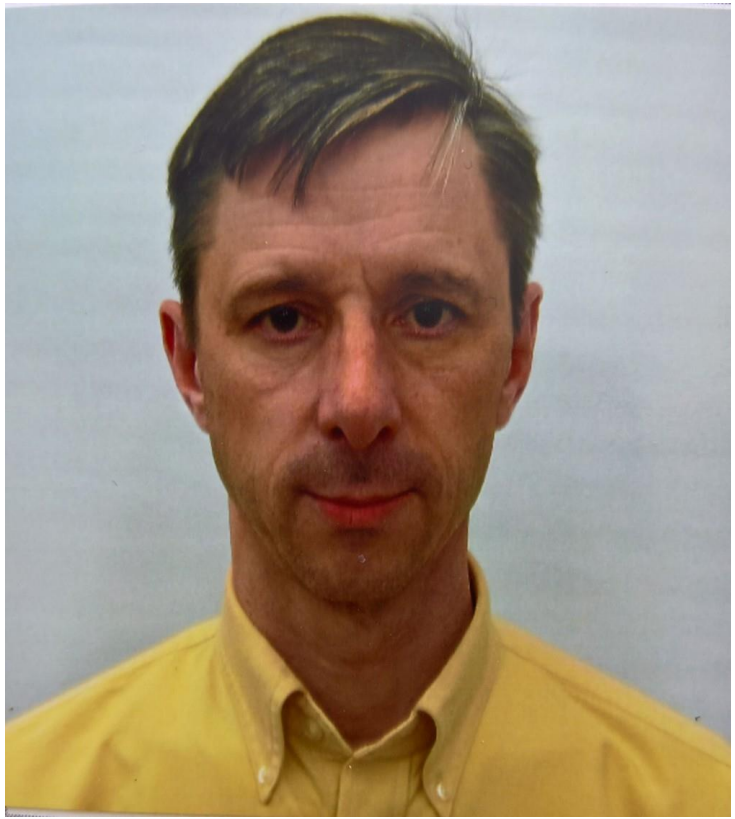


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New Developments in Fully Automated Dissolution Technology

Ahmedabad June 2018

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Regulatory Considerations for the Implementation and use of Fully-Automated Dissolution Systems

Debasish Tripathi, Ph.D.

Ahmedabad June 2018

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Summary

- Fully automated dissolution includes instrument actions and data management.
- Degassing with Helium works, contrary to the FDA paper statement.
- The sampling “zone” height should be assigned as a point, with a tolerance.
- Companies could benefit from creating data workflow maps, since full automation includes data automation.
- Vibration from external sources is likely larger than sources such as heater/circulator and spindle rpm.
- If/when vibration regulations are created, automated systems should incorporate vibration monitoring in time as an additional part of the dataset.
- Automation can reduce fraud.

Pharmaceutical Manufacturing has evolved towards Automation

- Manual
- Semi-automated
- Fully-automated
  - Multi-layer tablets
  - Multi-tip tooling
  - Real-time feedback with integration of NIR and Raman

So too has Pharmaceutical Dissolution Testing

Automation Levels

Manual

Semi-Automated

Fully-Automated

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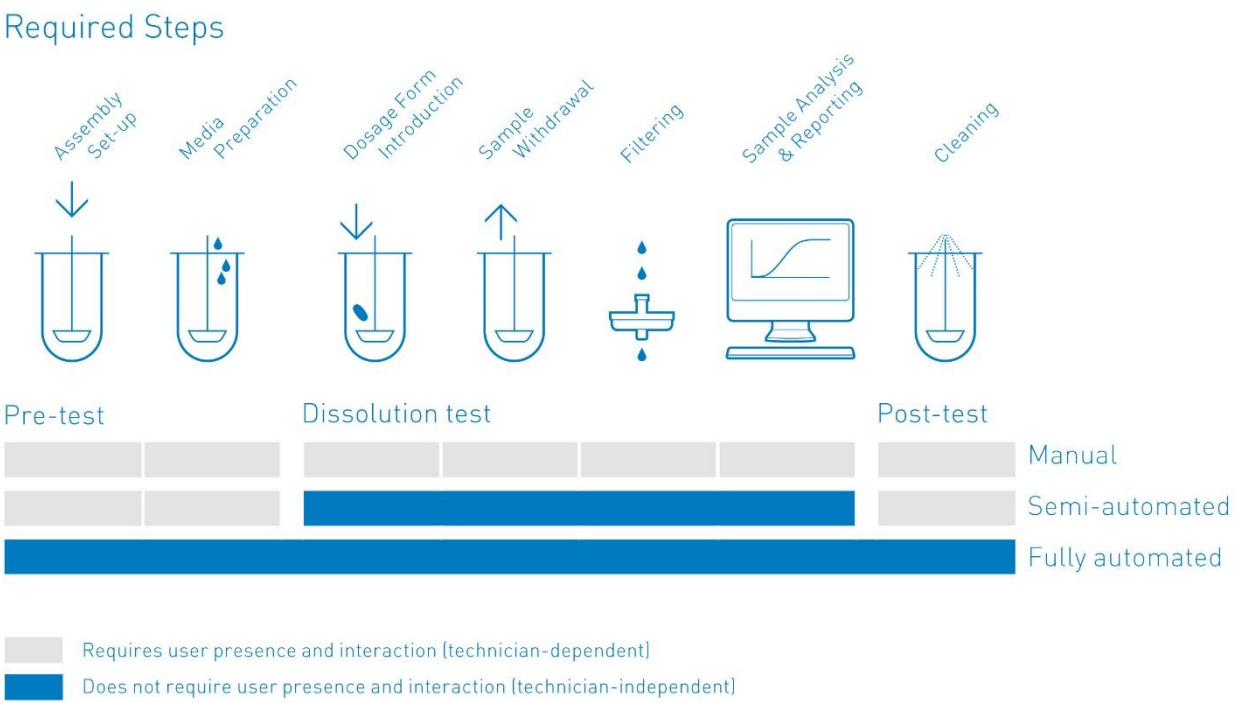
Levels of Automation



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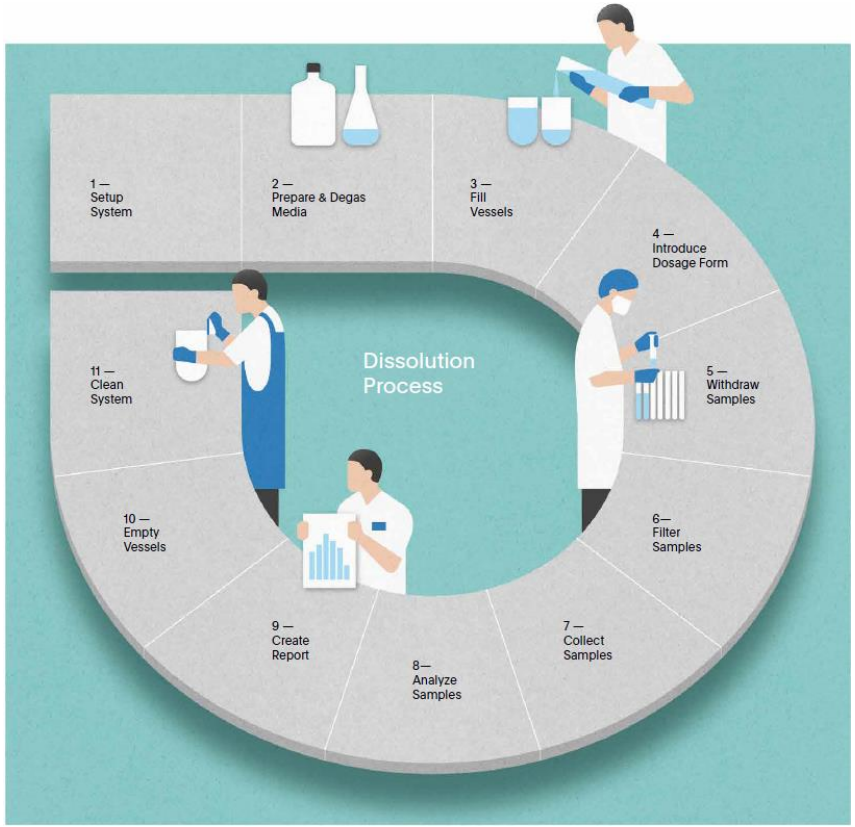

What do you *not* want to automate?

