Automation of Potency Assays:
it's not plug-and-play, it's a journey

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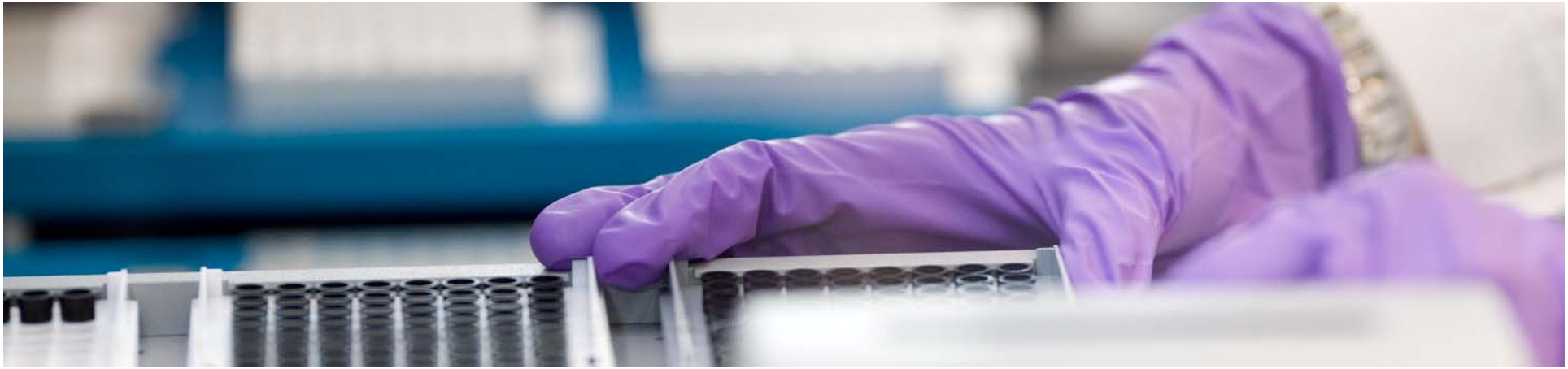


Overview

To automate or not to automate,- *why/when* ⇔ **What is special for Bioassays** ***Automation of automation?***

→ *our considerations on relevant factors*

Setting-up automation

Technical pitfalls *just one example*

Automation & GMP

Acceptance & Concerns

User/training concepts

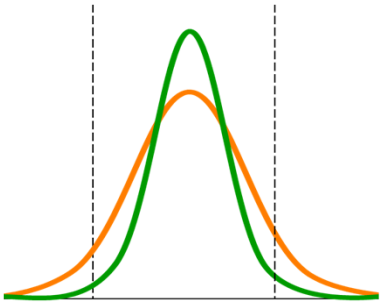
Vision *new horizons for assay formats*

To automate or not to automate
- *why/when automation?*

“usual” expectations:

Increase of throughput /efficiency gain

Lowering failure rates

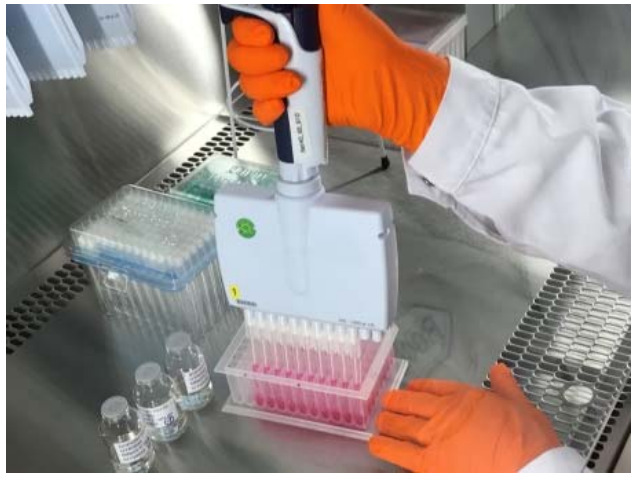


Easier Transferability

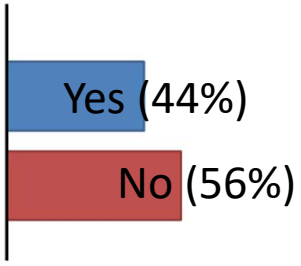
Ergonomic reasons

What is special for bioassay?

Many complex and repetitive pipetting (up to 430 pipetting steps/assay)

