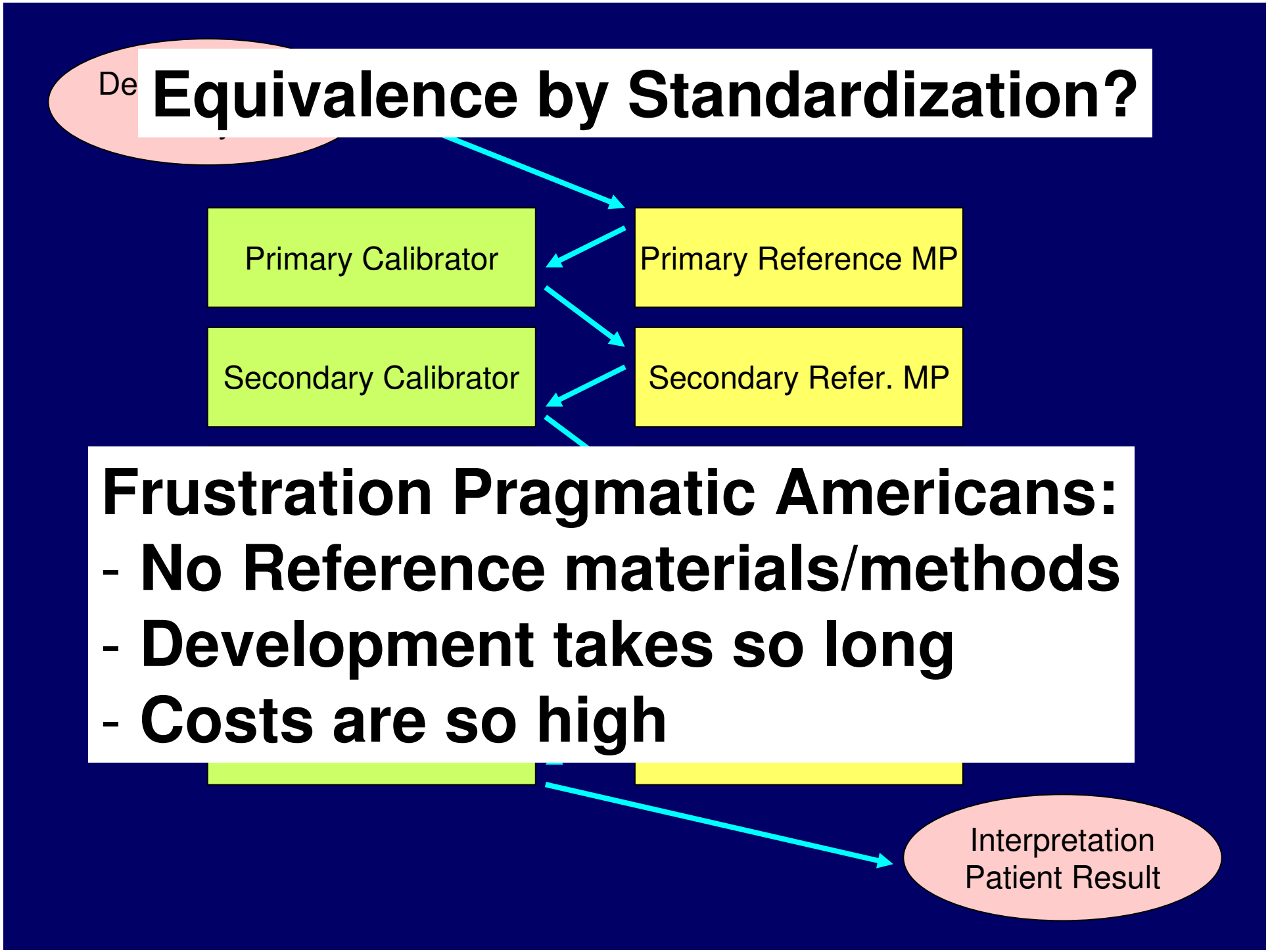
"Results between different methods should be equivalent, within clinically meaningful limits, to enable optimum use of clinical guidelines for disease diagnosis and patient management"

Clin Chem 2011;57:1108-17

Traceability Chain



Standardization


De
Equivalence by Standardization?
Primary Calibrator
Primary Reference MP
Secondary Calibrator
Secondary Refer. MP
Frustration Pragmatic Americans:
- No Reference materials/methods
- Development takes so long
- Costs are so high
Interpretation
Patient Result

Tweede Benadering

Naspeurbaarheid Laboratorium Resultaat

“Traceability”

Standaardisatie: Échte Waarheid
Referentie Methode
Absoluut IJkpunt

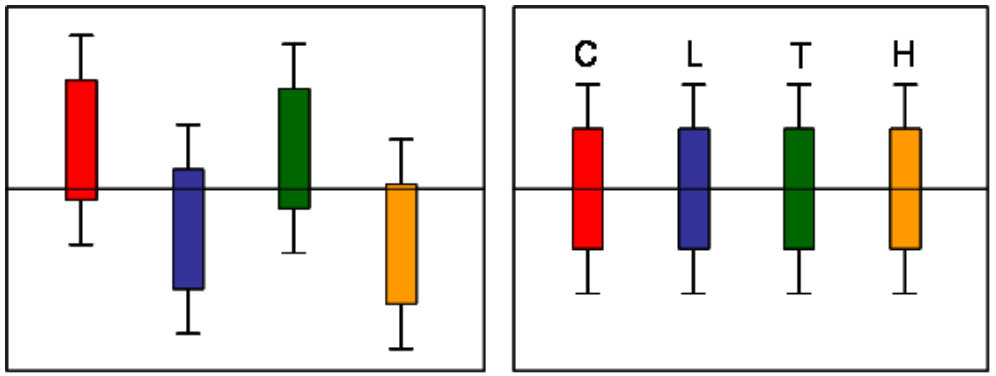
Tweede Benadering
Naspeurbaarheid Laboratorium Resultaat
“Traceability”