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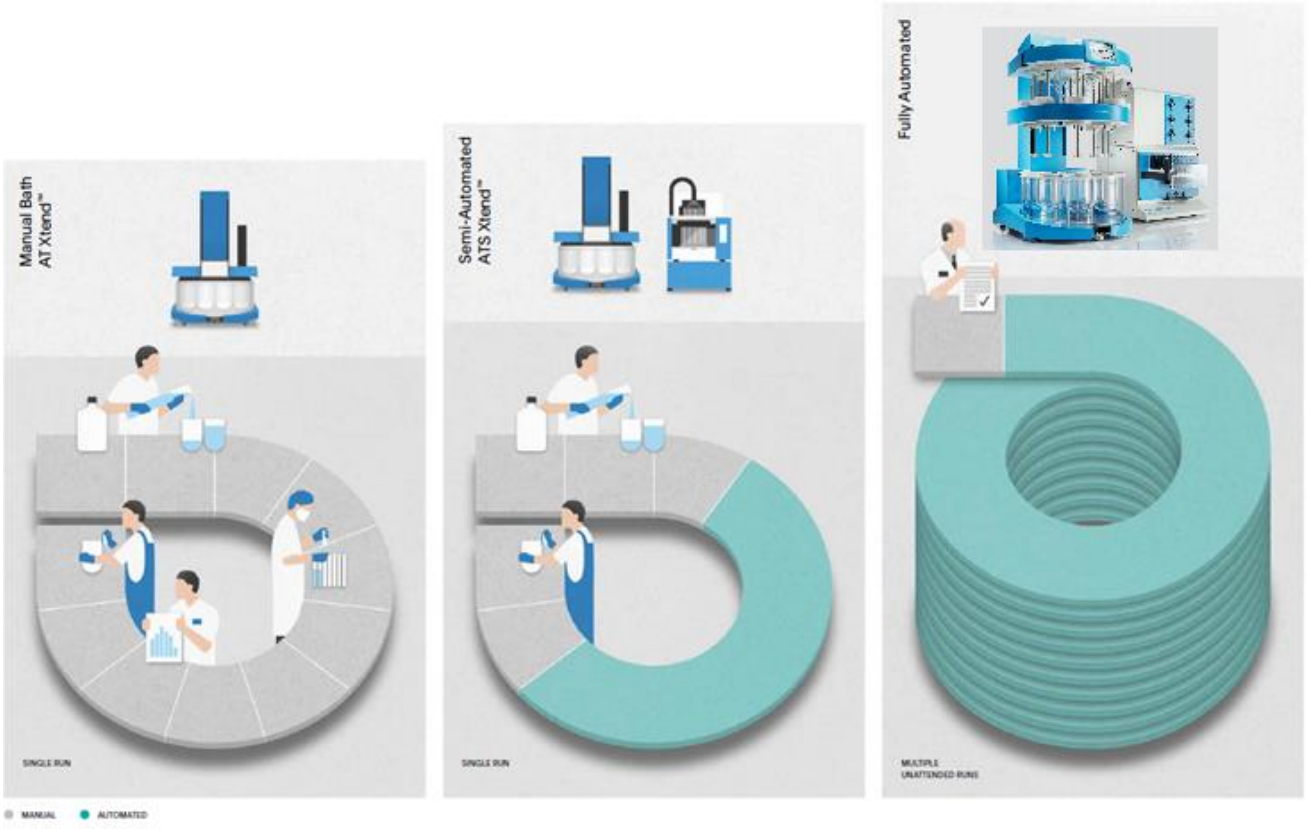
How *efficient/reproducible* do you want to be?



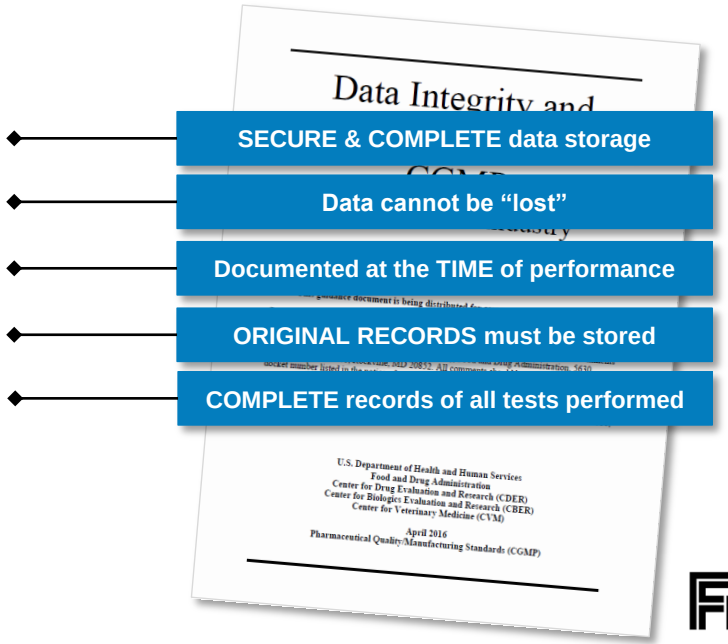
Increasingly cGMP VIOLATIONS involving DATA INTEGRITY

In recent years, FDA has increasingly observed CGMP violations involving data integrity during CGMP inspections. This is troubling because ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect the public health. These data integrity-related CGMP violations have led to numerous regulatory actions, including warning letters, import alerts, and consent decrees. The underlying premise in §§ 210.1 and 212.2 is that CGMP sets forth minimum requirements to assure that drugs meet the standards of the Federal Food, Drug, and Cosmetic Act (FD&C Act) regarding safety, identity, strength, quality, and purity.[2] Requirements with respect to data integrity in parts 211 and 212 include, among other things:

- § 211.68 (requiring that "backup data are exact and complete," and "secure from alteration, inadvertent erasures, or loss");
- § 212.110(b) (requiring that data be "stored to prevent deterioration or loss");
- §§ 211.100 and 211.160 (requiring that certain activities be "documented at the time of performance" and that laboratory controls be "scientifically sound");
- § 211.180 (requiring that records be retained as "original records," "true copies," or other "accurate reproductions of the original records"); and
- §§ 211.188, 211.194, and 212.60(g) (requiring "complete information," "complete data derived from all tests," "complete record of all data," and "complete records of all tests performed").

Electronic signature and record-keeping requirements are laid out in 21 CFR part 11 and apply t certain records subject to records requirements set forth in Agency regulations, including parts 210, 211, and 212. For more information, see guidance for industry *Part 11, Electronic Records Electronic Signatures — Scope and Application*.[3] The guidance outlines FDA's current thinking regarding the narrow scope and application of part 11 pending FDA's reexamination of part 11 as it applies to all FDA-regulated products.

Increasingly cGMP violations involving DATA INTEGRITY



Data must be “ALCOA”:

The FDA has been using the ALCOA acronym as a guide to their expectations regarding evidence (both paper-based, electronic, and hybrid) for years and most other health inspectorates have similar expectations. As such, it is immensely useful in developing strategies to prospectively generate strong evidence in both research and manufacturing.

ALCOA – Standard for evidence, *T.J. Kuhn*, Good Practice for the Pharmaceutical Industry from the Quality Assurance Perspective, July 2008

What is similar among the global data integrity guidances?

FDA Guidance on Data Integrity: “For the purposes of this guidance, *data integrity* refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (**ALCOA**).”

WHO Guidance on Good Data Management: “Data on which these decisions are based should therefore be complete as well as being accurate, legible, contemporaneous, original and attributable; commonly referred to as “**ALCOA**”.

MHRA Data Integrity Definitions and Guidance (regarding Data Review): “This procedure should enable data corrections or clarifications to be made in a GMP compliant manner, providing visibility of the original record, and audit trailed traceability of the correction, using **ALCOA** principles”

- **A**ttributable
- **L**egible
- **C**ontemporaneously Recorded
- **O**riginal or true copy
- **A**ccurate

ALCOA+

- **A**ttributable
- **L**egible
- **C**ontemporaneously Recorded
- **O**riginal or true copy
- **A**ccurate

Complete	all data including any repeat or reanalysis performed
Consistent	all elements of the analysis follow on and are dated/time stamped in the expected order
Enduring	recorded in a permanent and maintainable form for the useful life
Available	for review, audit, or inspection over the lifetime of the record

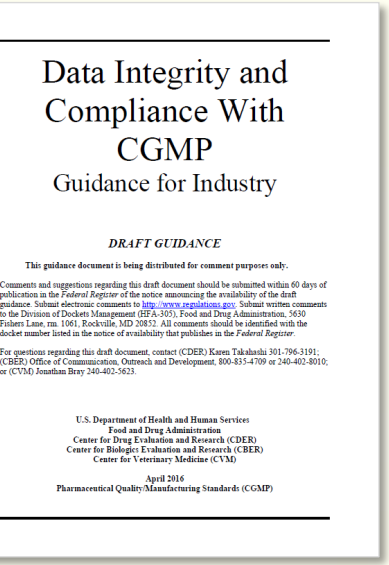
What if there is no AUDIT TRAIL?

If no audit trailed system exists a paper based audit trail to demonstrate changes to data will be permitted until a fully audit trailed (integrated system or independent audit software using a validated interface) system becomes available. These hybrid systems are currently permitted, where they achieve equivalence to integrated audit trail described in Annex 11 of the GMP Guide. If such equivalence cannot be demonstrated, it is expected that facilities should upgrade to an audit trailed system by the end of 2017.