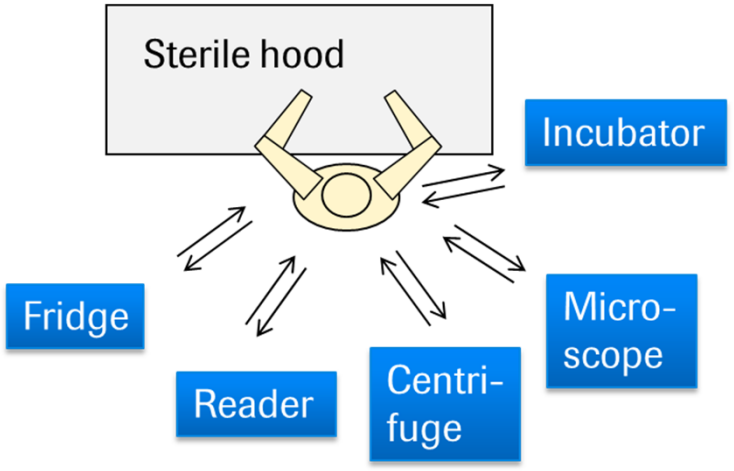


I had health problems/pain because of working on a laminar flow/pipetting

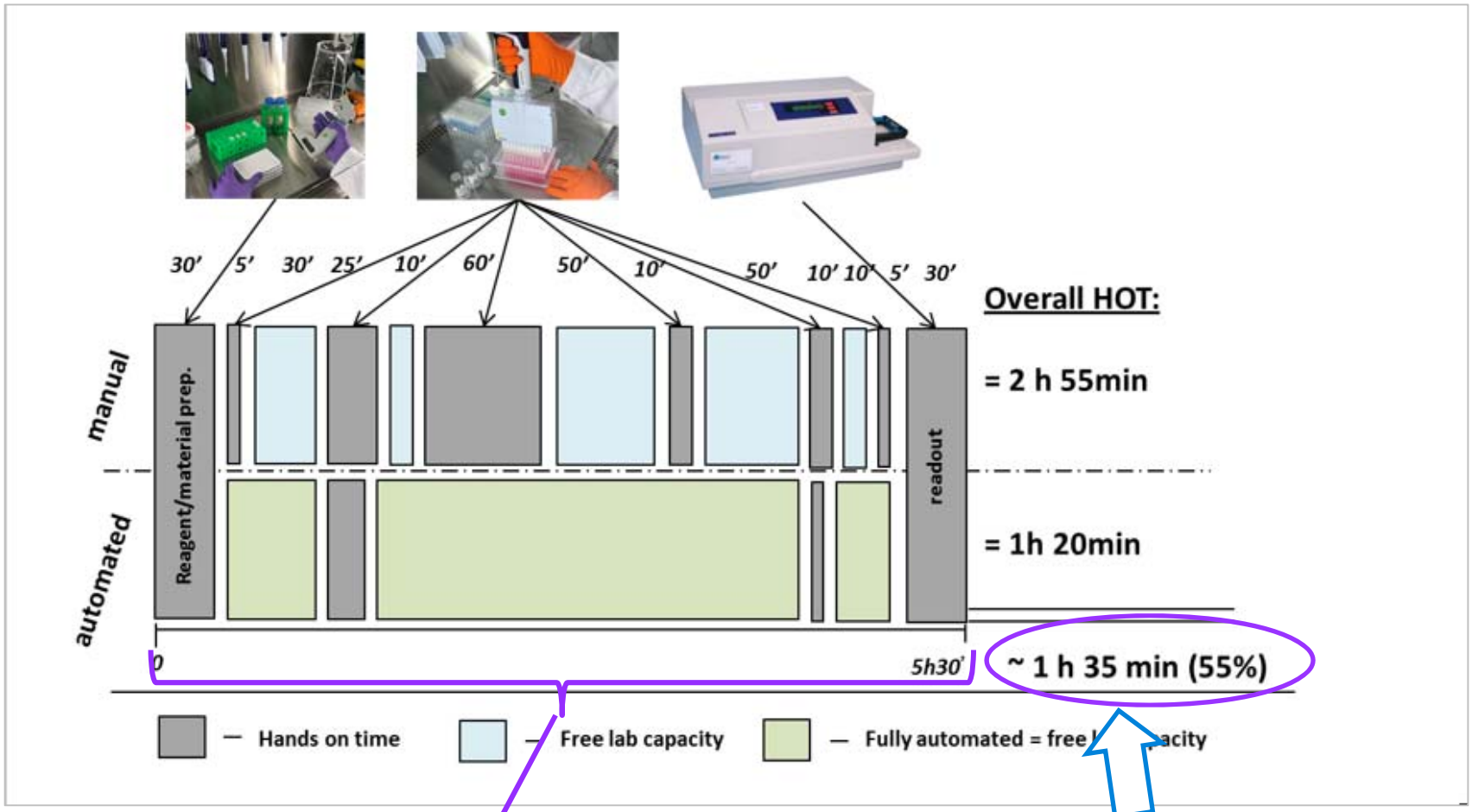


Result survey Bioassay labs Basel&Kaiseraugst, 34 responses

Sterile handling of cells and heterogenous workpackages



Efficiency gain*: time saving*

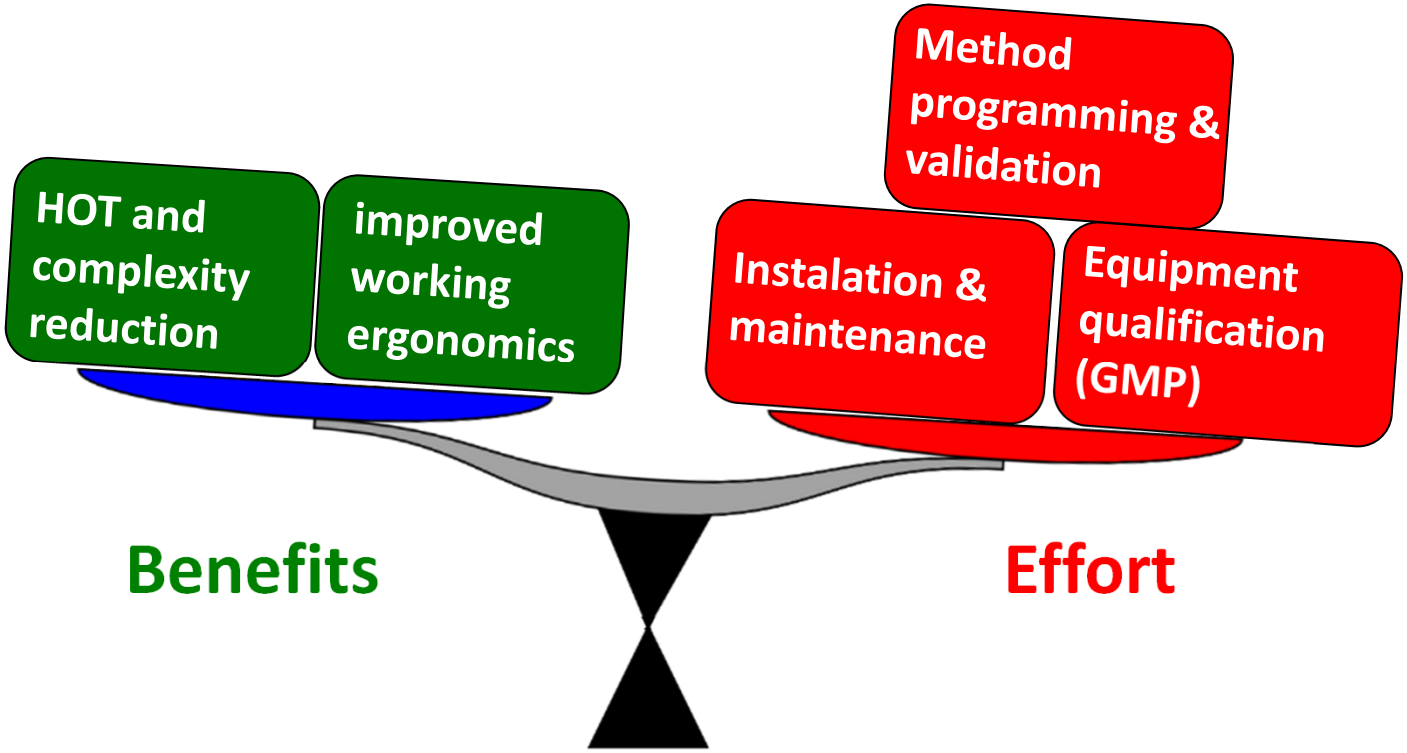


No savings in overall-time

HOT-reduction x no. of assay/year
= time-saving/year

?

Balance benefit *from* – vs. effort *for* automation



Does automation pay off *for us*?
A multitude of factors

- No. of samples per time period
- No. of different assays
- No. of labs involved
- Extend to which assays can be automated
- ……

Does automation pays off only *for high-throughput*?

Roche

No. of samples per time period

No. of different assays

few different assays with high number of samples — ***high throughput***

vs.

many different assays with few samples — ***high diversity***

No. of labs involved

Extend to which assays can be automated

.....