Standaardisatie: Échte Waarheid
Referentie Methode
Absoluut IJkpunt

Harmonisatie: Relatieve Waarheid
Arbitraire Referentie Methode
Arbitrair IJkpunt

AACC Harmonization Initiative

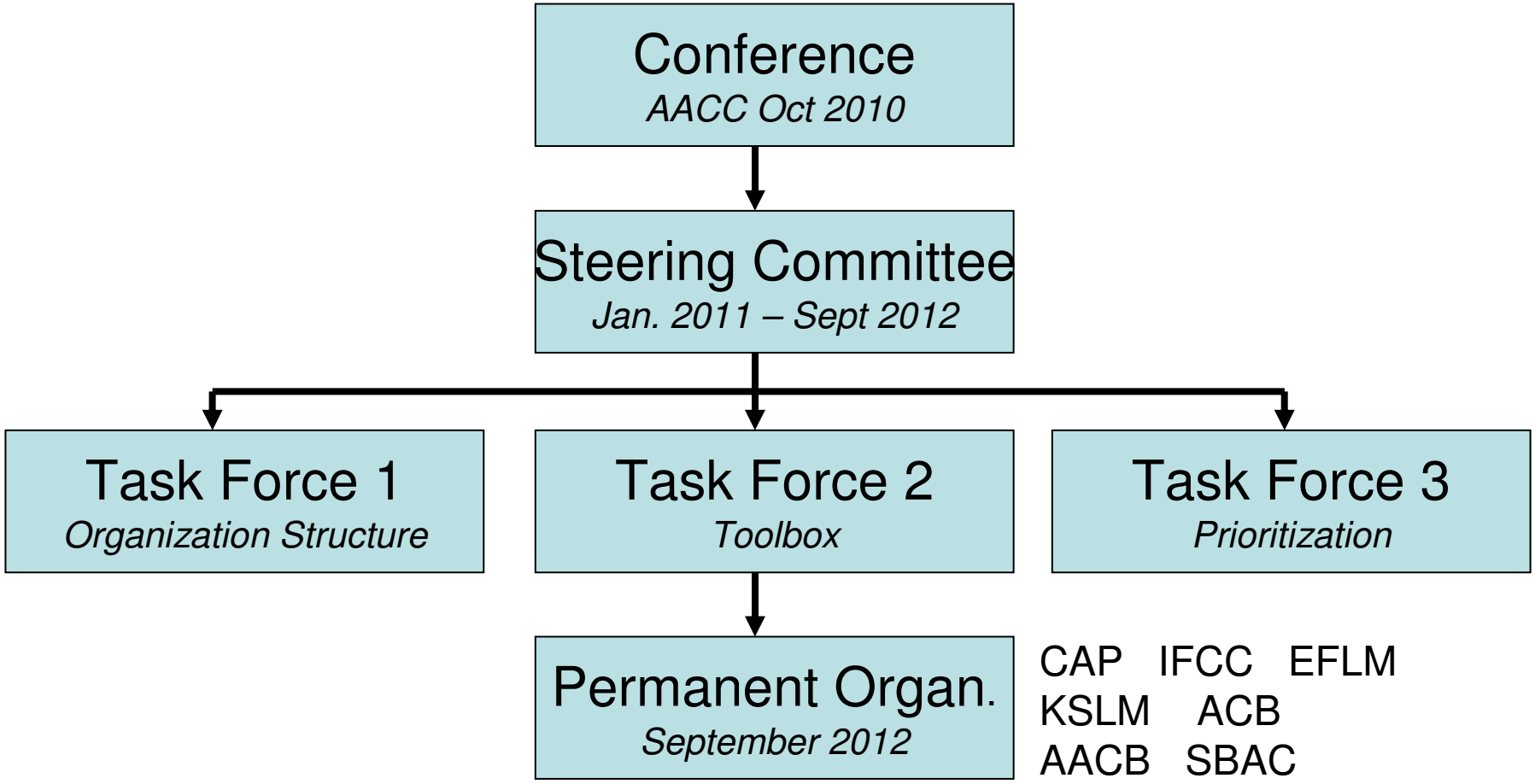
Perfect is the Enemy of Good



Clinical Lab Test Harmonization

You want something to happen

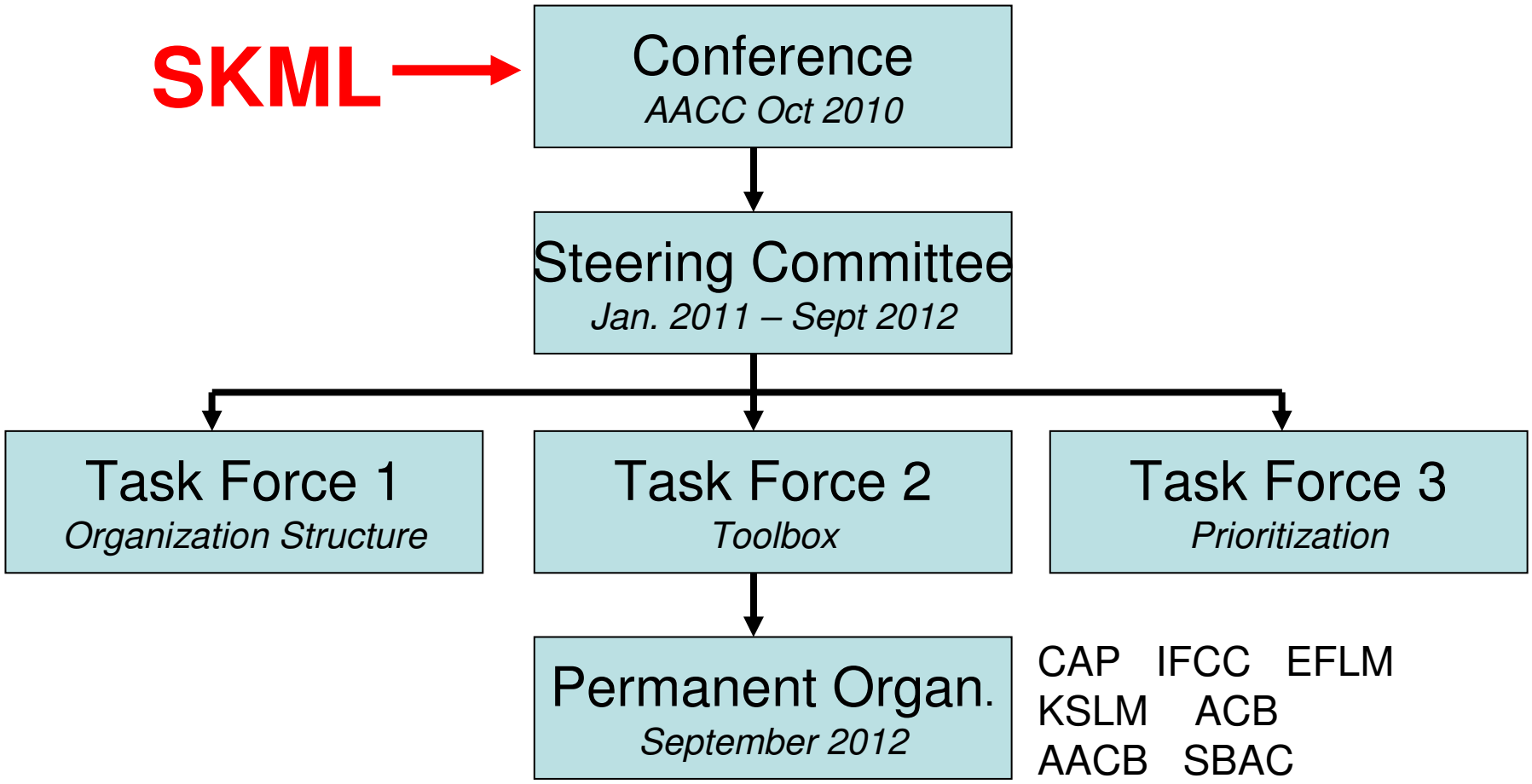
The American Approach



Let's Start Doing It

You want something to happen

The American Approach



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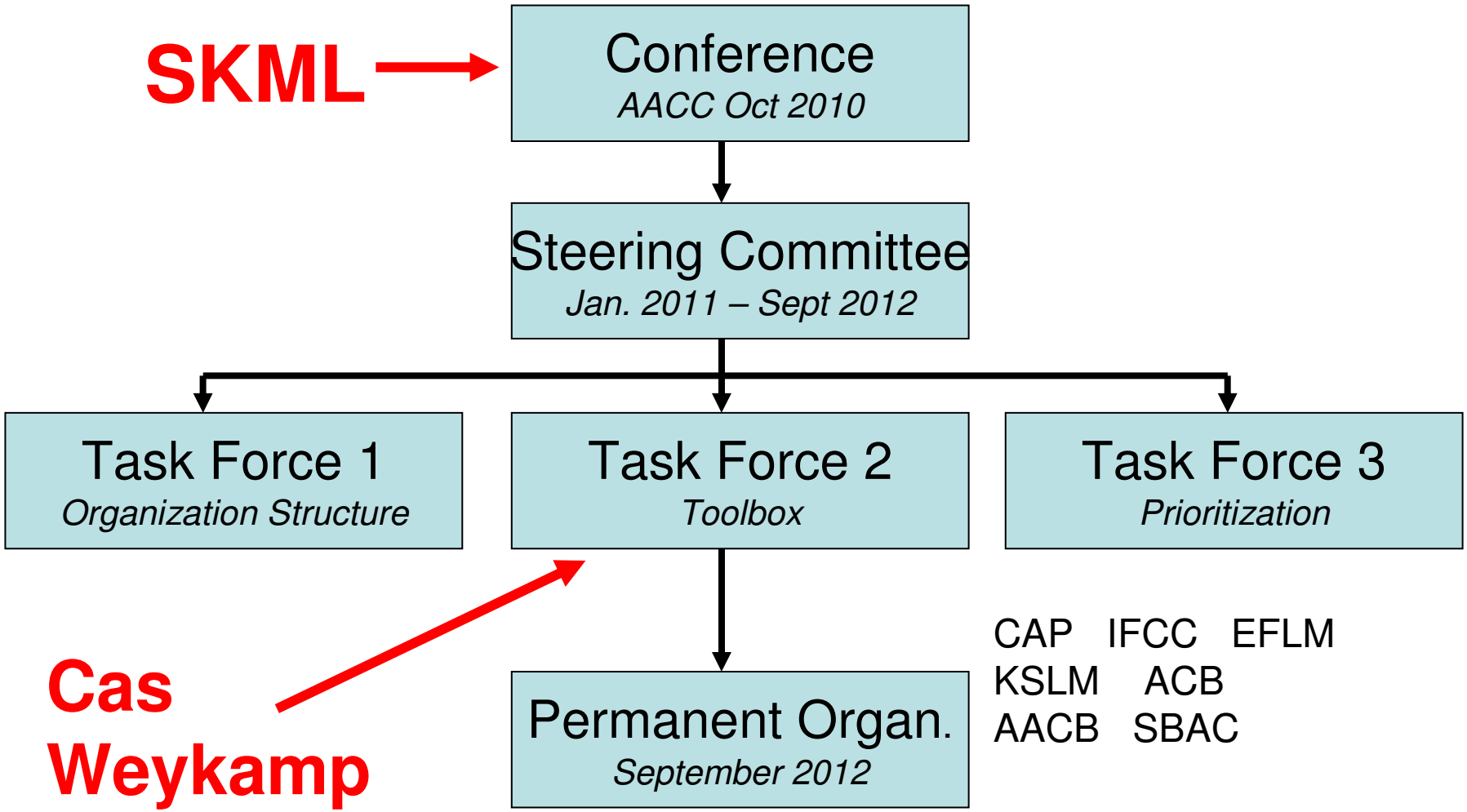

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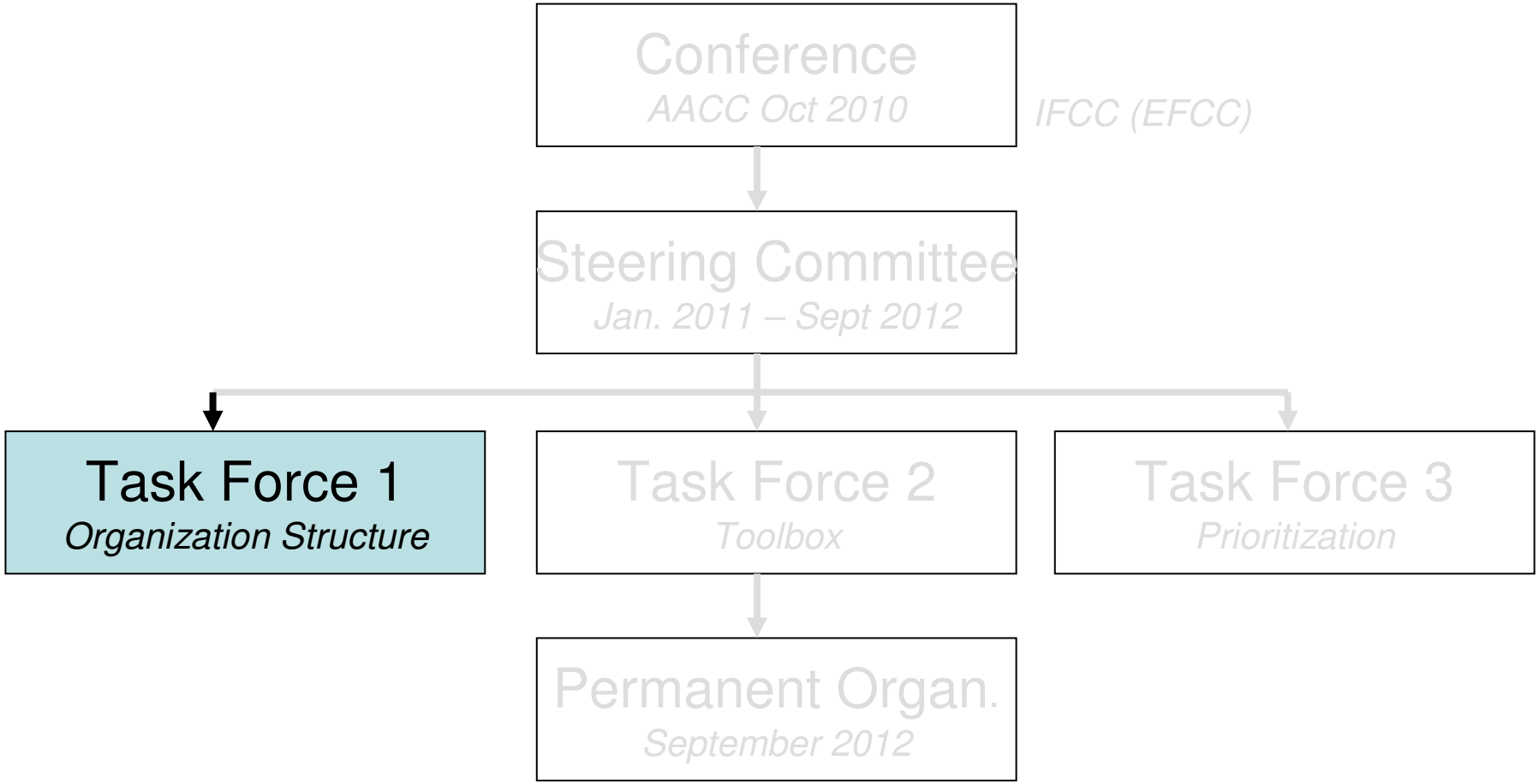
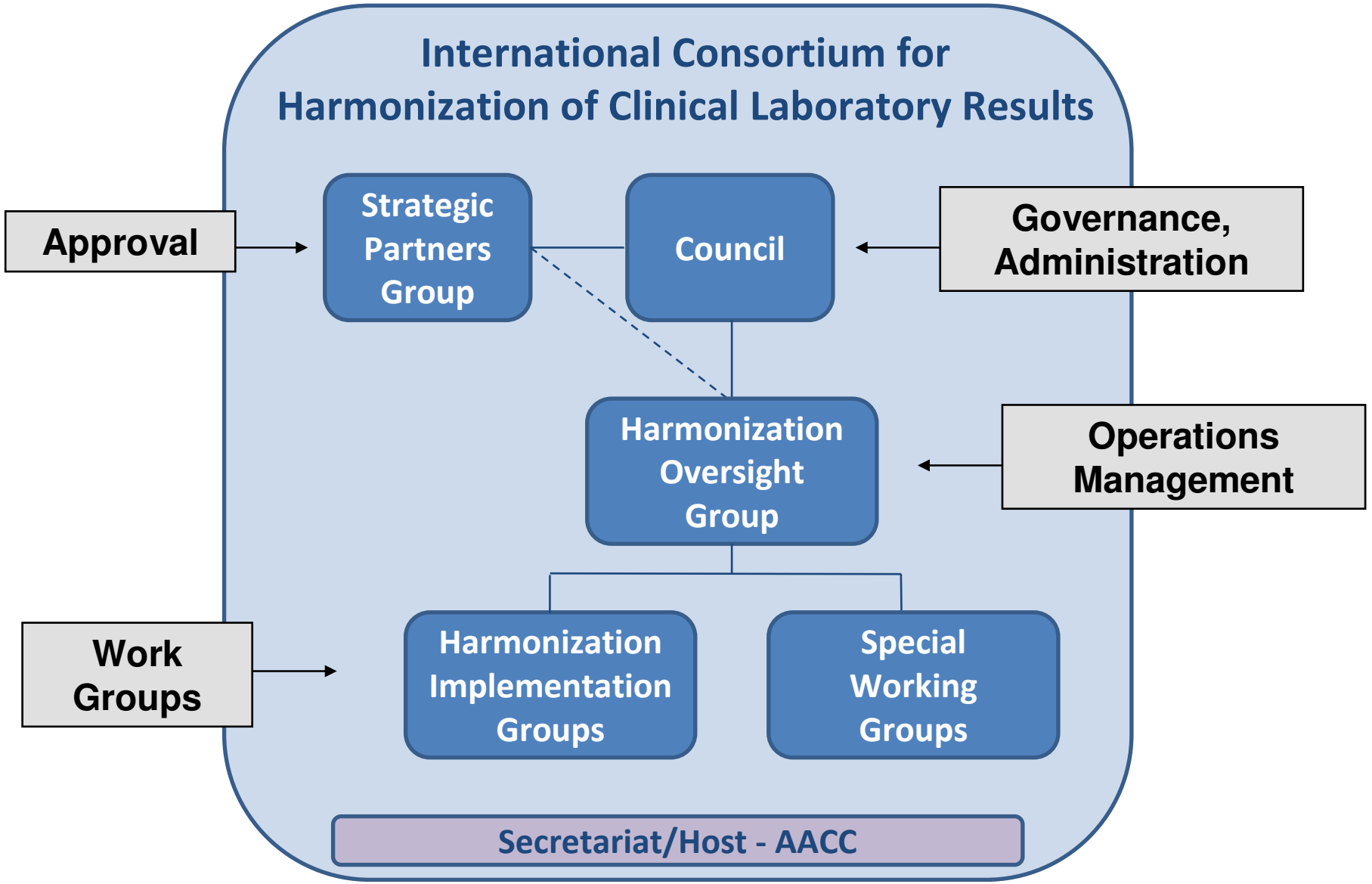