FDA

Medicines and Healthcare Products Regulatory Agency

What's the DIFFERENCE to 21 CFR, Part 11



Data Integrity and Compliance With CGMP

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

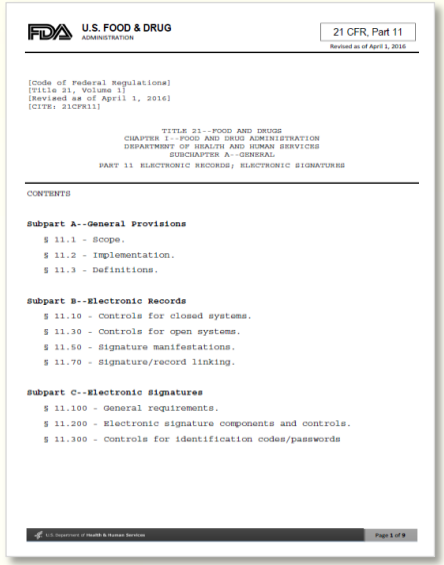
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Karen Takahashi 301-796-3191; (CBER) Office of Communication, Outreach and Development, 800-833-4709 or 240-402-8010; or (CVM) Jonathan Bray 240-402-5623.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

April 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Data Integrity and Compliance with cGMP, Guidance for Industry, April 2016



U.S. FOOD & DRUG ADMINISTRATION

21 CFR, Part 11

Revised as of April 1, 2016

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2016]
[CITE: 21CFR11]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL
PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

CONTENTS

Subpart A--General Provisions

§ 11.1 - Scope.
§ 11.2 - Implementation.
§ 11.3 - Definitions.

Subpart B--Electronic Records

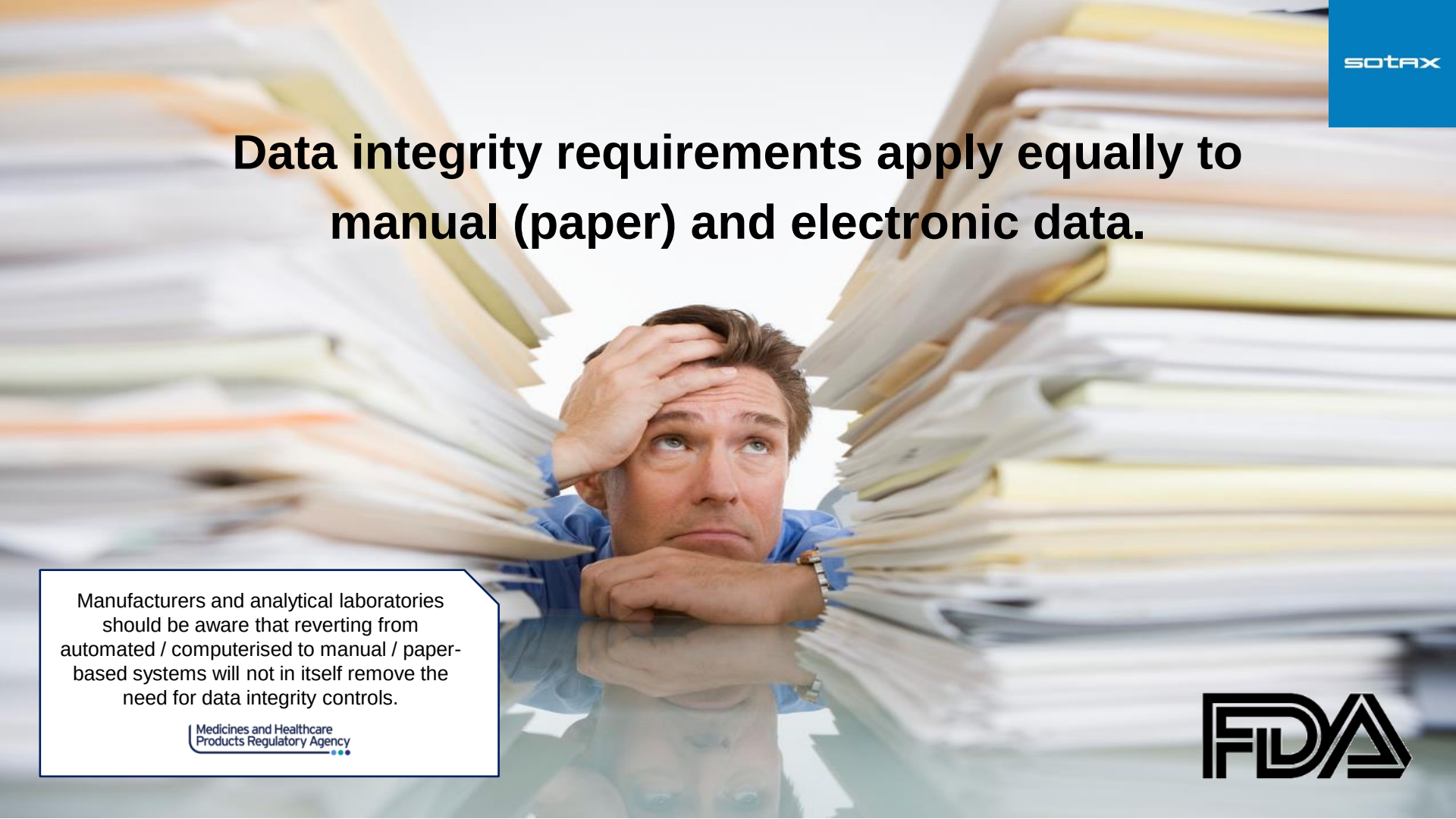
§ 11.10 - Controls for closed systems.
§ 11.30 - Controls for open systems.
§ 11.50 - Signature manifestations.
§ 11.70 - Signature/record linking.

Subpart C--Electronic Signatures

§ 11.100 - General requirements.
§ 11.200 - Electronic signature components and controls.
§ 11.300 - Controls for identification codes/passwords

Code of Federal Regulations Title 21 (21 CFR, Part 11), April 2016

Data integrity requirements apply equally to manual (paper) and electronic data.



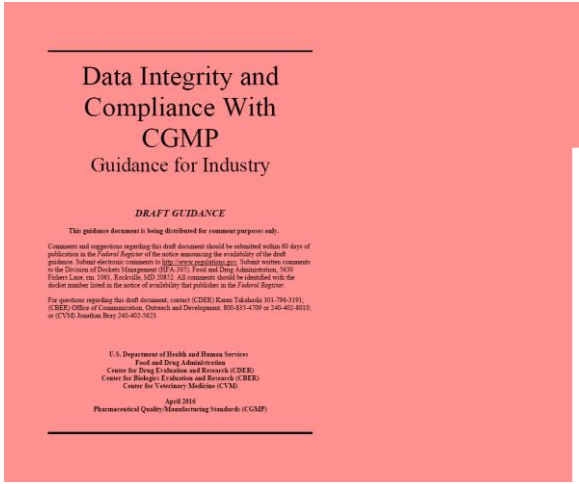
Manufacturers and analytical laboratories should be aware that reverting from automated / computerised to manual / paper-based systems will not in itself remove the need for data integrity controls.

Medicines and Healthcare Products Regulatory Agency

FDA

DATA INTEGRITY “includes” 21 CFR, Part 11

- DATA INTEGRITY is about **ALL DATA**
- 21 CFR, Part 11 is “only” about **ELECTRONIC data**



Data Integrity and Compliance With CGMP
Guidance for Industry

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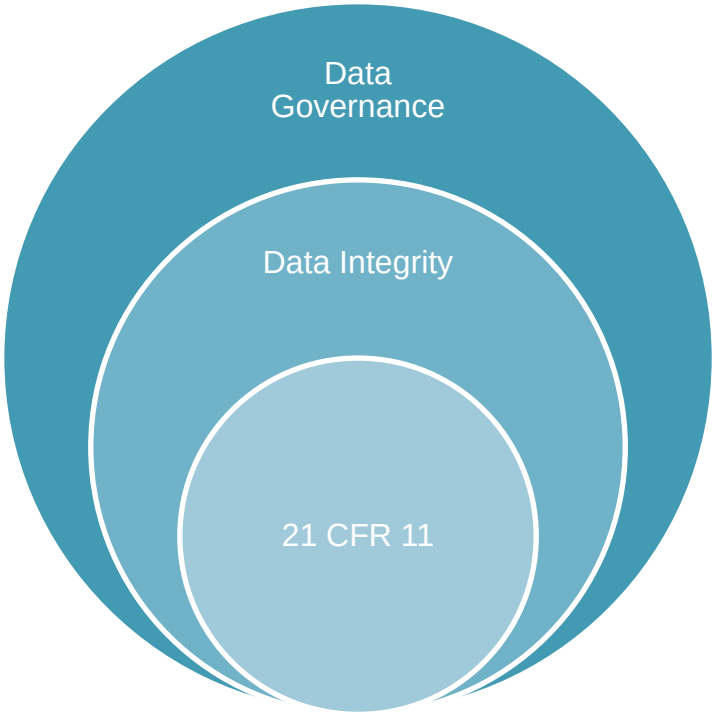
Data Integrity and Compliance with cGMP, Guidance for Industry, April 2016

Code of Federal Regulations Title 21 (21 CFR, Part 11), April 2016

What about “Data Governance”?

- Data Governance (MHRA): The sum total of arrangements to ensure that data, irrespective of the format in which it is generated, is recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data lifecycle.
- Data Life Cycle (MHRA): All phases in the life of the data (including raw data) from initial generation and recording through processing (including transformation or migration), use, data retention, archive, retrieval, and destruction.