«rare assays»:

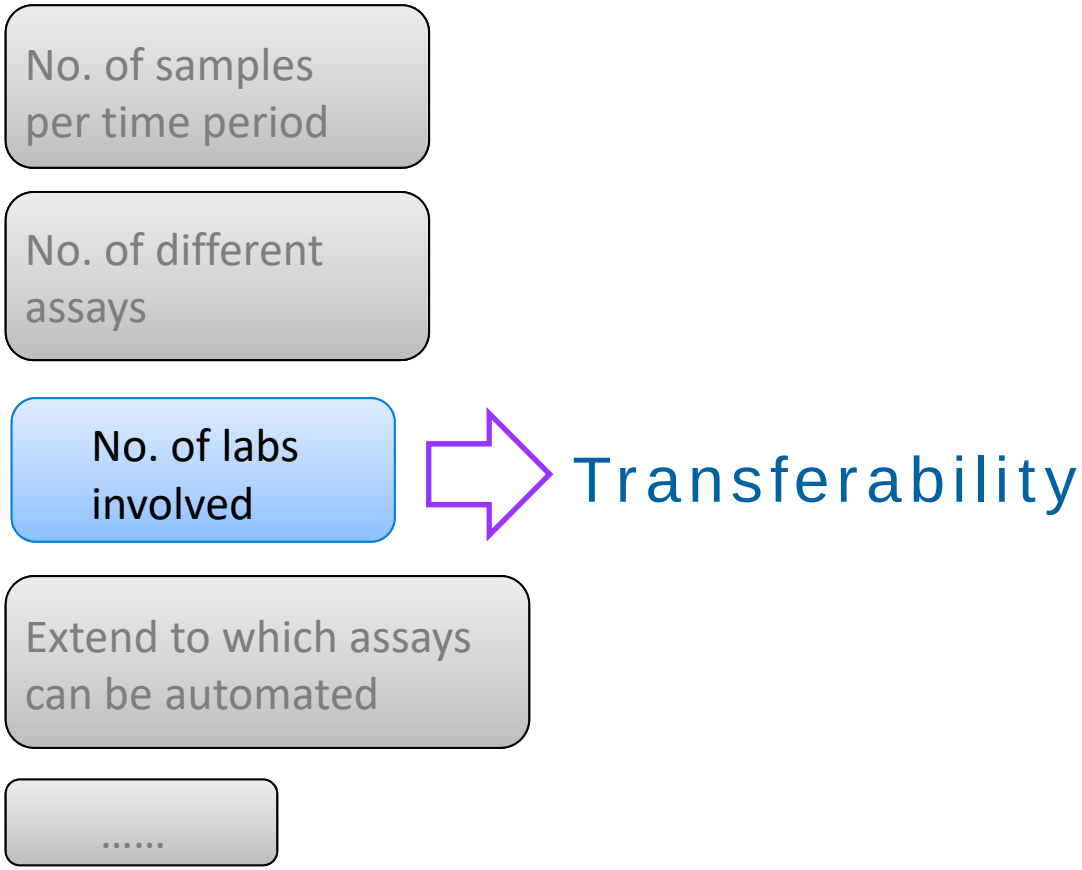
→ routine is lost

→ require each time re-familarization

→ increase of failure rate and time needed

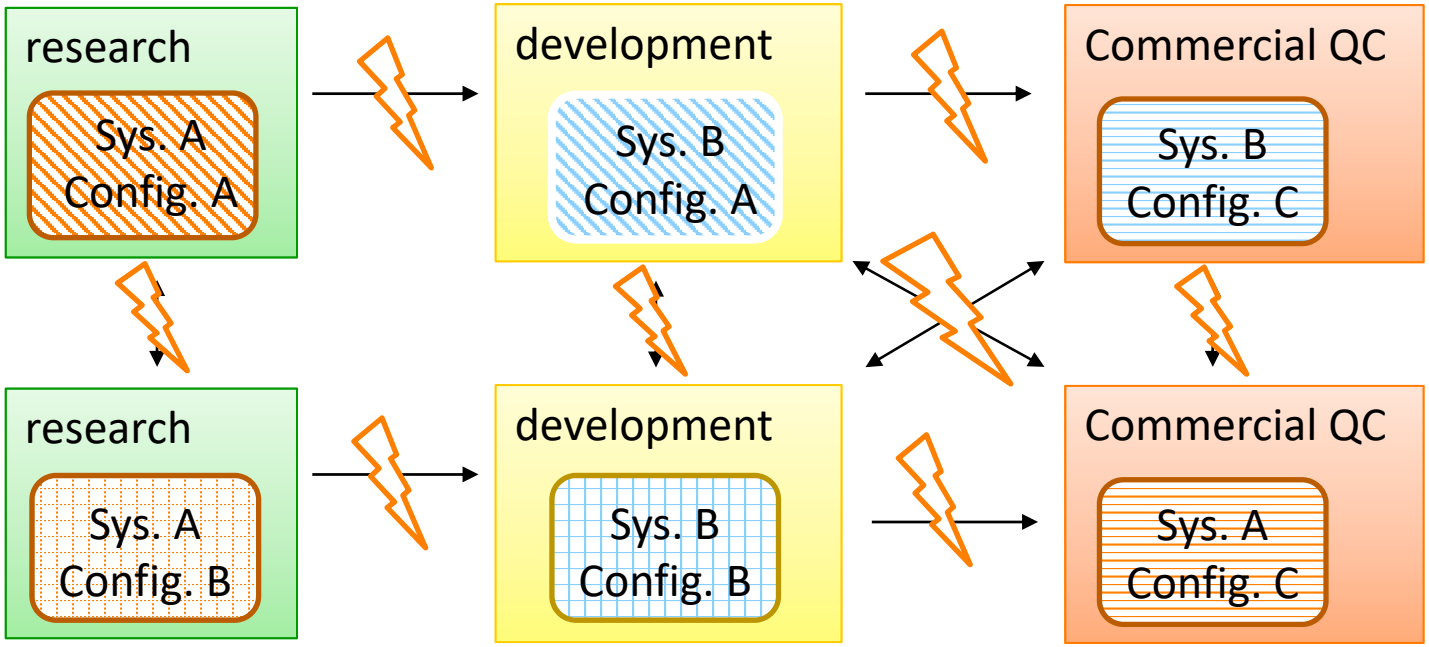
Automation as tool to cope with high diversity