Let's Start Doing It

AN INFRASTRUCTURE FOR HARMONIZATION



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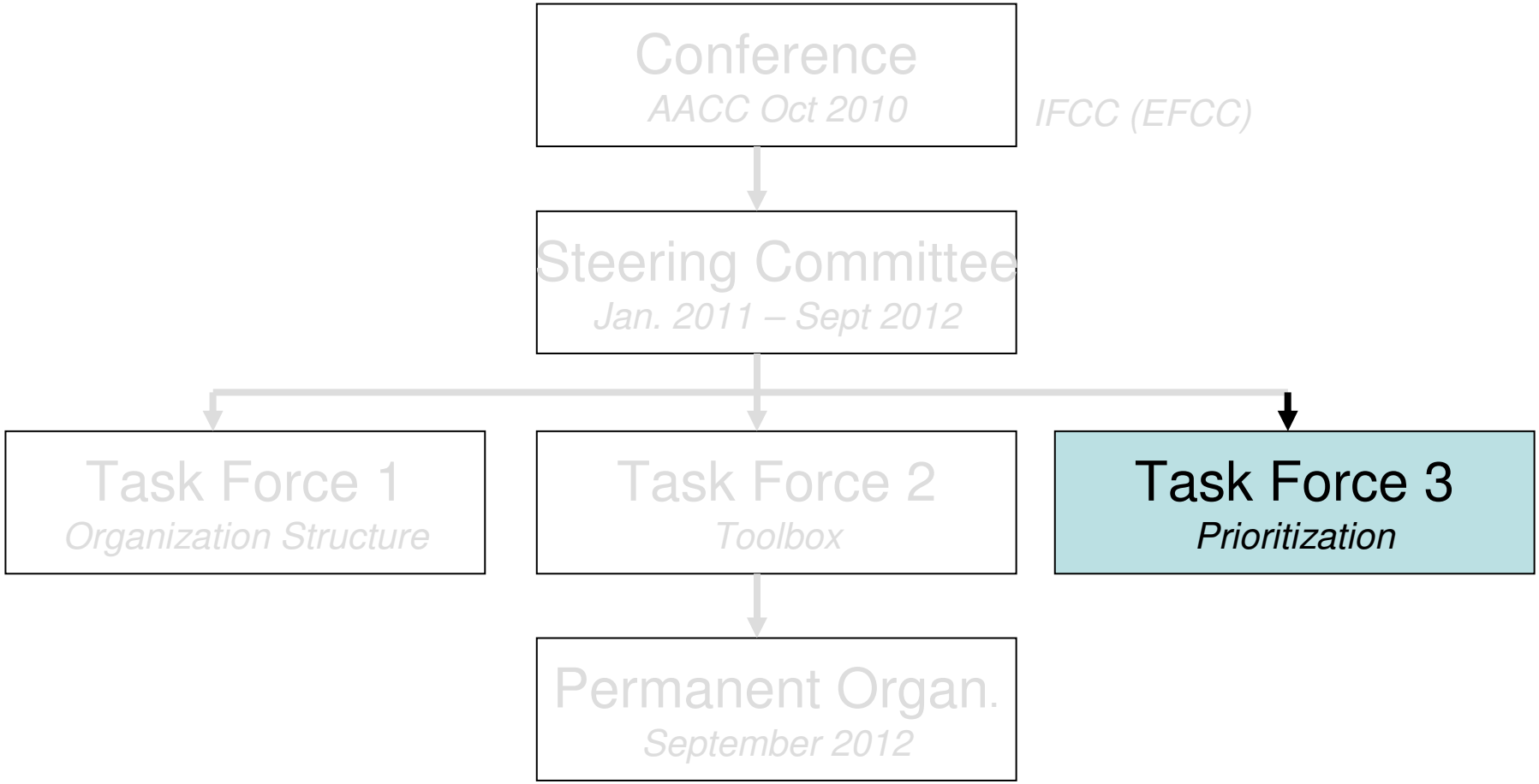

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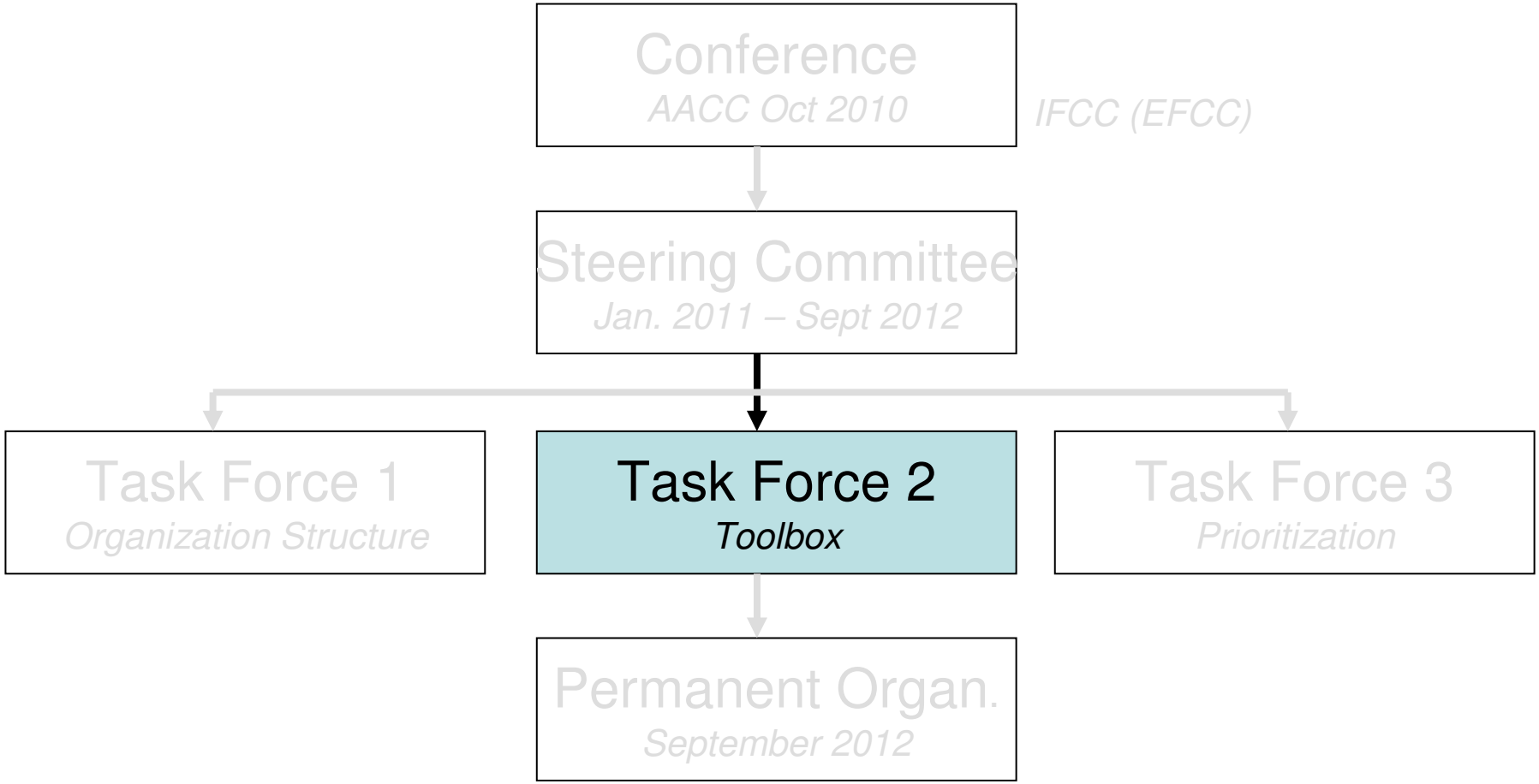
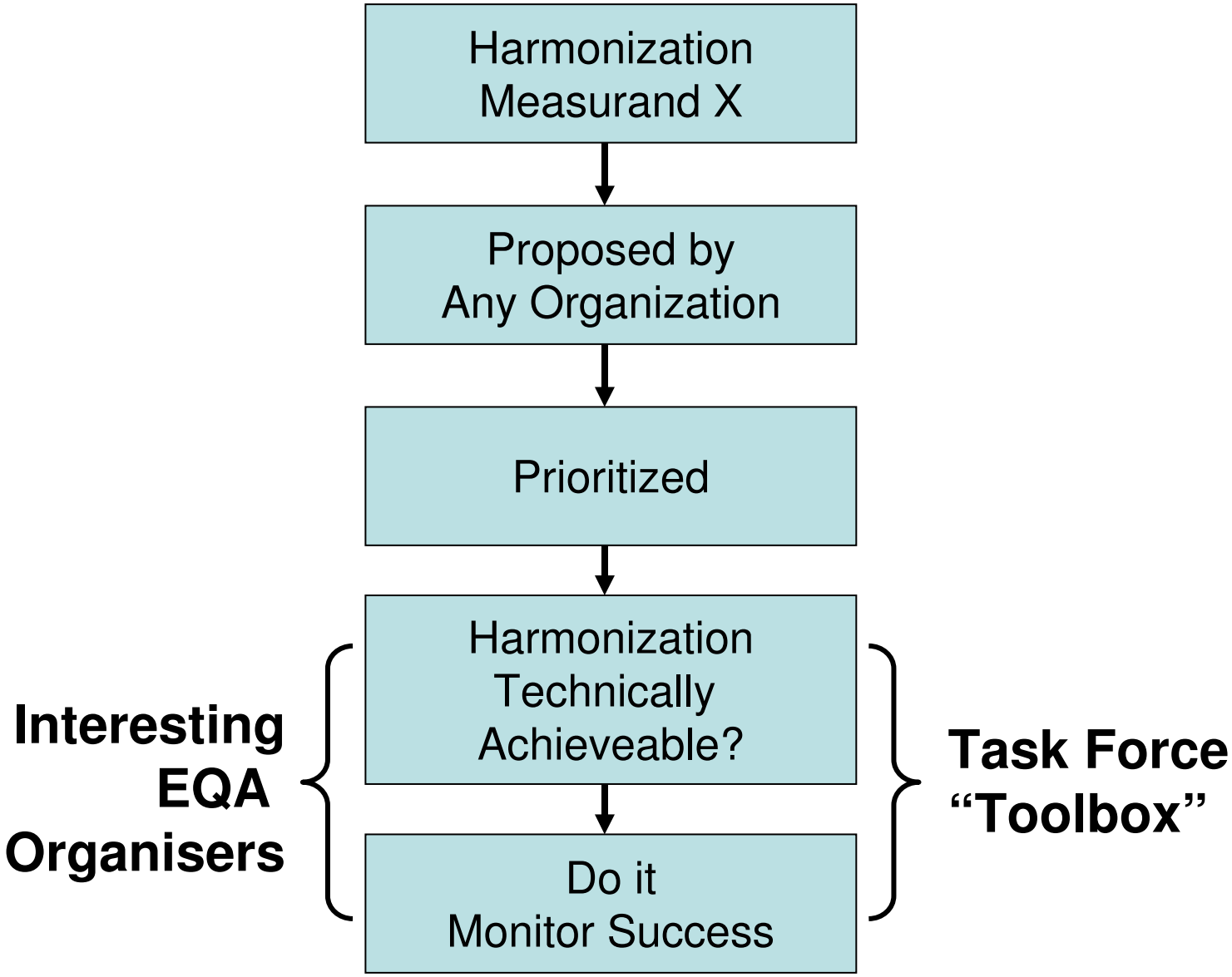