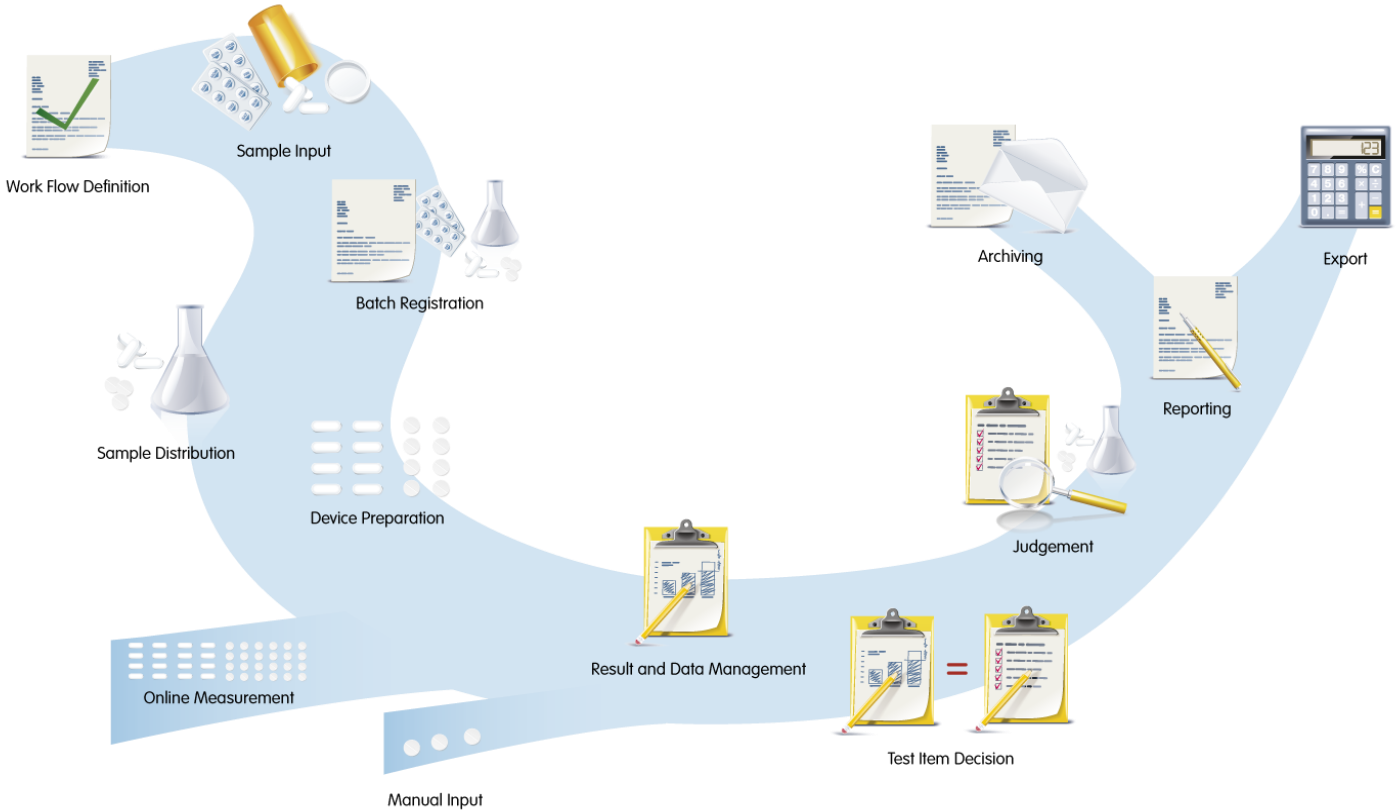


Software Evaluation

Topics:

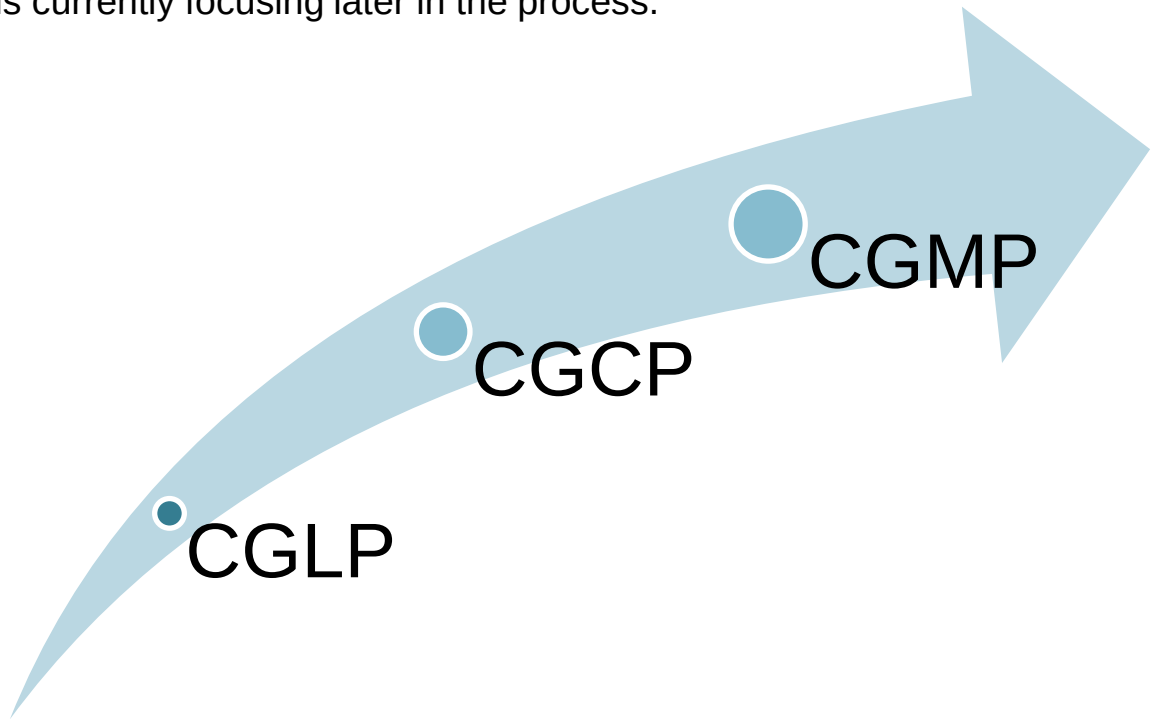
- Audit Trail Review Strategies
- The use of Filters
- Segregation of Roles
- System Configuration
- Electronic Signing
- Data Transfer and Control Strategies

Workflow Map



Is Data Integrity Enforcement Uniform across all CGxPs?

No, Enforcement is currently focusing later in the process.



But **Yes**, the general principles remain the same through all CGxPs.

What is similar among the global data integrity guidances?

PIC/S :

- Members include regulatory agencies, such as the FDA, MHRA, WHO and others.
- An effort to harmonize inspections and enforcement

Data with “built in” data integrity

FOUNDATION MEMBERS

abbvie · AMGEN · BAYER · Baxter · Biogen · Boehringer Ingelheim · Bristol-Myers Squibb · Genentech A Member of the Roche Group · gsk · Lilly · MERCK INVENTING FOR LIFE · novo nordisk · Pfizer

Announcements

Allotrope Connect Workshop in Waldbronn, Germany (Hosted by Agilent)

This event occurred the week of April 23rd with a Public Workshop on April 25th.

Click here to see the agenda. Click here to view the presentations.

Allotrope in the News

Allotrope Foundation Releases the First Version of the Allotrope Ontologies (March 20, 2018 Press Release)

- http://www.allotrope.org/

Managing Human Factors how automation can help

Managing Human Factors and how Automation can help: Cressey Fraud Triangle

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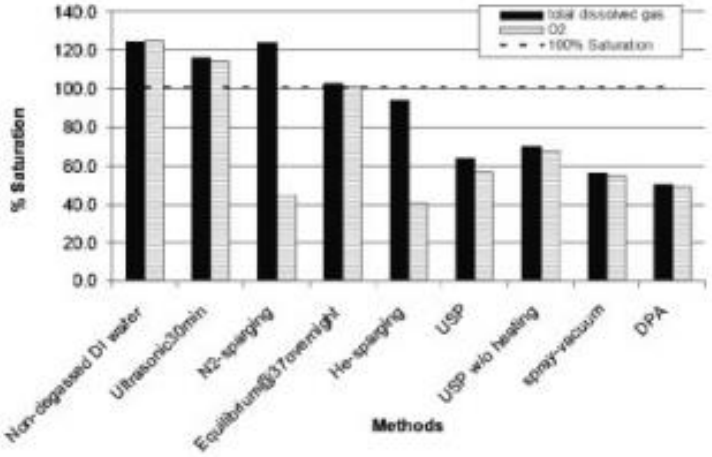
Media Preparation: Degassing

- Manual Degassing:
  - Is the person properly trained and following an SOP?
  - Did they follow the SOP this time?
  - When they added the media to the vessels did they do so in a reproducible (Accurate) way?
  - Is there an audit trail of these activities?
- Semi-Automated:
  - Was the semi-automated system calibrated and ready for use?
  - Typically, operation is simpler and less prone to variation, since a programmed routine is executed by the system
  - Is there an audit trail? Perhaps.
- Fully-Automated:
  - All parameters for degassing should already be programmed in the fully-automated method. Users will not be able to change this, and dispensing to the vessels is executed in the same way every time.

Media Preparation: Degassing



- What does the USP <711> say?
- What has the FDA published on Degassing?

with nondegassed medium. Helium or nitrogen sparging can reduce dissolved oxygen to a low level; however, these methods may be unsuitable for degassing of dissolution media since the oxygen is simply replaced by another gas.

For future dissolution work in our laboratory, total dissolved gases will be kept at less than 60% saturation at room temperature. This level allows for some reaeration during media transfers and the increase in % saturation which occurs upon heating to 37°C.

[NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed before testing.[5]]

[5] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 min. Other validated deaeration techniques for removal of dissolved gases may be used.

Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter. **GAO, Z., MOORE, T.W., et al.** 7, 2006, JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 95, pp. 1606-1613.

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Media Preparation: Degassing

Table 2. Percent Saturation for Various Degassing Methods and Corresponding Percent Dissolution Results for the NCDA#2 Tablet (10 mg Prednisone)

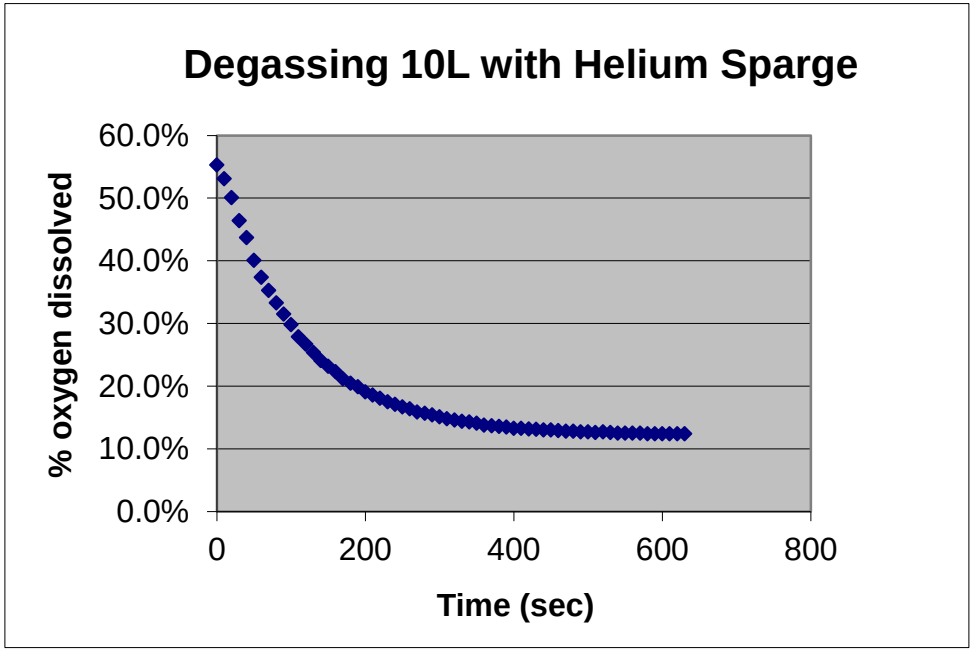
	Measured % Saturation (Average of 3 to 10)			% Saturation Adjusted to 37°C		% Dissolution
Degassing Methods	Test Temp (°C)	Total Gases	O_2	Total Gases	O_2	30 minutes Average 6
Nondegassing D.I. water	23	100 ± 1	95 ± 4	125	125	59 ± 4
Ultrasonic	23	101 ± 3	96 ± 2	116	114	55 ± 2
N_2 sparging	23	101 ± 1	35 ± 5	124	45	67 ± 4
He sparging	23	86 ± 2	31 ± 10	94	41	34 ± 4
USP method	33	55 ± 8	47 ± 9	64	57	33 ± 5
USP method without heating	23	56 ± 4	49 ± 6	70	68	31 ± 2
Spray vacuum	23	43 ± 9	39 ± 10	56	55	32 ± 1
DPA	23	40 ± 4	37 ± 5	50	49	35 ± 3
Equilibrium method: 30°C	28	98 ± 1	97 ± 2	113	114	42 ± 2
Equilibrium method: 35°C	31	98 ± 1	97 ± 4	106	106	36 ± 3
Equilibrium method: 37°C	33	97 ± 1	95 ± 3	103	101	37 ± 3
Equilibrium method: 41°C	35	93 ± 2	94 ± 1	96	97	N/A
Vacuum method: 5 min	23	90 ± 9	63 ± 21	111	81	45 ± 9
Vacuum method: 7 min	23	80 ± 6	58 ± 18	99	75	35 ± 2
Vacuum method: 10 min	23	75 ± 5	55 ± 14	92	71	33 ± 2
Vacuum method: 15 min	23	73 ± 1	48 ± 2	90	63	N/A
Vacuum method: 20 min	23	63 ± 1	35 ± 1	79	45	N/A

- Despite FDA statement regarding the use of He for degassing:

Dissolution results using He degassing are the same within error as the USP method.

Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter. **GAO, Z., MOORE, T.W., et al.** 7, 2006, JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 95, pp. 1606-1613.

Media Preparation: Degassing

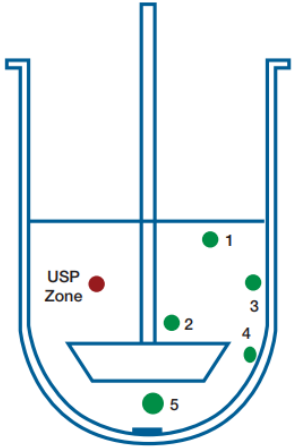


- How does automation benefit media preparation?
  - Automated degassing is programmable and consistent.
  - Time from prep to use is normalized making re-aeration consistent from run to run

> Transfer of the deaerated medium causes a faster rate of reaeration when compared to that which occurs during the dissolution process.

Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter. **GAO, Z., MOORE, T.W., et al.** 7, 2006, JOURNAL OF PHARMACEUTICAL SCIENCES, Vol. 95, pp. 1606-1613.

Sampling: The Zone



- What does the USP say?
- Why is there is no specification on the tolerance of the placement of the sampling Zone.

times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution medium* and the top of the rotating basket or blade, NLT 1 cm from the vessel wall. [NOTE—Where multiple sampling times are specified, replace the aliquots

9. The USP specifies an impossibly narrow sampling zone for Apparatus 1 and 2. Must the sample be taken exactly half way from the surface of the medium and the top of the stirring element? ⊖

The sampling zone specified in <711> is longstanding and admittedly does not describe a practical range within the vessel. The consistency of results when a well characterized material is tested can be used as a measure of variability not attributable to the sample.

Evaluation of Various Sampling Zones in the USP Apparatus 1 (Basket) and 2 (Paddle) Using USP Lot P Prednisone Tablets Reference Standard. **Kikwai-Mutua, L., et al.** s.l. : AAPS, 2006.

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Sampling: The Zone

FIGURE 2. USP Sampling Zone (Red Circle) and Five Sampling Zones (Green Circles) Evaluated in USP Apparatus 2.

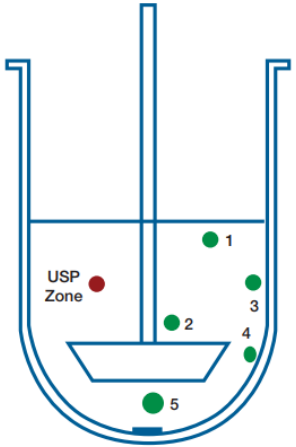
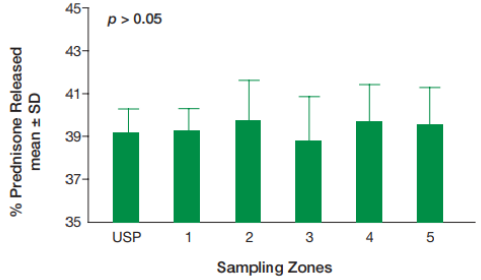


FIGURE 4. Percentage (%) Prednisone Dissolved at 30 Minutes in Apparatus 2 at All Sampling Zones.



Sampling at various zones within the USP dissolution Apparatus 1 and 2 showed no significant differences in dissolution results, suggesting that fluid mixing was uniform after 30 minutes and that the point of sampling during dissolution testing does not impact experimental results.

- What does the USP say?
- Why is there is no specification on the tolerance of the placement of the sampling zone?

Evaluation of Various Sampling Zones in the USP Apparatus 1 (Basket) and 2 (Paddle) Using USP Lot P Prednisone Tablets Reference Standard. **Kikwai-Mutua, L., et al.** s.l. : AAPS, 2006.