Does automation pay off *for us*?
A multitude of factors



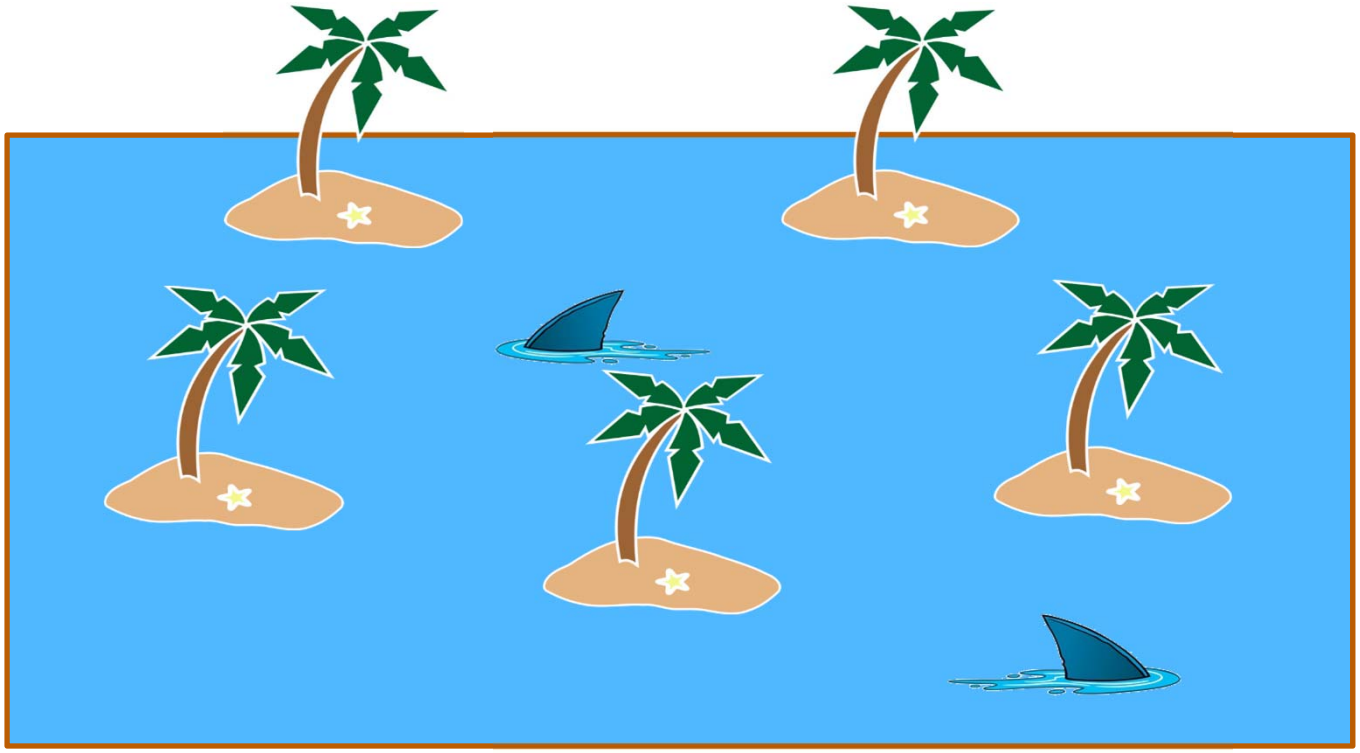
Transferability

Exchange of automated assays between labs



different, not harmonized automation solutions

→ *no direct exchange of methods/ no smooth&easy transferability*



Don’t let us re-invent the wheel x-times,

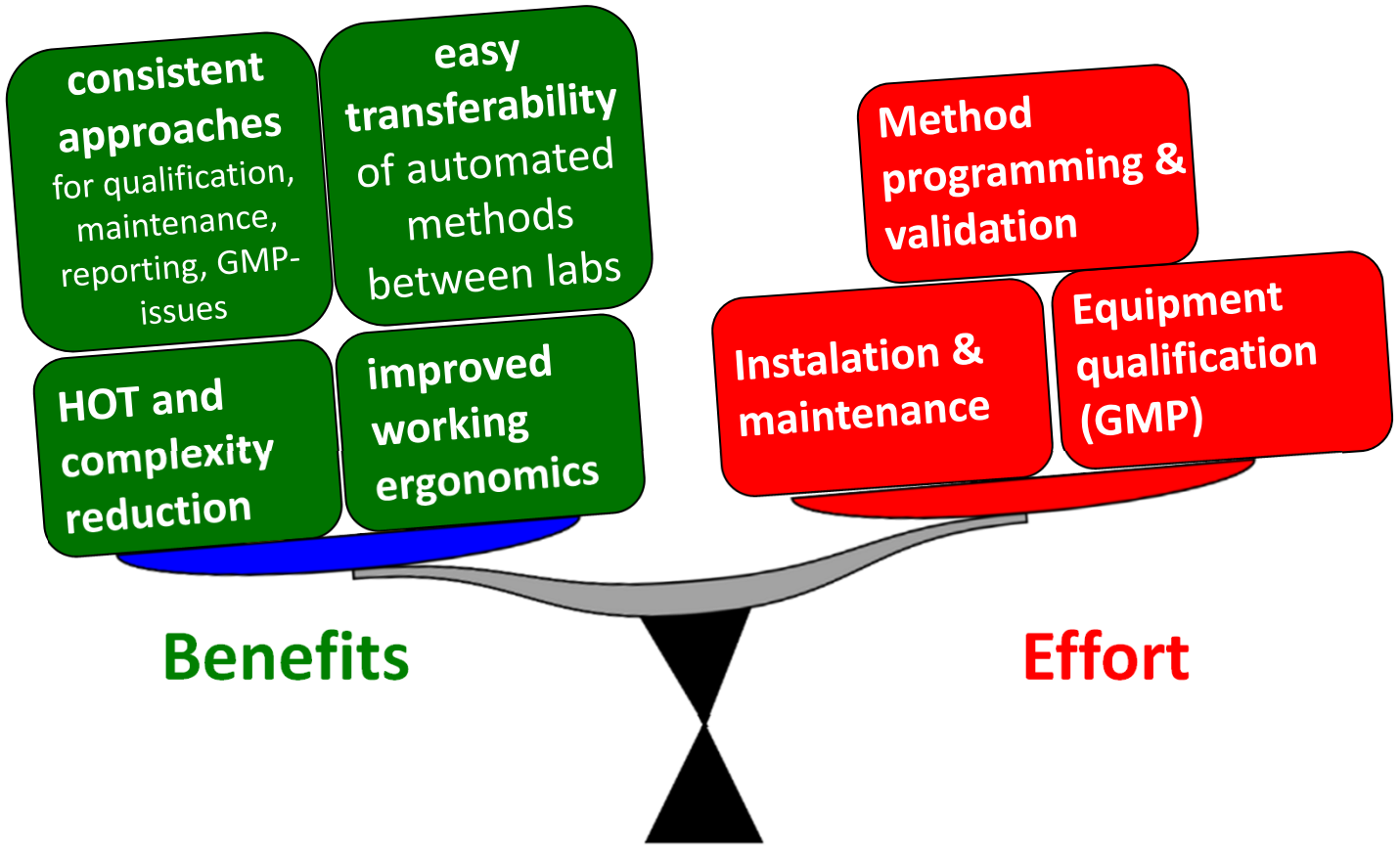
have x-times the effort,

for ending up with x isolated solutions

→ starting point for the *Roche Global Bioassay Automation Team*

The *Roche Global Bioassay Automation Team*

Balance benefit *from* – vs. effort *for* automation



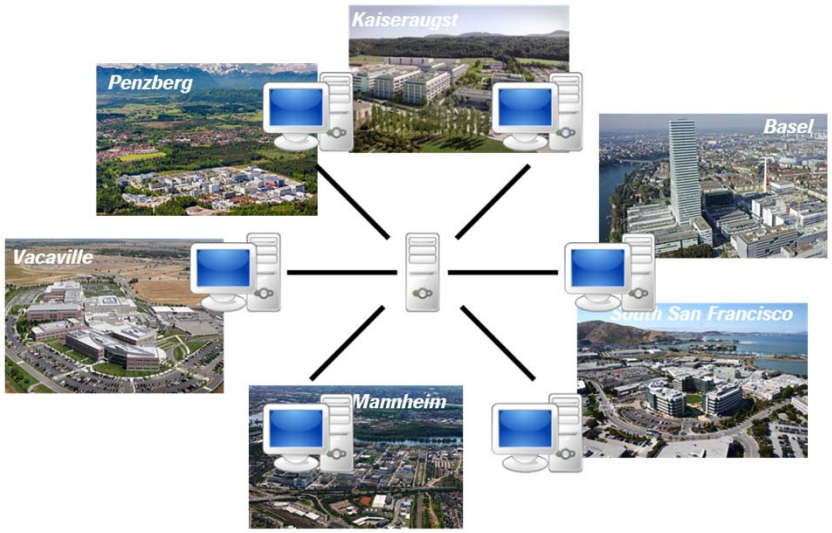
HAMILTON-STAR Global Standard System defined

defined standard configuration

Pipetting channels, prepared for 96-head, gripper, no HEPA-filter, Balance for volume verification, …..

configurable deck-layout (carrier solution)

System specified in detail (part numbers) in a document



Storage and exchange of method-files via central server

Does automation pay off *for us*?
A multitude of factors

- No. of samples per time period
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- Extend to which assays can be automated
- ……

Bioassays can be automated to different extends

Sample preparation automation

= *manual* performed bioassay + *automated* pipetting

"Semi-" automated bioassay

= *manual* cell suspension preparation