Let's Start Doing It


Harmonization
Measurand X
Proposed by
Any Organization
Prioritized
Harmonization
Technically
Achieveable?
Do it
Monitor Success
Interesting
EQA
Organisers
Task Force
“Toolbox”

The Process of Harmonization

How do you do it?

Mission Statement Task Force Toolbox:

"Develop a Toolbox of…….
……Technical Procedures
……that can be used
……to achieve Harmonization
……for any Measurand"

Harmonization is Technically Achieveable

?

Harmonization is Technically Achieveable

Unit to express Degree of harmonization

Intermethode CV

Degree of Harmonization

- Before harmonization
- After Harmonization
- Desired

Example Troponine

-Intermethode CV before: 73%
-Intermethode CV after: 18%
-Intermethode CV desired: 10%

Harmonization Technically Achieveable?

It is better but is an intermethod CV of 10% worth doing an effort?

Toolbox

Create Tools that allow to gather

<u>Essential Information</u>….

Two Methods; same samples measured fivefold

Method A	Method B
100	100
26	101
144	103
87	102
68	100

Harmonization achieveable?

Two Methods; same samples measured fivefold

Method A	Method B
100	100
26	101
144	103
87	102
68	100

Harmonization achieveable?

No, Method A is not reproducible

Two Methods; 5 Patients measured

Method A	Method B
20	20
40	40
60	56
80	61
100	62

Harmonization Achieveable?

Two Methods; 5 Patients measured

Method A	Method B
20	20
40	40
60	56
80	61
100	62

Harmonization Achieveable?

Questionable; Method B not linear high levels

Two Methods; 5 patients measured

Method A	Method B
100	100
50	100
100	50
50	50
100	80

Harmonization Achieveable?

Two Methods; 5 patients measured

Method A	Method B
100	100
50	100
100	50
50	50
100	80

Harmonization Achieveable?

Mission impossible: Heterogeneity

Two methods; 5 patients measured

Method A	Method B
20	40
40	80
60	120
80	160
100	200

Harmonization achieveable?

Two methods; 5 patients measured

Method A	Method B
20	40
40	80
60	120
80	160
100	200

Harmonization achieveable?

Yes – Calibration – Simple Factor 2

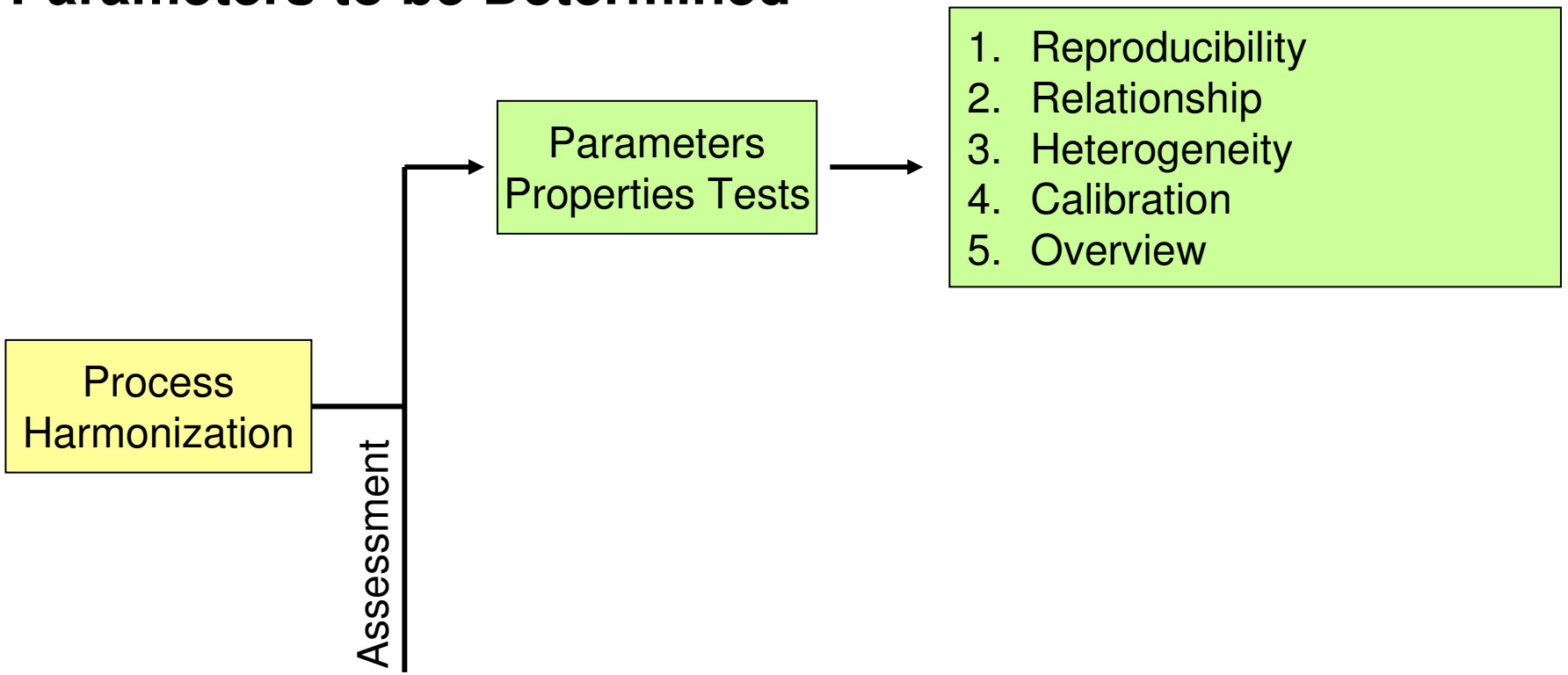
Lessons Exercises

4 Properties of the methods determine
If harmonization is achieveable:

1. Reproducibility Methods (not)
2. Linearity Methods (not/complicated)
3. Heterogenity reagents/epitopes (not)
4. Way of Calibration (yes)

To estimate achieveability of harmonization these parameters are to be assessed

Parameters to be Determined



If properties of tests allow harmonization

…. .in principle

Two things are required to achieve harmonization

…..in practice

- Calibrators
- Method Value Assignment

One more Exercise

Candidate Calibrator assayed with 4 patient samples with method A and method B

Sample	Method A	Method B
Calibrator	60	60
Pat 1	20	40
Pat 2	40	80
Pat 3	60	120
Pat 4	80	160

Candidate Calibrator Suitable?