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Sampling: Probe Effect

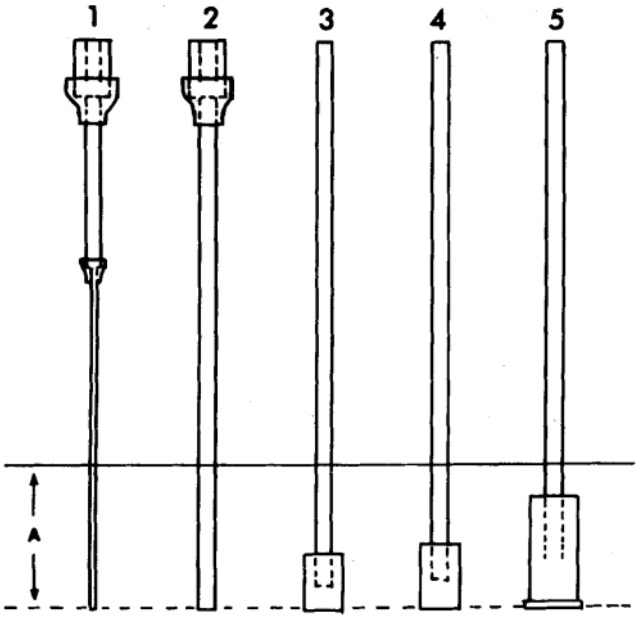


Figure 1—*Sampling probes, showing immersion depth (A).*

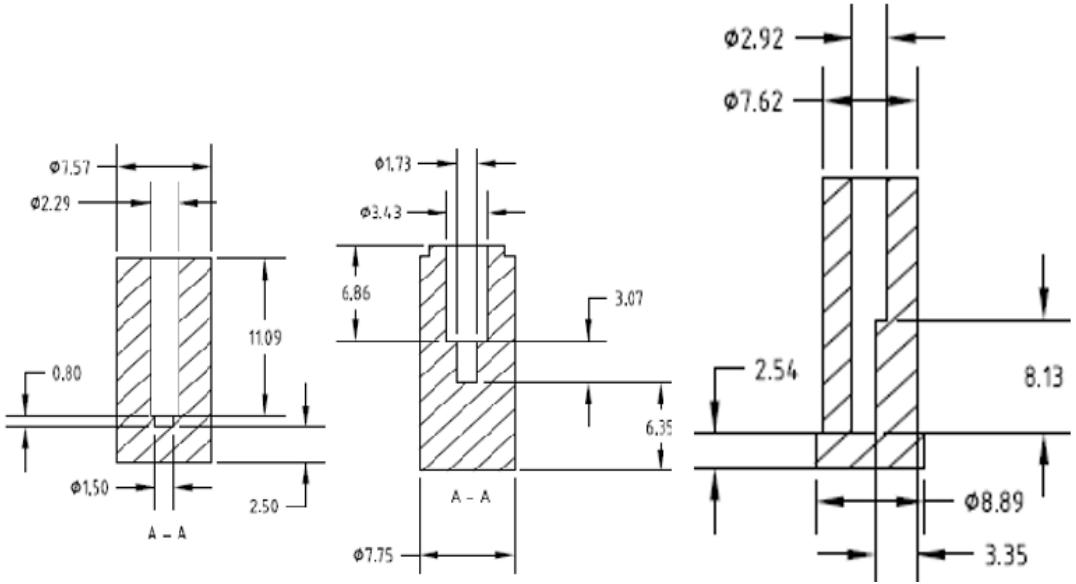
Table I—Effect of Sampling Probes on Dissolution Rate

Probe	Probe Volume, mm^3	Dissolution[a], % of label claim	Increase in Dissolution, %
None	—	41.4	—
1	44	41.4	0
2	177	43.0	1.6
3	466	45.1	3.7
4	706	46.4	5.0
5	877	48.4	7.0

[a] Average of 12 tablets.

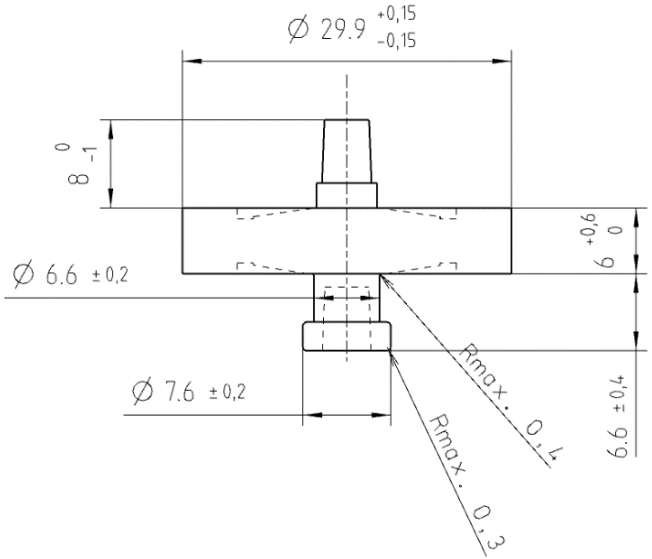
Wells, C.E.; Effect of Sampling Probe Size on Dissolution of Tableted Drugs. J. Pharm. Sci. Vol 70, No. 2. February 1981. pp. 232-233.

Sampling: Tip Filter Design Differences



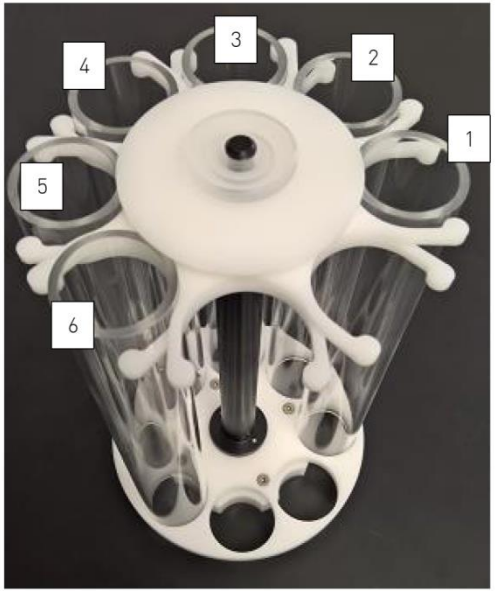
- Lack of standardization increases potential for variation in results.
- Depends on product: highly flocculant or basket methods may be less sensitive.
- Choice affects the sampling height and affects automated sampling settings.
- Beware of potential collisions with paddle.
- Secondary filtration prior to LC may be necessary.

Sampling: Automating Filters



- Easier to standardize.
- Available in a variety of pore sizes and wider range of materials.
- Secondary filtration prior to LC is not required, since filtration down to 0.2 uM is possible.
- Costs have come down and are now more comparable to cannula filters.
- No change to hydrodynamics of the vessel.
- Outer dimensions are also a consideration.

Example: Automated Filter Study



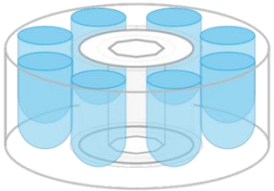
- Select a filter of similar material
- Automating a filter study.
- Works on any carousel style filter changer.
- Match the number of filter stacks to the number of vessels
- 3-3 and 2-2-2 are some of the more common choices.
- USP <1092> section 1.1 offers guidance on filter selection.

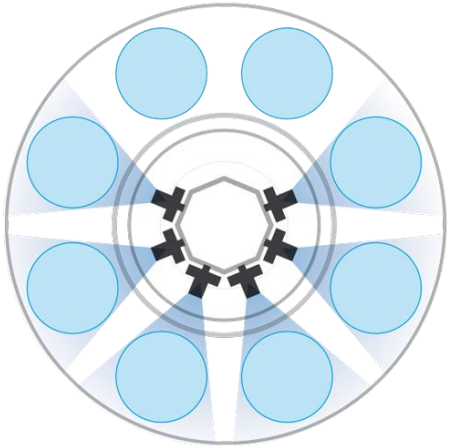
BN10010EN, Filter Selection and Validation for SOTAX Dissolution Systems, 2017.

Visual Observations

Visual Observations R&D visualization and OOS troubleshooting.

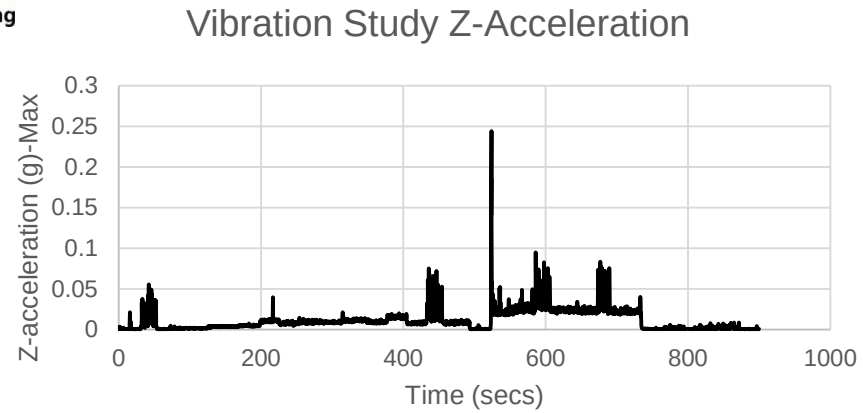
- CenterView™ video monitoring
- Take pictures or videos at individual timepoints
  - Camera can be adjusted and controlled in height & focal distance
  - Integrated indirect light
  - MDsoft: Video Data traceable part of the dataset
- Potential Future
  - Quantitative vs. Qualitative video and image analysis

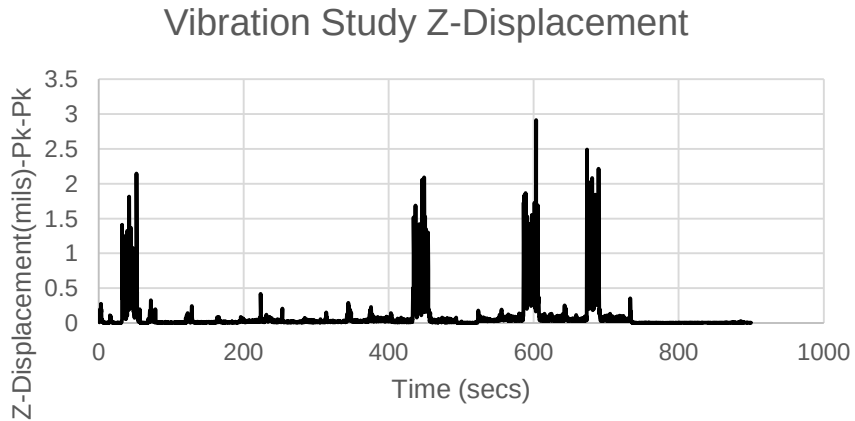




Tieu, K., Salt, A., Wirges, J. et al. AAPS PharmSciTech (2014) 15: 1611. https://doi.org/10.1208/s12249-014-0191-y