+ *automated* pipetting

all other steps optional manual or automated

End-to-end automated bioassay

= *manual* cell suspension preparation

+ *automated* pipetting/thermo incubation /plate washing/readout

Requires integration of peripherie (off-deck-handling)

Off-deck integration

Sample dilutions and plating

Pipetting device

E2E requires integration of additional devices

Washer

Centri-fuge

Connecting device

Incu-bator

Reader

Shaker

+ minimized HOT

+ assays during nighttime

- higher effort for setup

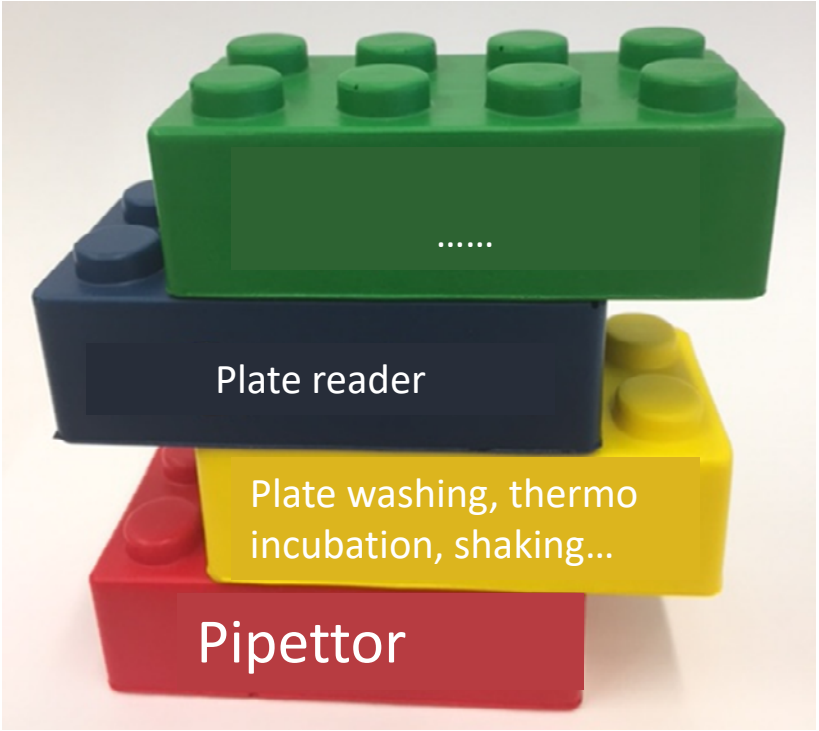
- system is blocked for whole assay duration time

Off-deck integration

Keep flexibility

Case-by-case decision to do certain/different worksteps manualy or automated

depending on number and type of assays to be performed in a workpackage

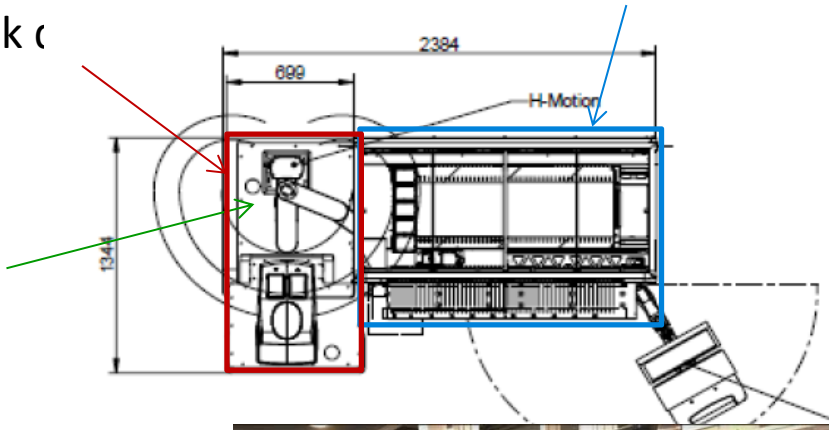


Our approach

Central pipetting unit for sample-dilutions and –plating only

Module with off-deck c
for E2E-automation

Both connected via
robotic arm

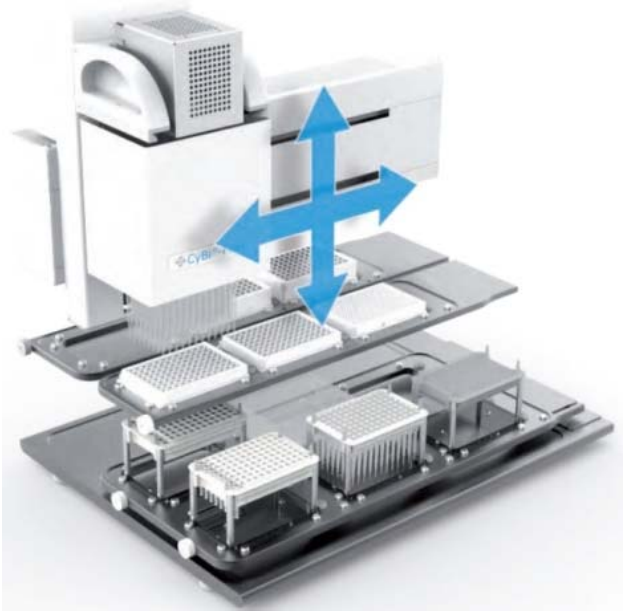


Alternative/ additional strategy: *the helping hand*

Only dilution and plating,

but easy-to-use, small footprint, rel. cheap

→ Several per lab → no bottle-neck by system-blocking



Setup for GMP-purposes in progress

Overview

To automate or not to automate,- *why/when automation?* ⇔ What is special for Bioassays *Automation of*