One more Exercise

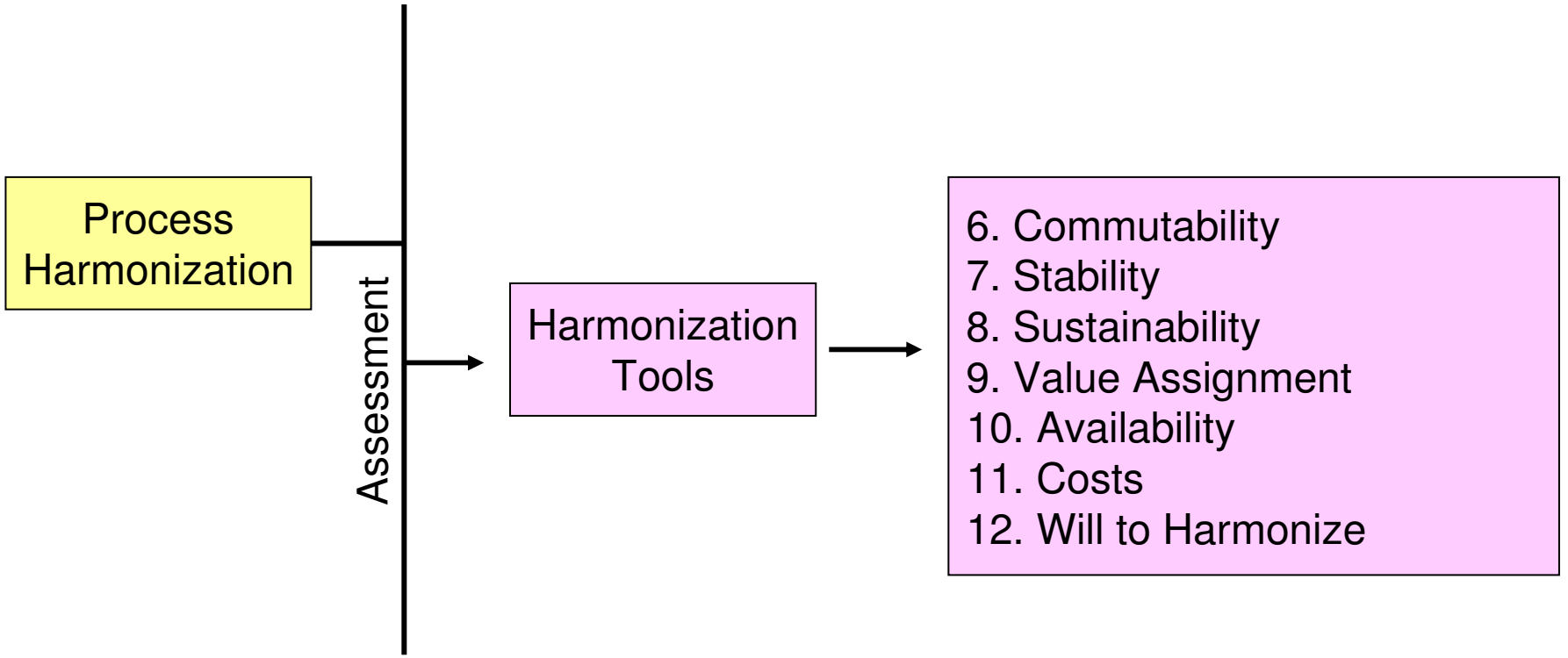
Candidate Calibrator assayed with 4 patient samples with method A and method B

Sample	Method A	Method B
Calibrator	60	60
Pat 1	20	40
Pat 2	40	80
Pat 3	60	120
Pat 4	80	160

Candidate Calibrator Suitable?

No, not commutable

Parameters of the Harmonization Tools



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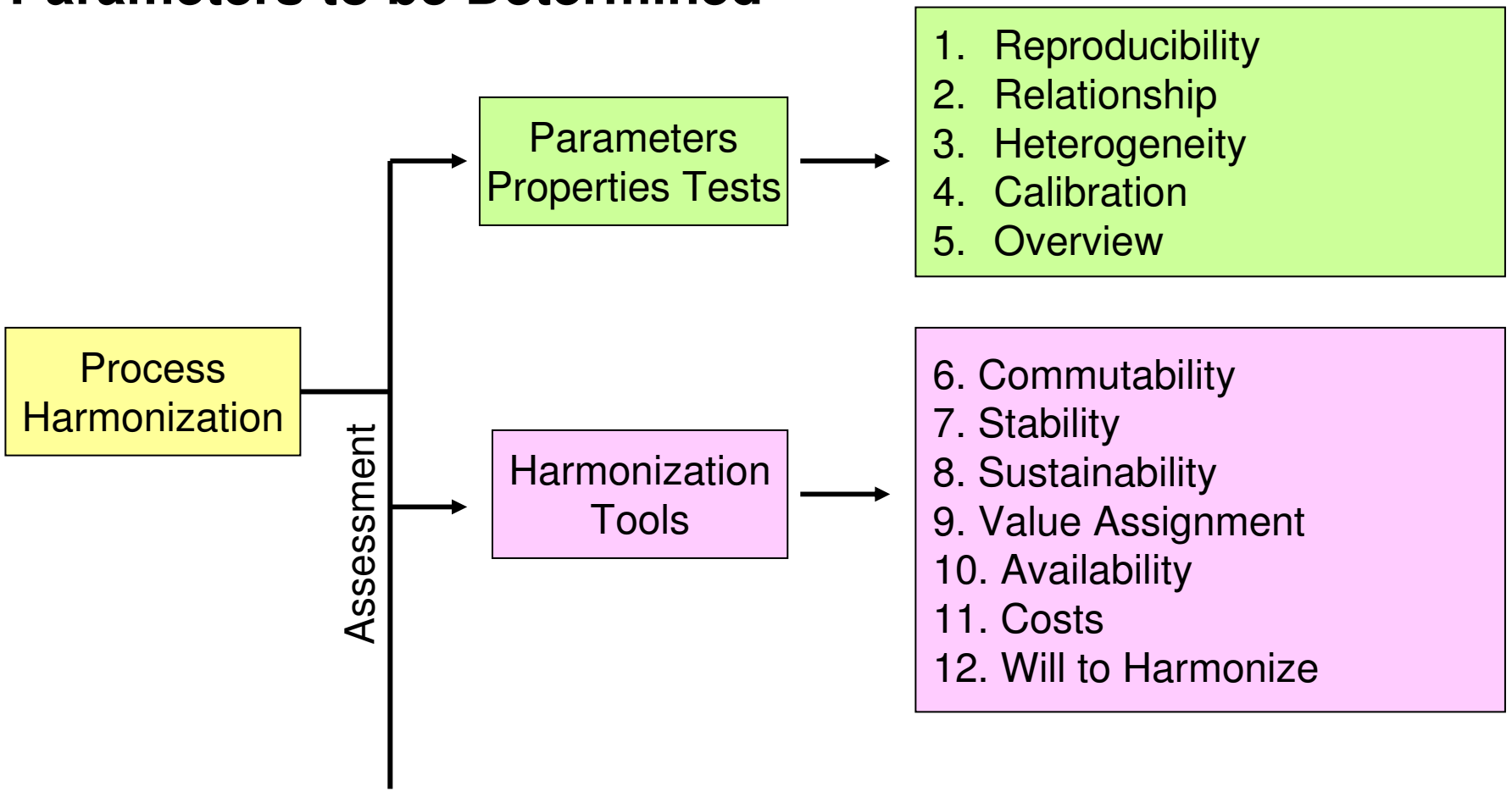

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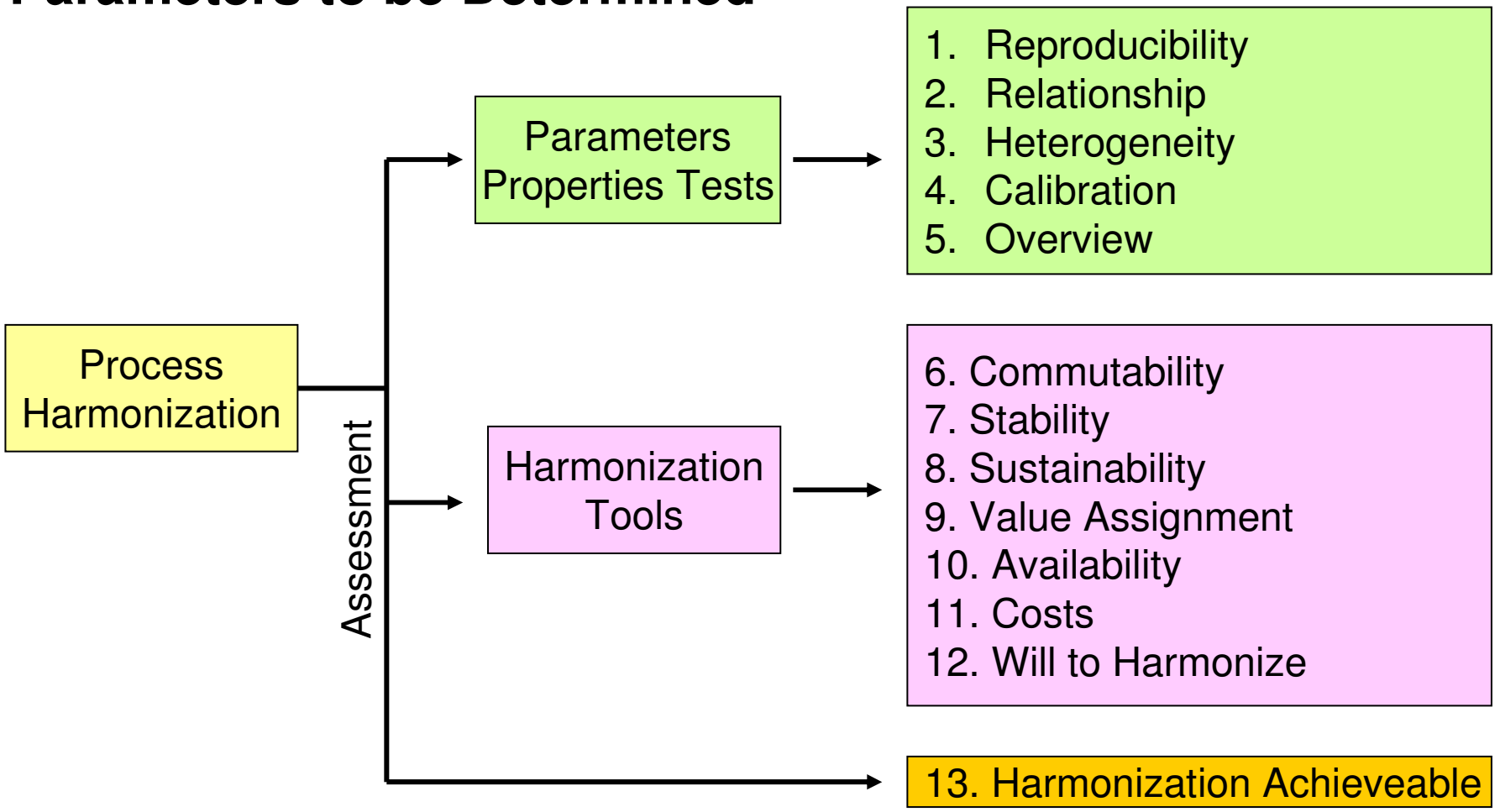