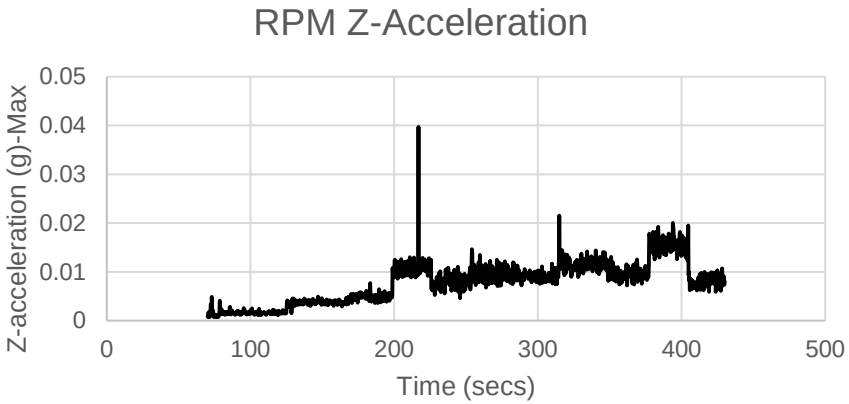
Vibration Study

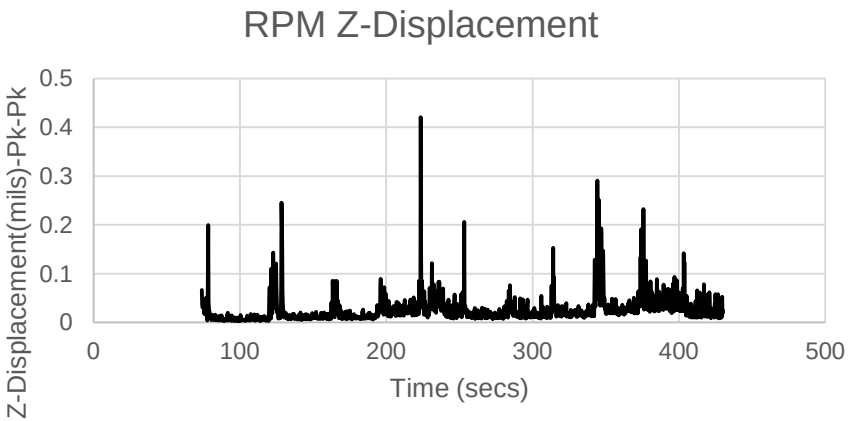




- Levels of vibration do not change linearly with rpm
- Heater/Circulator can change the baseline vibration level
- External vibration sources may be larger than vibration due to rpm

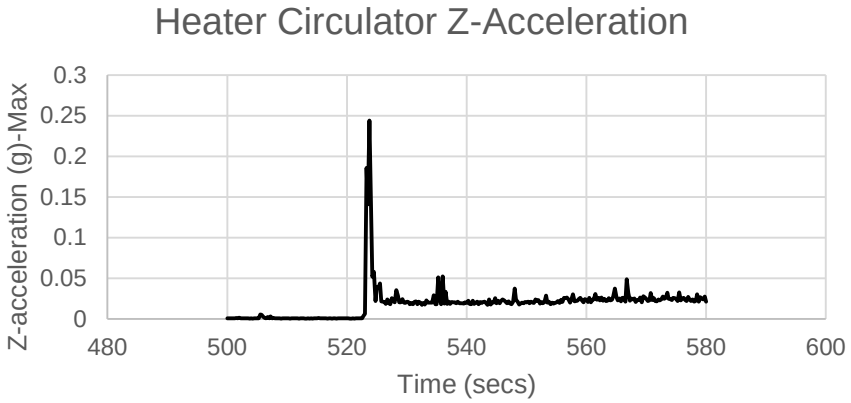
Vibration with RPM

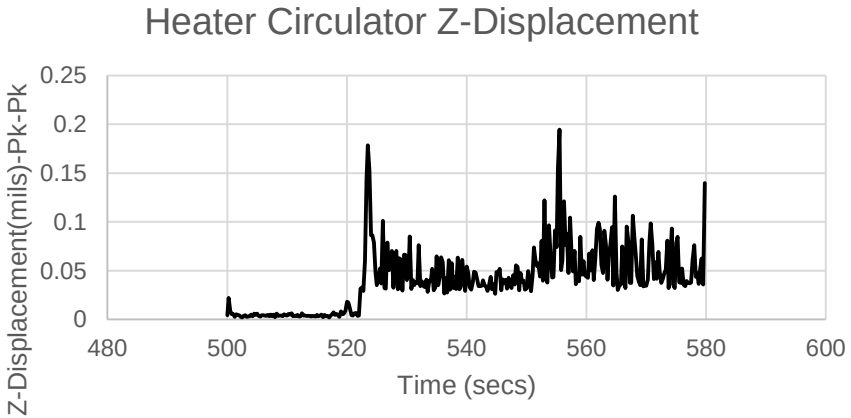




- Levels of vibration do not change linearly with rpm
- Motor and bath construction characteristics should be considered
- External vibration sources may be larger than vibration due to rpm

Heater/Circulator Vibration





- RPM and Heater/Circulator together, create a distinct vibration that is different than either individually and neither out-scaled the other
- External vibration sources may be larger than vibration due to Heater/Circulator

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Vibration: Automation

- Though there is currently no regulation regarding vibration, automated systems have demonstrated their ability to pass the PVT (prednisone testing), which holistically includes vibration as a potential influence on the test.
- As seen in the current dataset, external vibration sources may be larger sources of vibration than vibration due to spindle rpm or heater/circulators. However, external vibration sources may be of short duration and the level of effect that larger vibration events of shorter duration would have on dissolution as compared to longer duration vibration at lower levels requires further study.
- Vibration due to manual sampling would be less reproducible than vibration due to automated sampling systems.
- If/when regulations are created, automated systems can incorporate vibration monitoring as an additional part of the dataset.

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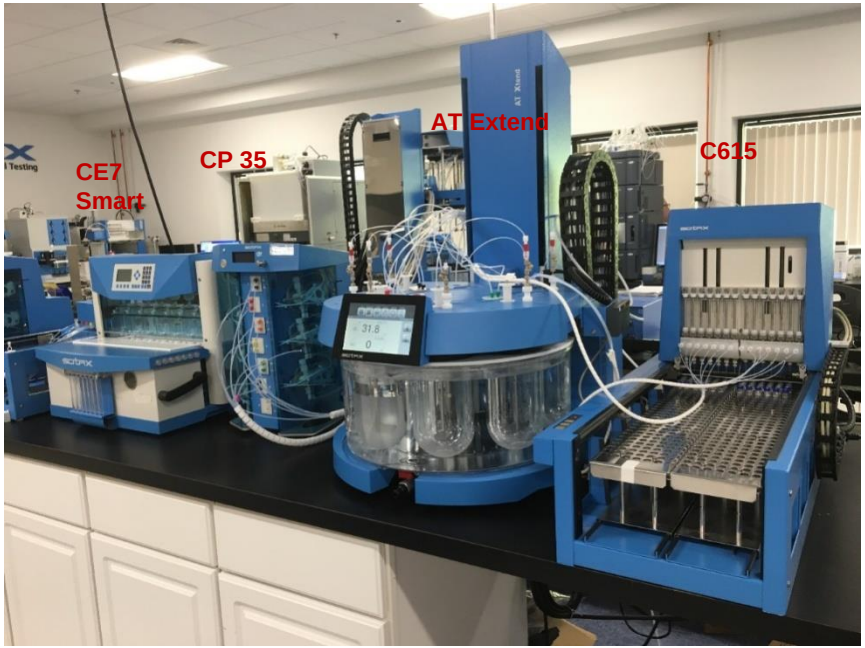
Summary

- Fully automated dissolution includes instrument actions and data management.
- Degassing with Helium works, contrary to the FDA paper statement.
- The sampling “zone” height should be assigned as a point, with a tolerance.
- Companies could benefit from creating data workflow maps, since full automation includes data automation.
- Vibration from external sources is likely larger than sources such as heater/circulator and spindle rpm.
- If/when vibration regulations are created, automated systems should incorporate vibration monitoring in time as an additional part of the dataset.
- Automation can reduce fraud.