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Setting-up automation

Technical pitfalls *just one example*

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Acceptance & Concerns

User/training concepts

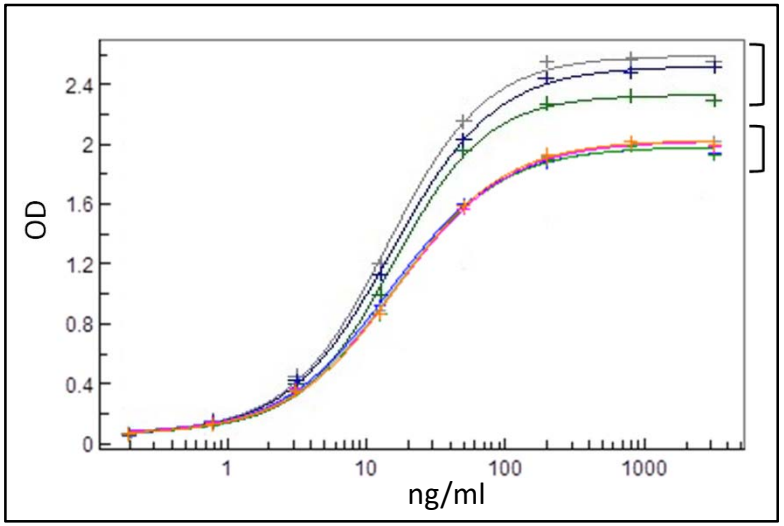
Vision *new horizons for assay formats*

Setting-up an automated assay

- its not plug-and-play

Our very first automated ELISA

Comparison with manual performance



first runs showed inconsistent results; partially high variances between automated and manual performed assays.

Technical pitfalls

Just one example

Spotting of position effects in automated assay for troubleshooting

Assay 1

Plate 1

92738	93875	94612	94129	93603	93308	95762	93481	94276	94332
31865	32606	32544	32608	32379	32383	33110	32663	32251	32573
7854	7929	7973	8079	7968	7956	8015	7944	8087	8000
2356	2402	2409	2398	2392	2423	2455	2430	2429	2421
838	840	849	850	844	852	852	859	852	849

Plate 2

112679	113350	115813	115748	114859	115757	116395	116516	116527	116165
8248	14021	14743	22033	20716	44231	45540	45517	44631	45085
2821	4050	4832	7114	6373	13131	12926	13180	13328	13057
1029	1603	1742	1960	2056	3435	3357	3346	3390	3274
462	579	671	652	763	1152	1125	1127	1129	1114

Plate 3

112756	115755	116182	113782	113137	115479	114873	115814	114772	115505
44276	44327	45033	45040	44347	44582	45292	45223	45045	44919
12736	13038	13129	13077	13073	13167	13196	13137	13094	13105
3386	3313	3354	3366	3371	3402	3443	3365	3383	3343
1121	1132	1146	1125	1124	1143	1155	1150	1139	1142

Assay 2

Plate 1

100653	101829	103199	103443	102133	101623	103274	103341	102546	102756
36637	37528	37731	37478	36647	37005	38136	38061	37733	37539
9132	9216	9432	9403	9131	9118	9433	9490	9398	9174
2839	2889	2950	2901	2839	2875	2954	3002	2947	2864
1004	1013	1034	1030	1009	1022	1025	1041	1022	1015

Plate 2

116376	119299	119820	117655	117178	119422	118632	119074	119494	118688
4081	8147	8096	13174	13608	47531	48366	48317	46959	47746
2133	2599	3391	4465	4636	14288	14216	14309	13786	14055
1011	963	1255	1470	1592	3663	3673	3554	3656	3591
449	531	525	602	673	1204	1248	1200	1217	1203

Plate 3

116067	118619	120371	117407	117531	118395	118094	118283	118696	118159
46613	46967	47770	47455	46999	47242	48184	48447	47409	47304
13530	14058	14299	14060	14060	14120	14314	14535	14057	14063
3659	3591	3691	3653	3647	3695	3733	3714	3711	3631
1207	1222	1238	1220	1223	1224	1269	1265	1240	1244

Assay 3

Plate 1

91664	93178	94433	91936	91996	92855	92131	92235	92376	91987
31635	31921	32107	32224	31881	32191	32928	32618	32310	32128
7795	7904	7940	7872	7938	7955	7976	7974	7862	7868
2442	2377	2416	2424	2403	2435	2447	2417	2453	2384
880	884	880	875	877	882	903	895	888	883

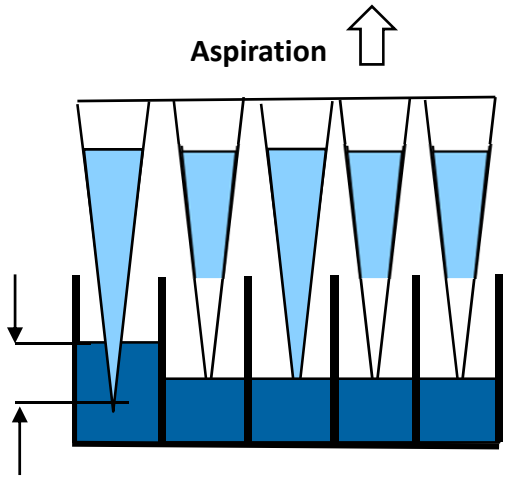
Plate 2

112240	114596	116243	114164	114269	115824	115167	115409	115611	115840
8728	12264	17281	17351	18855	45160	45670	45222	45815	45223
2935	3467	4631	6000	6072	13449	13417	13433	13360	12855
1278	1402	1629	1654	2007	3488	3458	3391	3461	3284
512	602	600	626	742	1145	1163	1143	1141	1138

Plate 3

113791	116122	117442	115212	114827	116089	114914	115191	115704	115164
45143	45117	45624	45693	45233	45388	45856	45840	45295	45366
12930	13328	13373	13348	13458	13424	13423	13421	13110	13458
3457	3362	3416	3432	3453	3487	3466	3390	3435	3445
1141	1132	1143	1143	1163	1151	1167	1162	1146	1171

Reason: minimal differences in absolute liquid levels led to partial aspiration of air



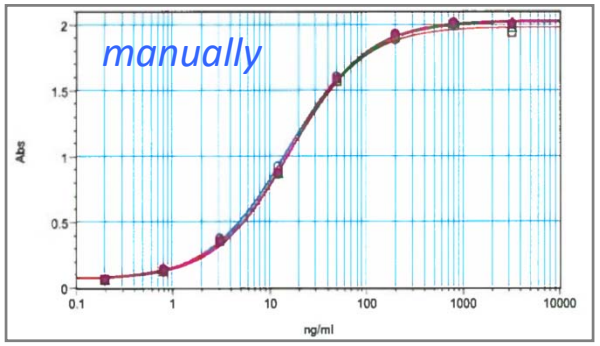
After adjustment of immersion depth, consistent results were obtained.