Information Required

To assess if harmonization
Is technically achieveable

1. Reproducibility
2. Relationship
3. Heterogeneity
4. Calibration
5. Overview

6. Commutability
7. Stability
8. Sustainability
9. Value Assignment
10. Availability
11. Costs
12. Will to Harmonize

13. Harmonization Achieveable

Experimental Design IHP

Samples included to get all information

Executed all relevant methods

32 Samples
of individual persons
healthy and diseased
assayed in triplicate

5 Mixtures
of the samples of the
individual persons

Linearity Panel
of 5 samples made from
the individual persons

3 Candidate Calibrators

2 Additional Batches
of one Candidate Calibrator

2 Stored Vials
of one Candidate Calibrator

Information Required

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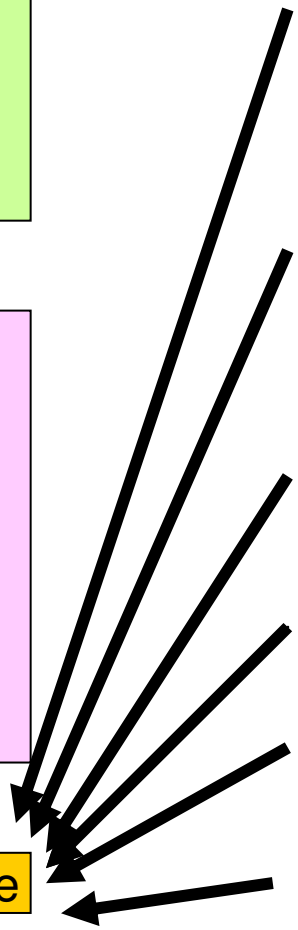


