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

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Hermann Beck, F. Hoffmann-La Roche
Overview

To automate or not to automate, why/when
What is special for Bioassays

→ 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:

- Lowering failure rates
- Increase of throughput /efficiency gain
- Easier Transferability
- Ergonomic reasons
What is special for bioassay?

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

Sterile handling of cells and heterogenous workpackages

Result survey Bioassay labs Basel&Kaiseraugst, 34 responses

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

Yes (44%)  
No (56%)
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

**Benefits**
- HOT and complexity reduction
- improved working ergonomics

**Effort**
- Method programming & validation
- Installation & maintenance
- Equipment qualification (GMP)
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 pay off only for high-throughput?

- **No. of samples per time period**
  - few different assays with high number of samples
  - high throughput
  - vs.
  - many different assays with few samples
  - high diversity

- **No. of different assays**
  - «rare assays»:
    - routine is lost
    - require each time re-familiarization
    - increase of failure rate and time needed

- **No. of labs involved**

- **Extend to which assays can be automated**

*Automation as tool to cope with high diversity*
Does automation pay off *for us*?

*A multitude of factors*

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- .......

**Transferability**
Transferability

Exchange of automated assays between labs

Different, not harmonized automation solutions

\(\rightarrow\) 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

**Benefits**
- consistent approaches for qualification, maintenance, reporting, GMP-issues
- HOT and complexity reduction
- easy transferability of automated methods between labs
- improved working ergonomics

**Effort**
- Method programming & validation
- Installation & maintenance
- Equipment qualification (GMP)
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

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- ....
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
Centrifuge
Incubator
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 manually 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 devices 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*
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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

<table>
<thead>
<tr>
<th>Assay 1</th>
<th>Plate 1</th>
<th>Plate 2</th>
<th>Plate 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Assay 2</td>
<td>Plate 1</td>
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<td>Plate 3</td>
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<tr>
<td>Assay 3</td>
<td>Plate 1</td>
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<td>Plate 3</td>
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<td></td>
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</table>

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
- *it's not plug-and-play*

After **19 revisions** of the initial automated method:
manually and automated performed standard-ELISA showed equivalent results.

<table>
<thead>
<tr>
<th></th>
<th>manually</th>
<th>automated</th>
</tr>
</thead>
<tbody>
<tr>
<td>N*</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>mean (PC)</td>
<td>94.5</td>
<td>94.8</td>
</tr>
<tr>
<td>CV [%]</td>
<td>5.8</td>
<td>3.5</td>
</tr>
<tr>
<td>variance</td>
<td>30.3</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Results TOS-Test

* from 2 x 54 single plate results

→ analysis of samples can be performed both manually and automated

overlays of 5 dose-response curves, 100% level
Setting-up an automated assay

assay performance automated vs. manually

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

→ Ideally you cannot 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

«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

optimized basis method used as framework for efficient programming of new methods

new method 1
Copy, change of steps and/or parameters
  e.g. change of pipetted volumes, incubation times, insertion or cancelation of steps...etc.

new method 2
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*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
- ....
User/training concepts

Not everyone needs to be an expert

Our approach

• **Superusers**: high level of expertise (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

I want to be the first working with the robot!

...lets see...

It’s easier for me just to take the pipette

It always worked without a robot

...but if all assays are automated, are we technicians still needed?

Finally, it’s the usual evolution of change:
polarization / scepticism → familiarization → 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

Expected increase in quality and efficiency, but exceeding of what can manually be accomplished, i.e. can only be done by a robot

Minimizing plate-position effects

More samples per assay, more data-points per sample
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

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Doing now what patients need next