Adobe Acrobat Document

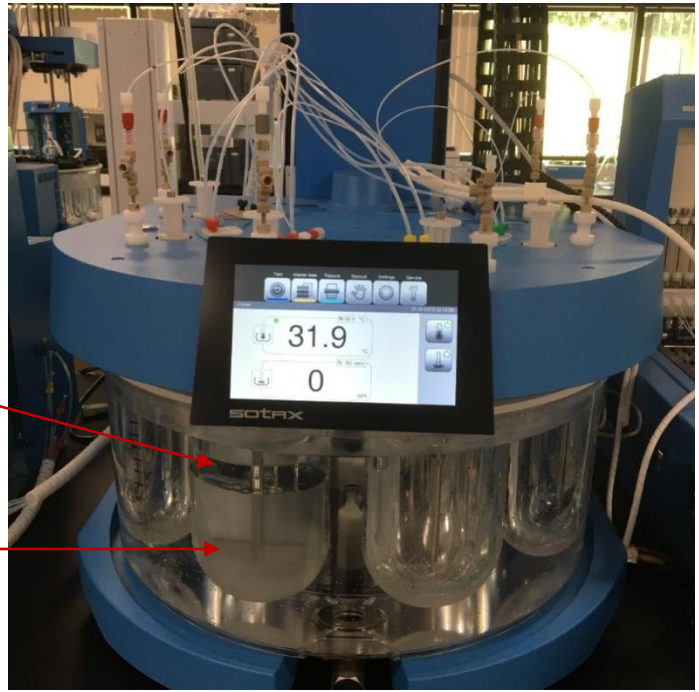
Biphasic Dissolution System

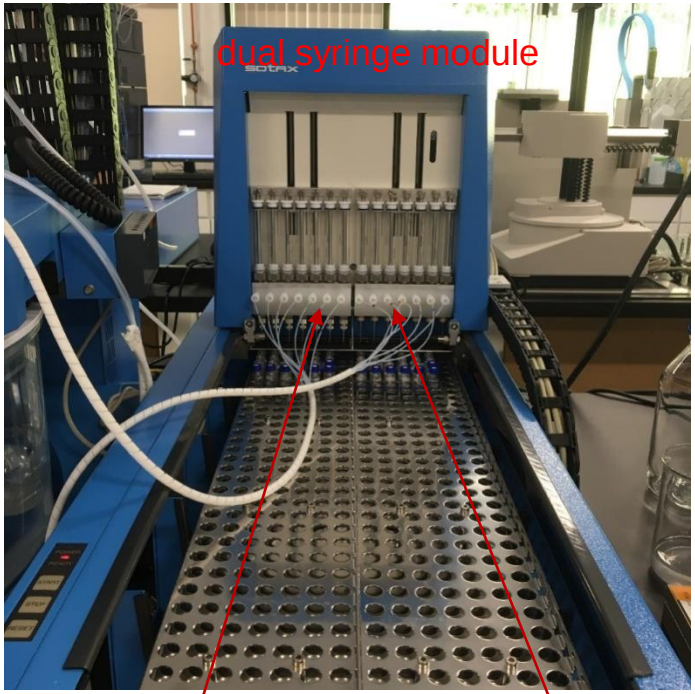
USP 4 + USP 2 + double Autosampler



Biphasic Dissolution System

CE7 Smart + AT Extend + Dual Syringe Module C615





Biphasic Dissolution System

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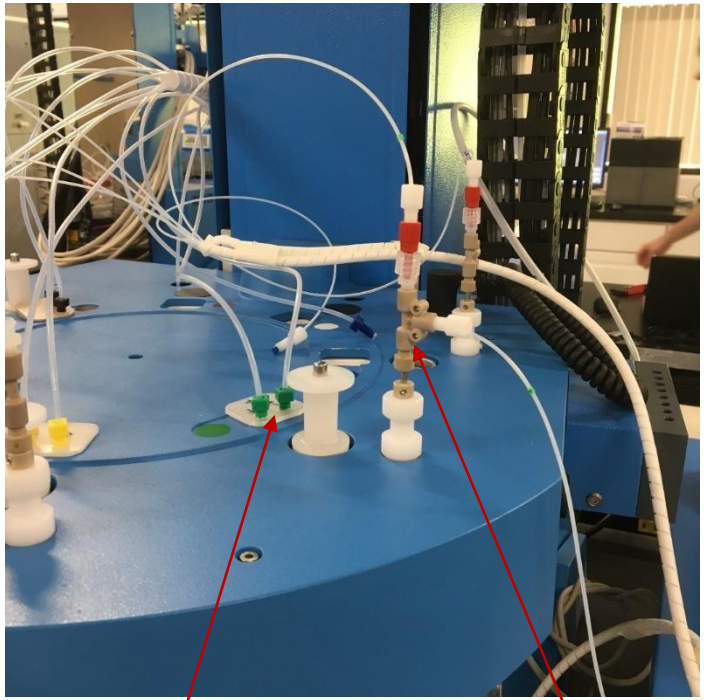

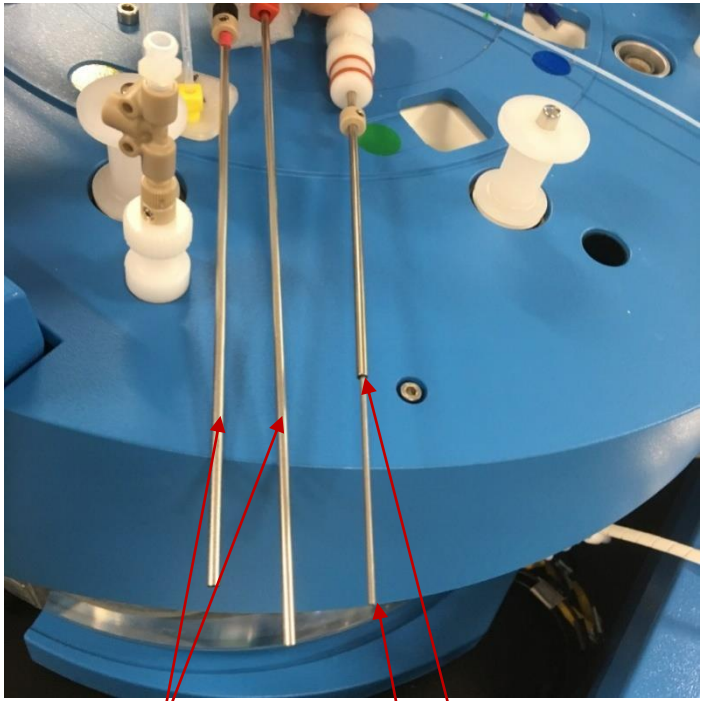

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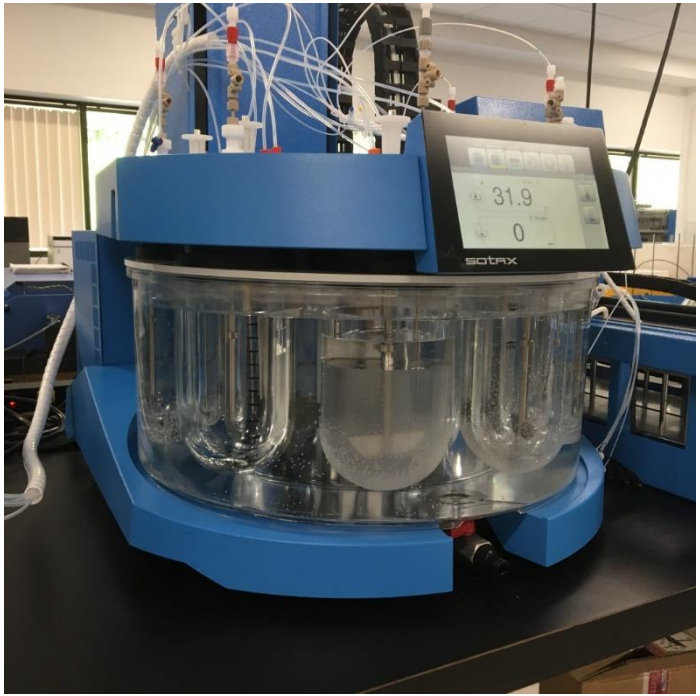

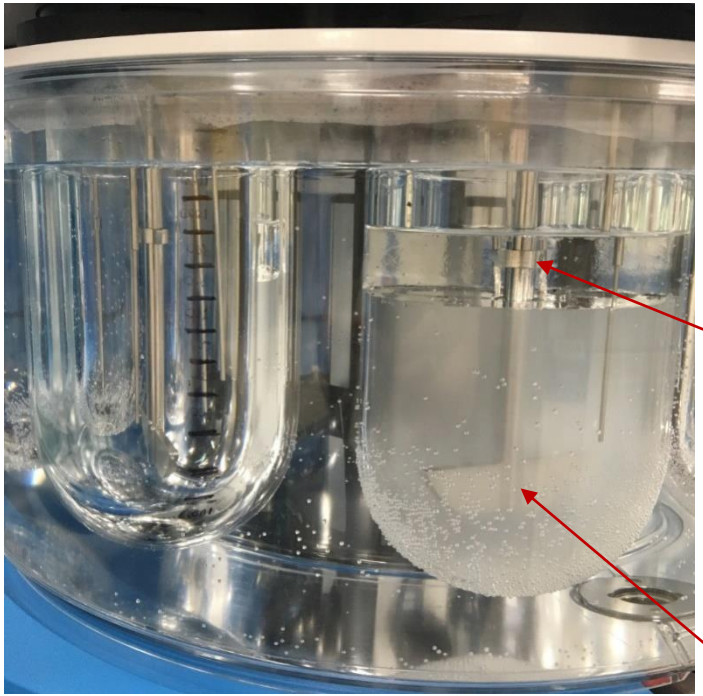

biphasic paddle – octanol phase

main paddle – aqueous phase