Conclusion

Results of Protocol

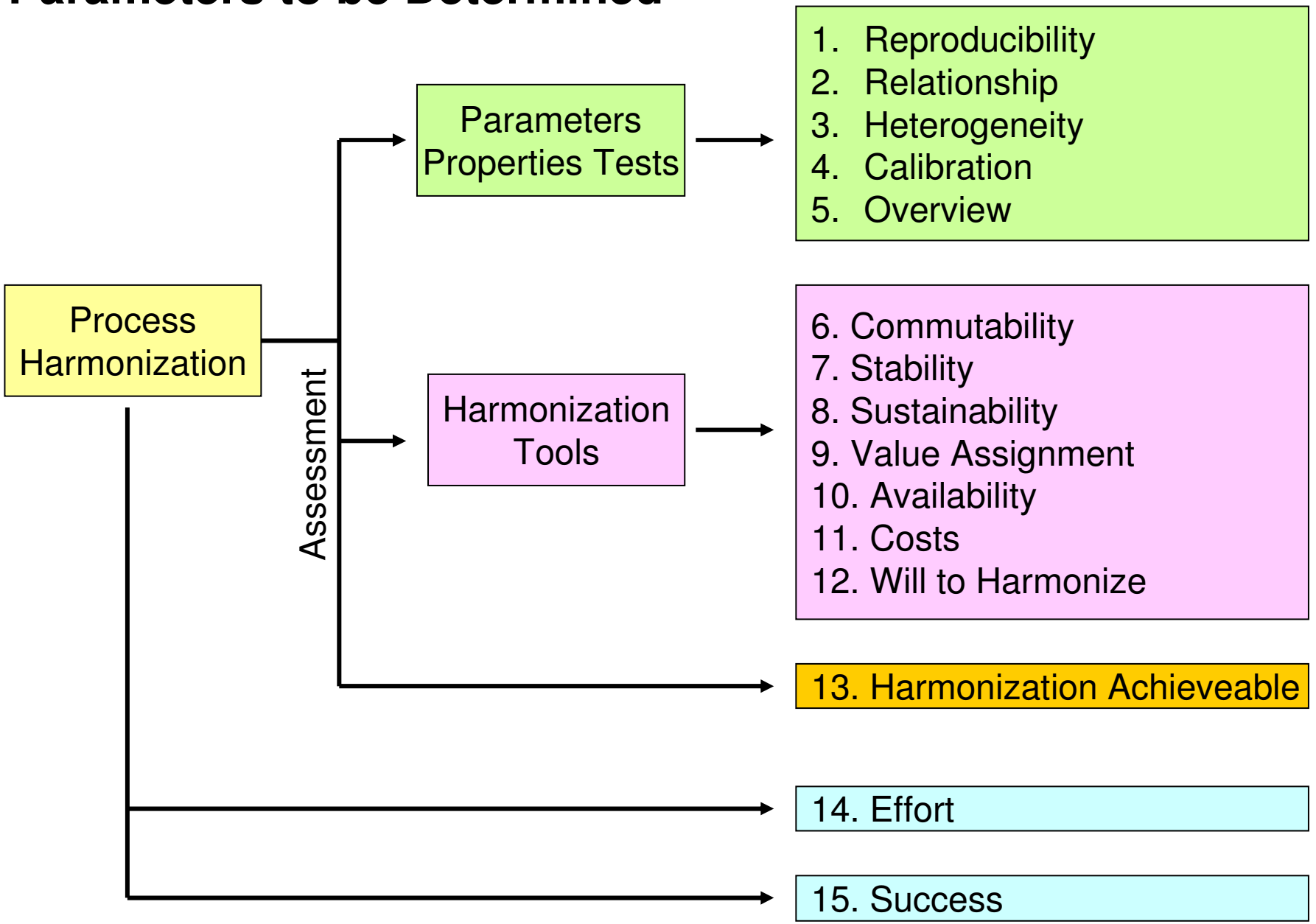
Discloses all essential information

Next

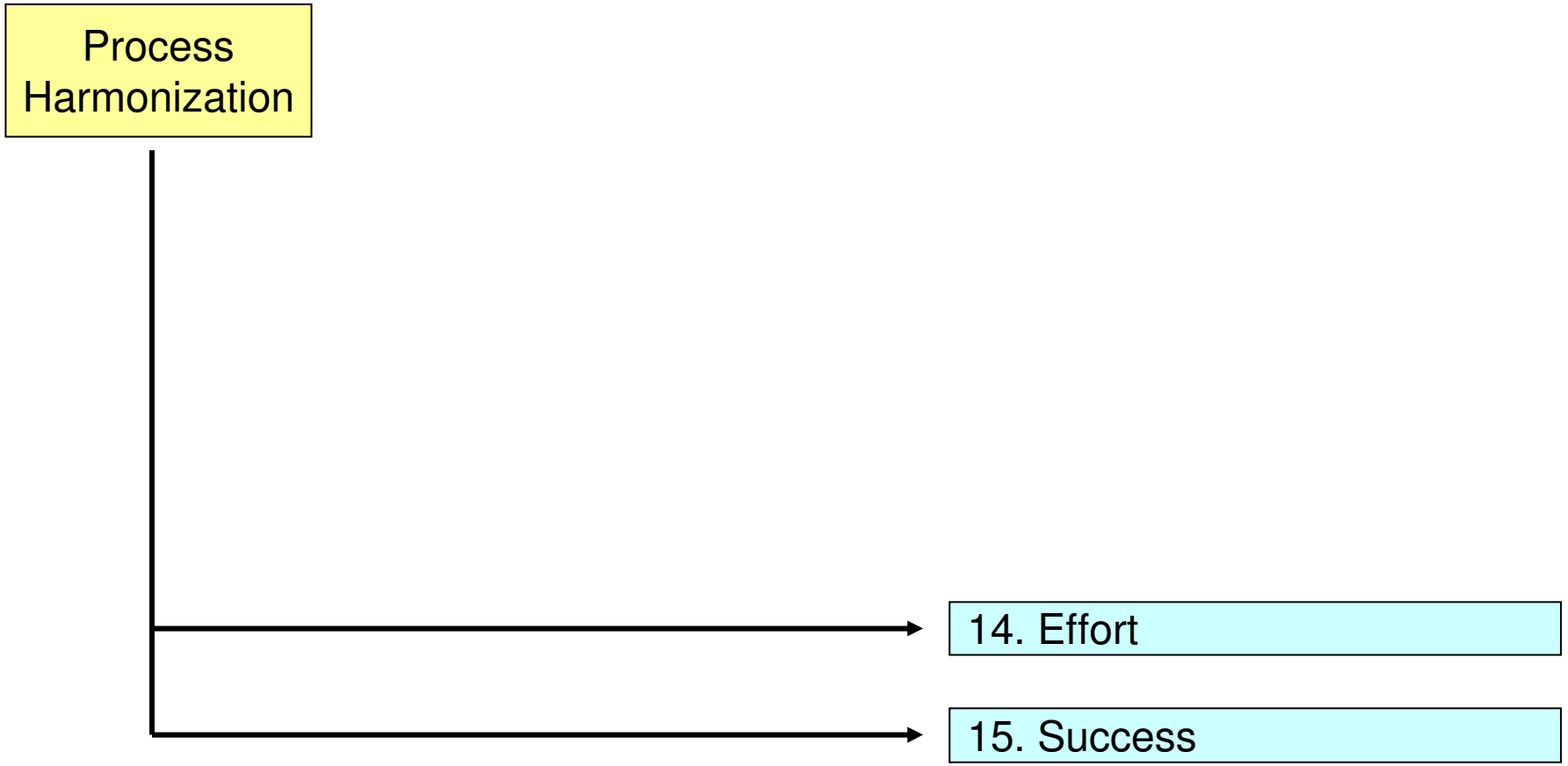
Do it and

Monitor Success

Parameters to be Determined

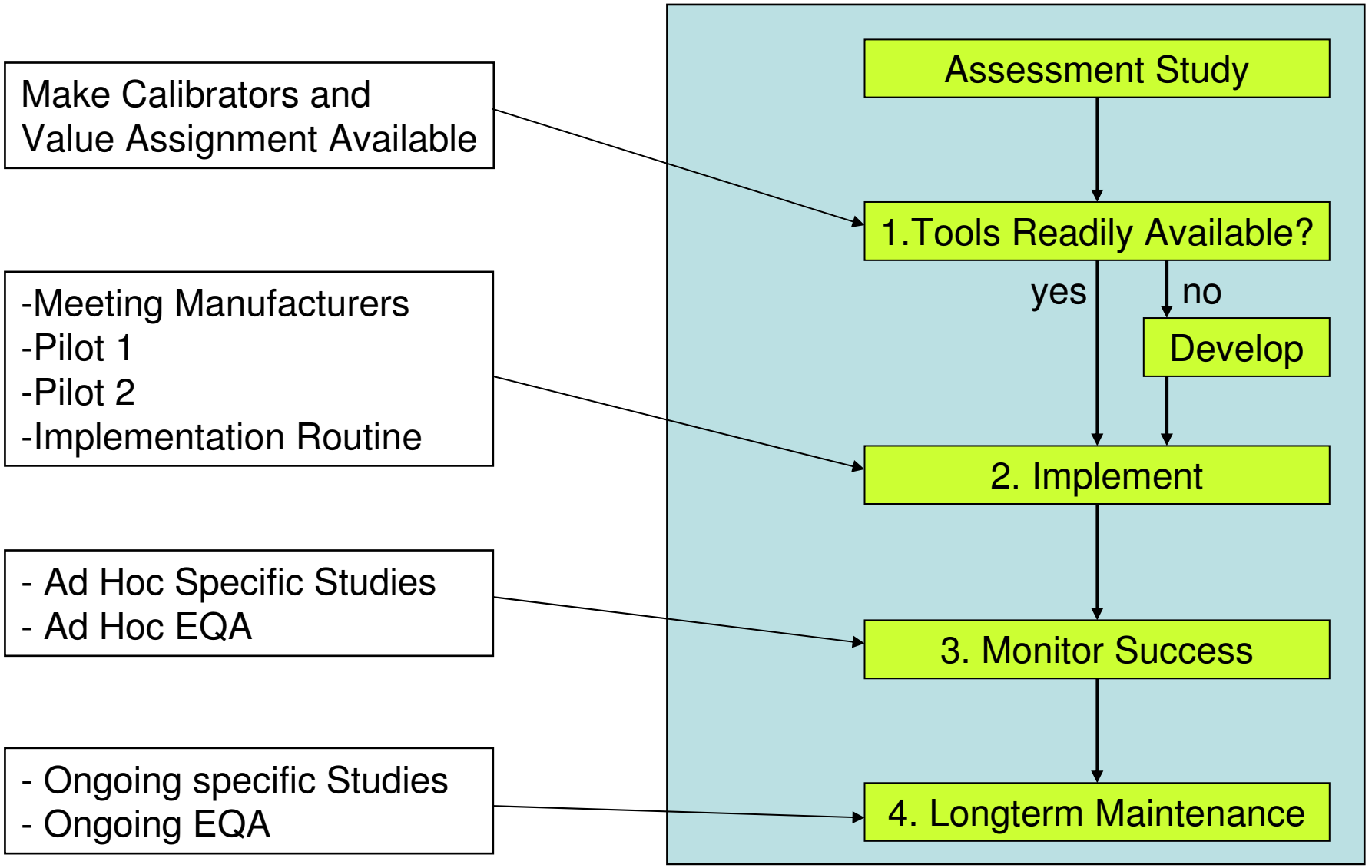


Parameters to be Determined

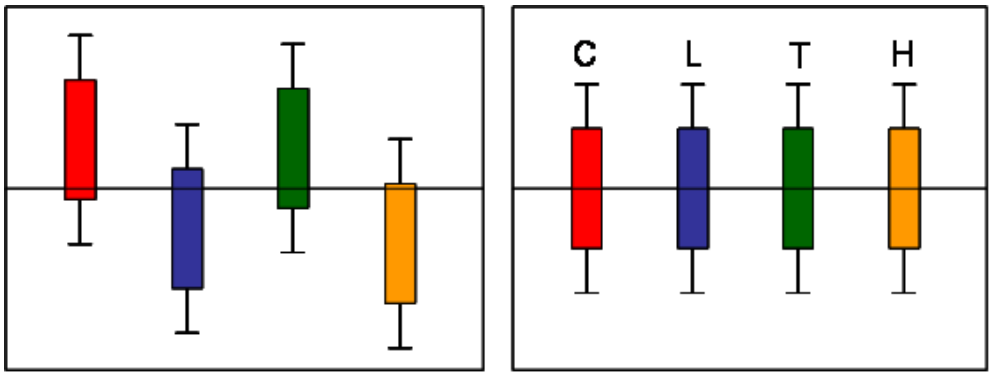


Effort and Success

Included in the Toolbox of HIG

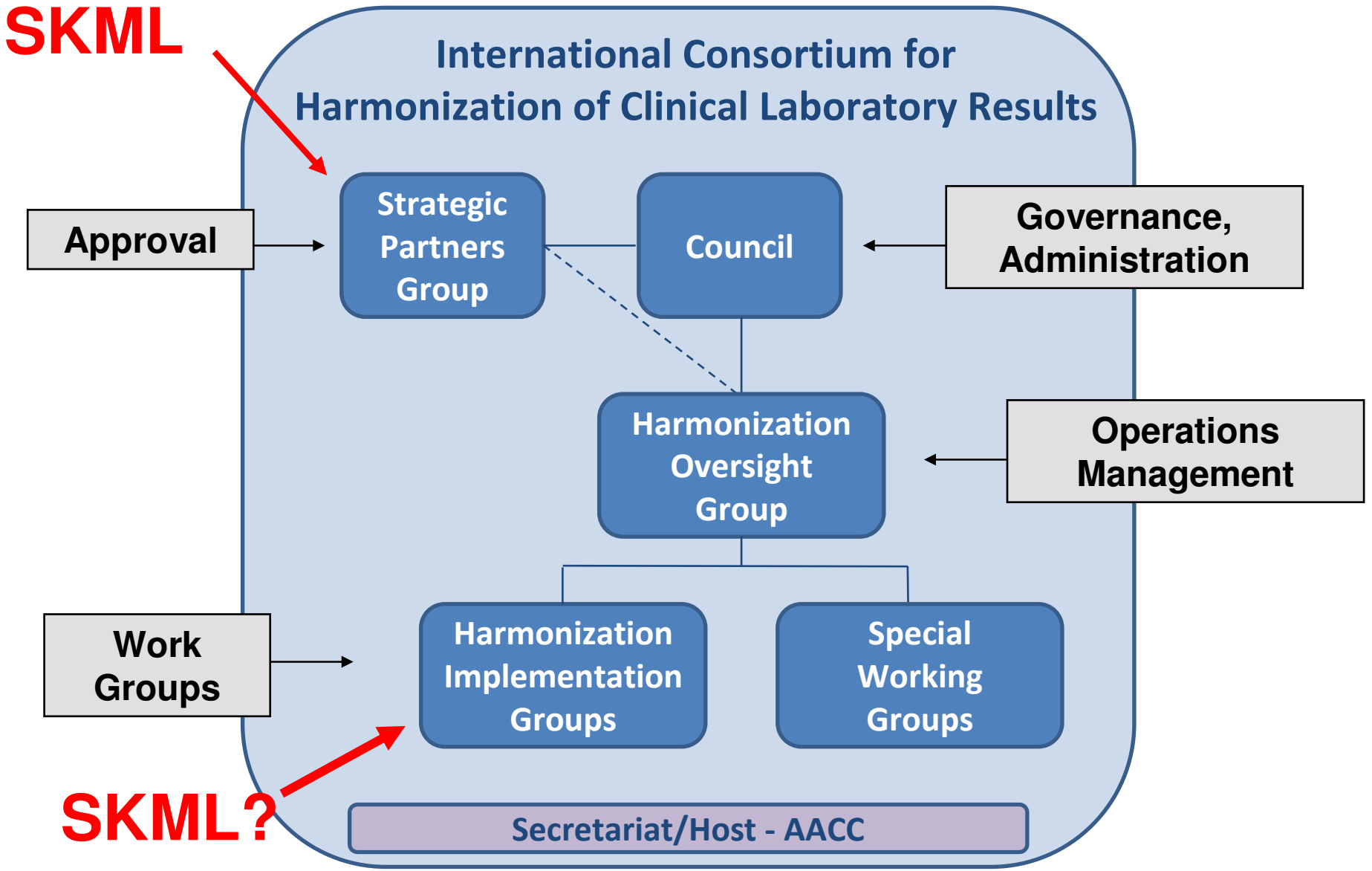


EQA organisers will play a vital role in The monitoring of Harmonization Efforts



Clinical Lab Test Harmonization

AN INFRASTRUCTURE FOR HARMONIZATION



Mooie Gereedschapskist…..
……Luchtfietserij?

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……Luchtfietserij?

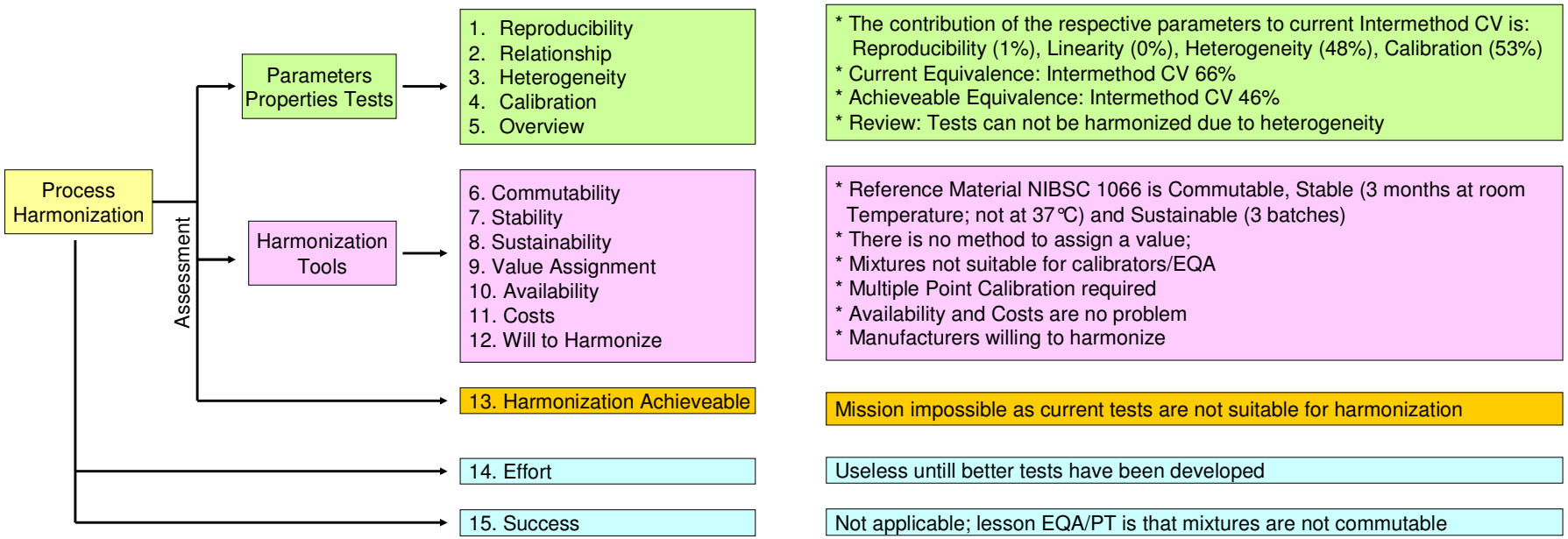
Doet SKML Iets?
……..Heeft SKML iets gedaan?

Mooie Gereedschapskist…..
……Luchtfietserij?

Doet SKML Iets?
……..Heeft SKML iets gedaan?