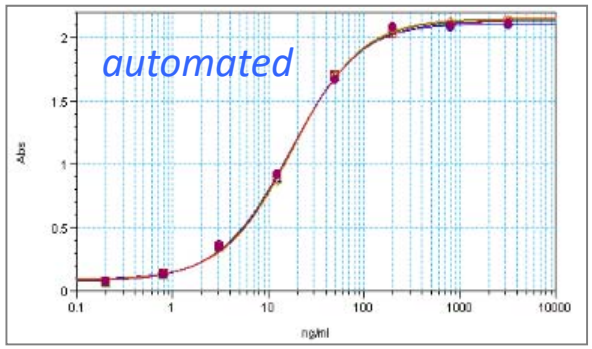
Fluorescein signal, deviation from average of wells with same theoretical concentration: **blue > 5%**; **red > 10%**

Setting-up an automated assay
- its not plug-and-play

After **19 revisions** of the initial automated method:

manually and automated performed standard-ELISA showed equivalent results.



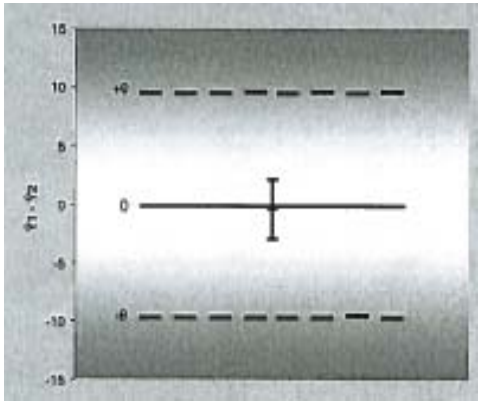


overlays of 5 dose-response curves, 100% level

	manually	automated
N*	18	18
mean (PC)	94.5	94.8
CV [%]	5.8	3.5
variance	30.3	10.8

** from 2 x 54 single plate results*

Results TOS-Test



→ *analysis of samples can be performed both manually and automated*

Setting-up an automated assay

assay performance automated vs. manually

Target: «like-for-like», *i.e. robot = another technician*

→ *Idealy you can not see*

in assay raw data, long-term trending data…

if assay was performed by

Technician A | Technician B | robot

→ To keep the flexibility to perform an assay manually or (partially) automated

The like-for-like concept and consequences for validation of automated assay

→ **possible approaches for validation:**
include robot as the additional technician in determination of

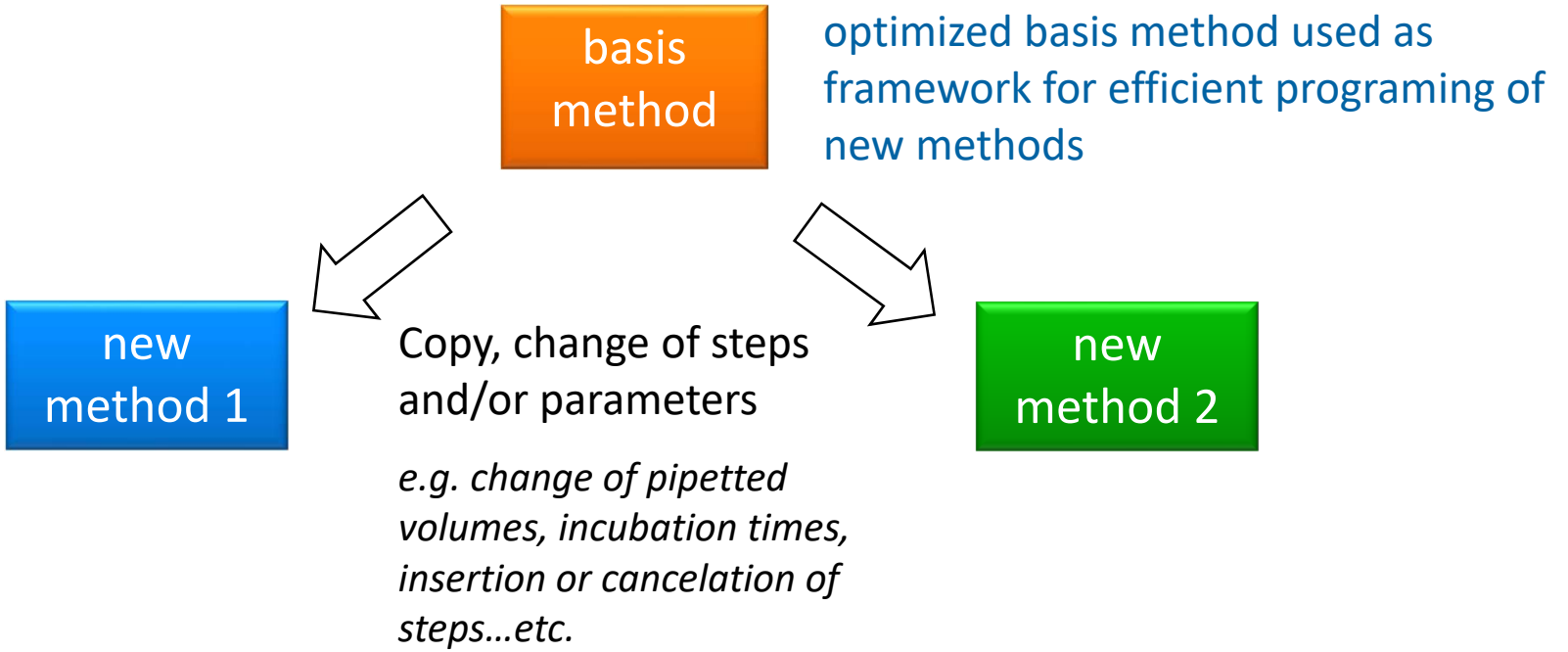
-Linearity/Accuracy
and/or
-Intermediate precision
and/or
-Robustness

or

«A robot is just a big pipette.

We do not validate our pipettes for every product. So why should we do it for a robot?»

the reward for hard labour:
fast and easy set-up of new methods



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Acceptance & Concerns

User/training concepts

Vision *new horizons for assay formats*

Automation & GMP

It may seem to be just a big pipette, but it's computerized!