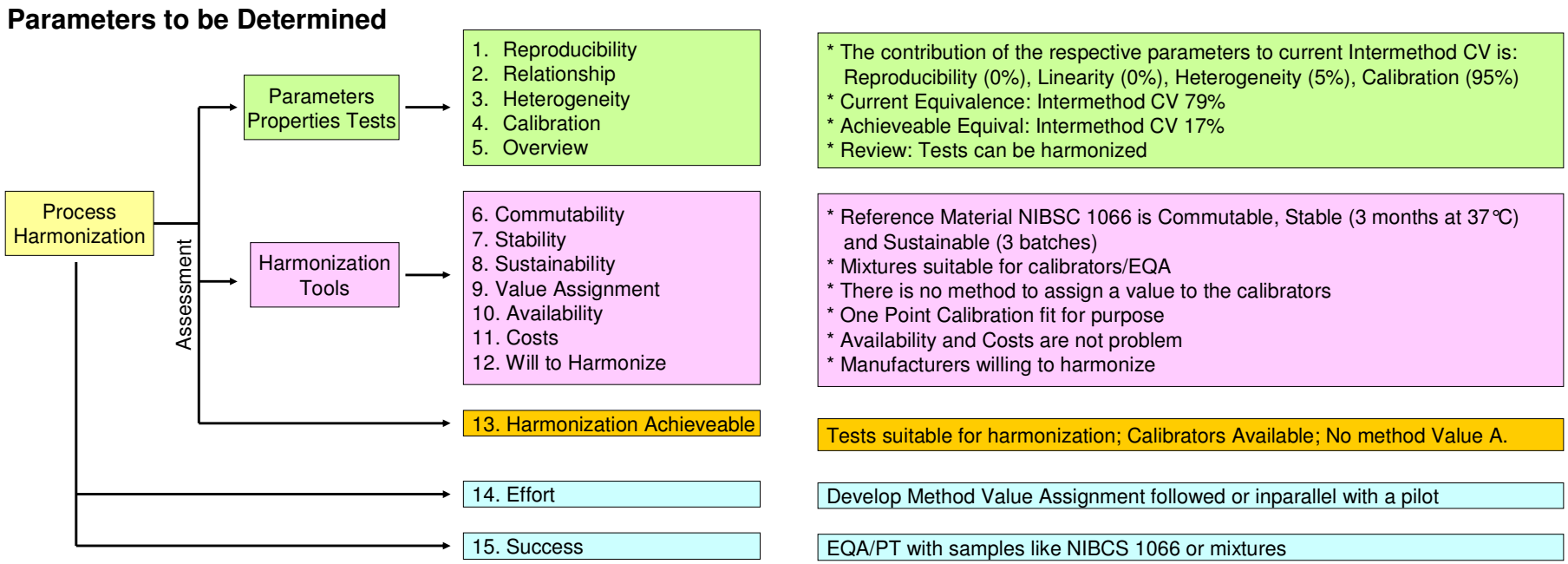
Inderdaad:
Sectie HIM heeft wat gedaan!

Pilot 1 to test AACC Toolbox: Reuma



1. Protocol is executable
2. Harmonization impossible due to Heterogeneity
3. NIBSC suitable calibrator
4. No method to assign values to calibrators
5. Mixtures do not behave like single donations

Pilot 2: a-CCP



1. Protocol is executable
2. Current Equivalence 79% Achieveable Equivalence 17%
3. NIBSC 1066 suitable calibrator/ one-point calibration
4. No method to assign a value to calibrator
5. Mixtures behave like single donations

Er was ook al wat gedaan
Harmonisatie aantal Eiwitten
IRMM: Referentie Preparaat CRM470

Er was ook al wat gedaan
Harmonisatie aantal Eiwitten
IRMM: Referentie Preparaat CRM470

Alle Fabrikanten Geconformeerd
Dus resultaat alle labs zelfde?

Er was ook al wat gedaan
Harmonisatie aantal Eiwitten
IRMM: Referentie Preparaat CRM470

Alle Fabrikanten Geconformeerd
Dus resultaat alle labs zelfde?

Zou het?

Sectie HIM van de SKML:
……..Dat gaan we testen

- **120 ampullen CRM470 gekocht**
- **Combi Immuno Chemie 2012.1A**

Als alles klopt: Recovery 100%

CRM 470 ingezet als Rondzendmonster

Eiwit	n	Target in g/L Bijsluiter CRM470	Overall Gemiddelde Rondzendin 2012.1A (Interlab CV %)	Recovery
Albumine	69	37.2	37.3 (5%)	100%
Haptoglobine	99	0.889	0.916 (5%)	103%
IgA	97	1.80	1.79 (4%)	99%
IgG	111	9.17	8.84 (6%)	96%
IgM	99	0.723	0.736 (5%)	102%
Transferrine	110	2.36	2.42 (5%)	103%
AAT	56	1.12	1.15 (8%)	103%
Overall				101%

Recovery CRM470 per Eiwit per Methode

Methode	Albumine	Haptoglo	IgA	IgG	IgM	Transferr	AAT	Overall
Overall	100	103	99	96	102	103	103	101
Abbott Architect	103	98	95	98	105	98	105	100
Beckman Immage	100	98	100	99	100	103	111	102
Beckman UniCel	99	102	99	96	108	104	111	103
Siemens Behring	96	99	102	100	103	98	102	100
Siemens ProSpec	102	100	103	102	101	94	101	101
Siemens VISTA	100	100	93	94	93	96	-	96
Olympus	102	90	91	99	98	106	107	99
Roche Cobas 6000	98	108	100	92	102	104	97	100
Roche Integra	106	104	104	94	103	101	91	100
Roche Modular	103	103	100	97	101	104	101	101

Elk jaar herhalen
…….Actueel Beeld Harmonisatie

Te duur (€120/ampul)

<u>Alternatief:</u>

- **Grote batch monsters gemaakt**
- **Afgeijkt op CRM 470**
- **Combi Immuno Chemie**

2013 – 2014 – 2015 – 2016 - 2017

“Doorloper”

Afijken op CRM 470?

Pragmatisch
Door Deelnemers Combi Immuno chemie
“Doorloper” = 2012.1B

Veel laboratoria
Lage Meetonzekerheid

IJken Rondzendmonster op CRM470

X = referentiewaarde rondzendmonster (doorloper)

Y = referentiewaarde CRM 470 zoals opgegeven
in bijslutier IRMM (9.17g/L)

Z = gemiddelde alle laboratoria gemeten in CRM470
(2012.1A) in de rondzending (8.84 g/L)

U = gemiddelde alle laboratoria gemeten in doorloper
(2012.1B) in de rondzending (8.59 g/L)

X = 8.59 x 9.17/8.84 = 8.91 g/L

IJken Rondzendmonster op CRM470

Eiwit	Gemiddeld Gemeten In rondzending 2012.1B (Interlab CV)	IJkfactor Afgeleid uit CRM470	Referentiewaarde In de doorloper
Albumine	35.5 (5%)	37.2/37.3	35.4
Haptoglobine	1.326 (4%)	0.889/0.916	1.287
IgA	2.05 (4%)	1.80/1.79	2.06
IgG	8.59 (6%)	9.17/8.84	8.91
IgM	0.824 (5%)	0.723/0.736	0.809
Transferrine	2.23 (4%)	2.36/2.42	2.175
AAT	1.32 (8%)	1.12/1.15	1.286

Recovery in CRM470 en Rondzendmonster

Methode	Albumine		Haptoglob		IgA		IgG		IgM		transferrine		AAT		Overall	
	CRM 470	Dr lop	CRM 470	Dr lop	CRM 470	Dr lop	CRM 470	Dr lop	CRM 470	Dr lop	CRM 470	Dr lop	CRM 470	Dr lop	CRM 470	Dr lop
Overall	100	100	103	103	99	99	96	96	102	102	103	103	103	103	101	101
AbbArch	103	105	98	99	95	95	98	101	105	105	98	99	105	104	100	101
Bec Imm	100	98	98	98	100	101	99	101	100	103	103	107	111	113	102	103
Beck Un	99	99	102	101	99	98	96	97	108	101	104	103	111	110	103	101
Sie Behr	96	105	99	107	102	102	100	99	103	106	98	101	102	102	100	102
Sie ProS	102	99	100	101	103	104	102	100	101	102	94	98	101	99	101	100
Sie VIST	100	102	100	102	93	92	94	88	93	100	96	98	-	-	96	97
Olympus	102	102	90	93	91	92	99	94	98	95	106	102	107	101	99	97
Roc6000	98	97	108	106	100	99	92	91	102	100	104	102	97	96	100	99
RocInteg	106	108	104	101	104	103	94	95	103	102	101	98	91	93	100	100
Roc Mod	103	102	103	104	100	100	97	95	101	103	104	105	101	100	101	101

Beklaagdenbankje

Categorie	n	Eiwit/Methode
Zalm Zalm (4+)	2	(AAT Beckman Immage) (AAT Beckman UniCel)
Zalm Geel (3+)	0	-
Geel Geel (2+)	2	(Albumine Roche (Integra) (Haptoglobine Roche Cobas 6000)
Geel Groen (1+)	6	-
Groen Groen (0)	67	-
LBlauw Groen (1-)	4	-
LBlauw LBla (2-)	4	(IgA Siemens VISTA) (IgA Olympus) (IgG Roche C6000) (AAT Roche Integr)
DBlauw LBla (3-)	2	(Haptoglobine Olympus) (IgG Siemens VISTA)
DBlauw DBLa (4-)	0	-

Effect op Fabrikanten?

Roche

Effect op Fabrikanten?

Graag willen wij u informeren over de her-standaardisatie van vier speciale eiwitten bepalingen namelijk de Tina-quant® α-1 Antitrypsine, Haptoglobine, IgG gen. 2, Prealbumine en Albumine. Het nieuwe ERM DA470k/IFCC is als referentie materiaal hiervoor gebruikt.

Intern onderzoek naar aanleiding van klantenmeldingen, afwijkingen in de externe kwaliteitsbewakingssystemen en onderlinge vergelijkbaarheid tussen Roche systemen hebben geleid tot een nieuwe master lot kalibratie van Tina-quant® α-1 Antitrypsine, Haptoglobine, IgG gen. 2, Prealbumine en Albumine bepalingen. Door deze master lot kalibratie wordt het huidige niveau van de C.f.a.s. PAC gejusteerd naar het referentiemateriaal ERM DA470k/IFCC.

De volgende aanpassing van de C.f.a.s. PAC zijn:

Bepaling	INTEGRA	Modular P	c501/c502	c701/c702
α-1 Antitrypsine	-12.4%	-5.1%	-12.7%	-12.7%
Haptoglobine	-3.8%	-6.9%	-7.6%	-7.6%
IgG Gen.2	None	+4.1%	+11.5%	+4.1%
Prealbumine	-9.6%	None	-6.4%	-6.4%
Albumine	+4.5%	+4.5%	+4.5%	+4.5%

De consequentie voor deze referentie standaardisatie tegen ERM DA470k/IFCC referentie materiaal is

Roche

Er is nog wel wat te doen
Ceruloplasmine

Methode	n	CRM470		Doorloper	
		Gemidd	SD	Gemidd	SD
Overall	29	0.169	0.017	0.274	0.036
Beckman Immage	9	0.187	0.015	0.316	0.024
Siemens Behring	5	0.164	0.009	0.266	0.009
Siemens Pro Spec	7	0.163	0.010	0.258	0.015
Olympus	1	0.170	-	0.260	-
Roche Cobas 6000	2	0.160	0.007	0.240	0.007
Roche Integra	1	0.140	-	0.260	-
Roche Modular	4	0.160	0.018	0.252	0.025

Samenvatting

1. Optimale Zorg Patienten:
   Verschillende Methoden – Dezelfde Resultaten
2. Standaardisatie –Harmonisatie
3. SKML: Theorie op wereldschaal
4. SKML: Praktijk in Nederland
   Initiërend: Reuma – aCCP
   Controlerend: Eiwitten – Combi – CRM 470
5. Werkt: Fabrikanten sturen bij
6. Einddoel: harmonisatie = optimale zorg


Dank voor uw Aandacht