→ CFR part11 compliance of software required

- User management, account administration
- Electronic records
- Electronic signatures
- Audit-trail (e.g. deletion of raw data)
- Data integrity
  - Access control
  - Data security
  - Audit trail
  - Data review
- Change control
- Virus protection/security concept
- Incident management
- Separation of development and GMP on the same system
- ….

It's complex & laborious, but doable

User/training concepts

Not everyone needs to be an expert

Our approach

- **Superusers:** high level of expertize (can program, attended vendors trainings). At least 2.

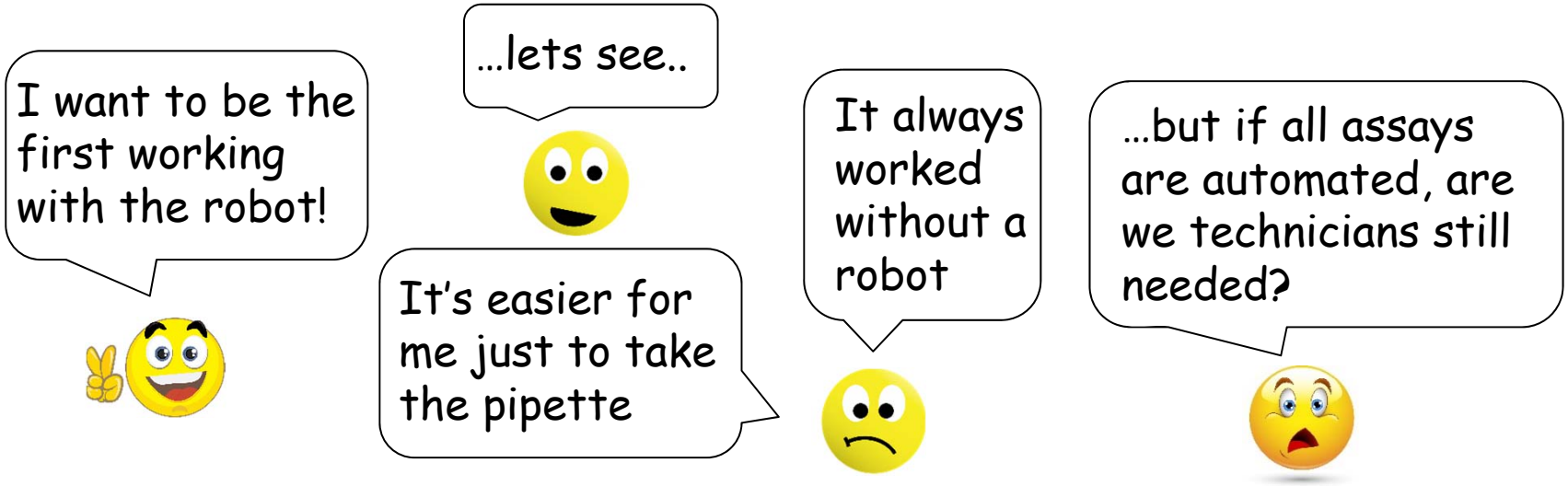
  System qualification & maintenance; develop methods; troubleshooting; connected to global network; train the users... → link between lab/users to global network and vendor….

- **Users:** trained by superusers; contact superuser for troubleshooting or any other questions. Potentialy all technicians performing assay.

  Run automated GMP-methods.

Automation has a dimension beyond business-cases and technical items

When implementing automation you may face a brought spectrum of motivation, acceptance, reservations and concerns



Finally, it's the ususal evolution of change:

polarization / scepticism → familarization → implicitness

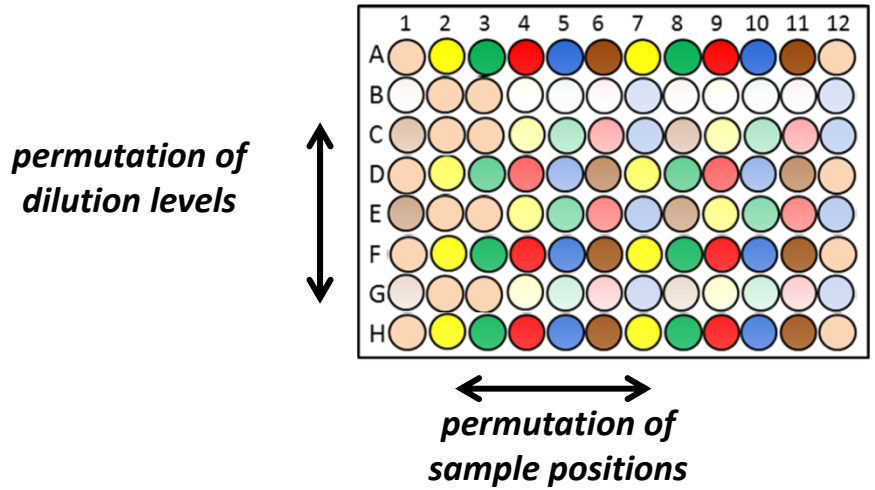
How could we work without it?

…I would never go back

Vision

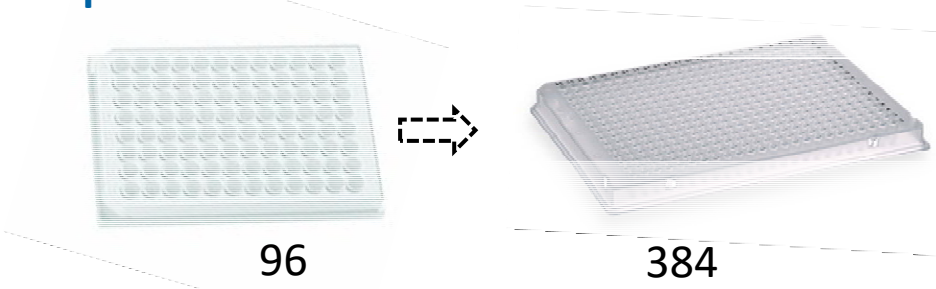
new horizons for assay formats

Automation should allow e.g. to use **more complex assay formats**



Minimizing plate-position effects

384 well plates



More samples per assay, more data-points per sample

→ **Expected <u>increase in quality and efficiency</u>, but** exceeding of what can manually be accomplished, i.e. ***can only be done by a robot***

Summary

- If automation is of benefit *below the bottom-line for your organization* depends on a multitude of factors,- many of them are difficult to be calculated just as a business case, many are work-task and organization specific
- Match/adapt extend of automation with your specific needs.
  - A *modular setup* for a stepwise implementation and usage of automation provides flexibility
- when implementing automation be prepared for
  - many technical obstacles and that a steep learning curve is needed
  - that psychological barriers of staff may be an issue
- Automation & GMP: possible, but complex,- a particular challenge
- Automation opens new horizons regarding assay formats

Acknowledgment

the *Roche Global Bioassay Automation Team*

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Christel Richter

Doing now what patients need next