TEXAS A&M UNIVERSITY
Irma Lerma Rangel
College of Pharmacy

Innovative Formulations and Delivery Technologies: Practical aspects from development to FDA approvals

National Academy of Science, Engineering, and Medicine Workshop

Technical and Regulatory Barriers in Pharma Manufacturing

June 2-3, 2020

Mansoor A. Khan, R.Ph., Ph.D.

Professor and Vice Dean, Presidential Impact Fellow

Texas A&M University, Rangel College of Pharmacy, College Station, TX.

Outline

- Drugs and Drug Products/Delivery Technologies that are not well understood enough – Evolving
- Drugs and Drug Products/Delivery Technologies that are fairly well studied through science – Lagging behind in approvals

- Drugs and drug products/Delivery Technologies that are understood and approved, but may have barriers for effective utilization and marketing –

  Background/need for modernization of pharmaceutical manufacturing
  Consistency in regulations ensures readiness to develop and adopt technology
  Regulatory pathway for 3D products – A new opening

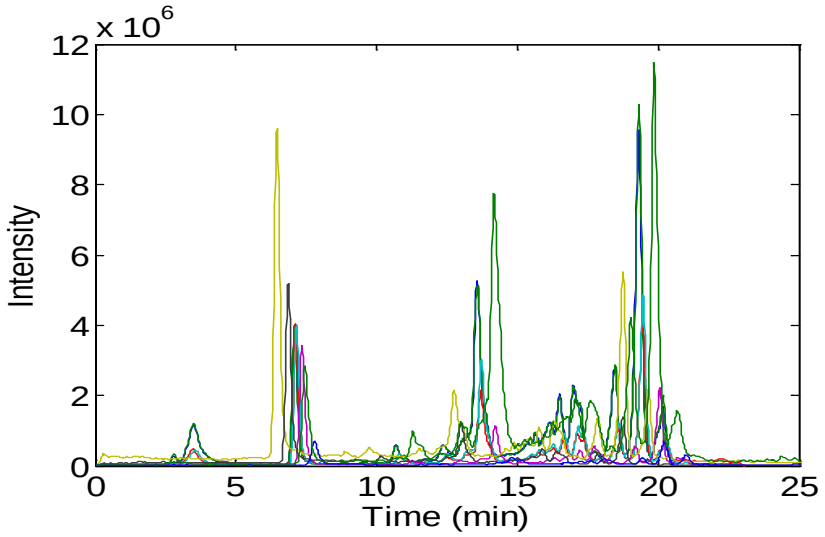
- Drugs and drug products/Delivery Technologies that are understood and approved, but generic products have no access.

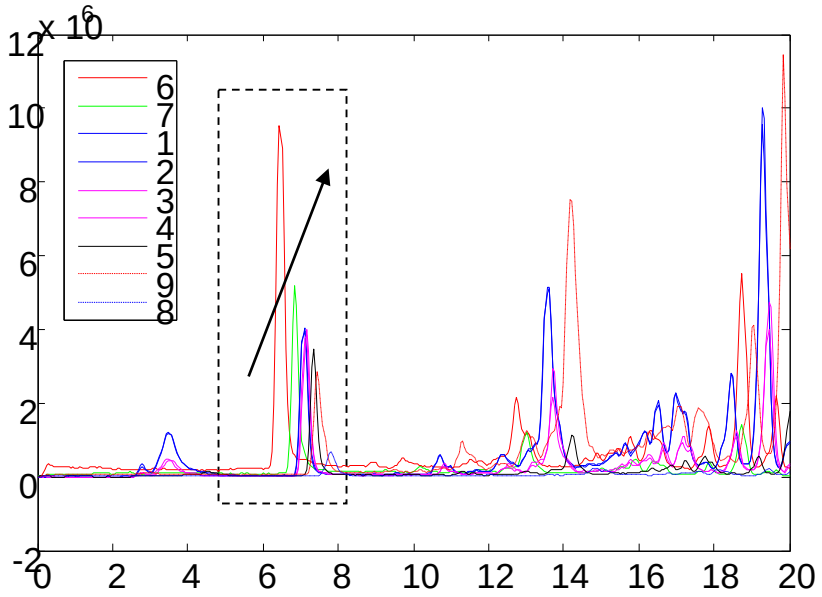
  Science can overcome regulatory hurdles; A few practical examples

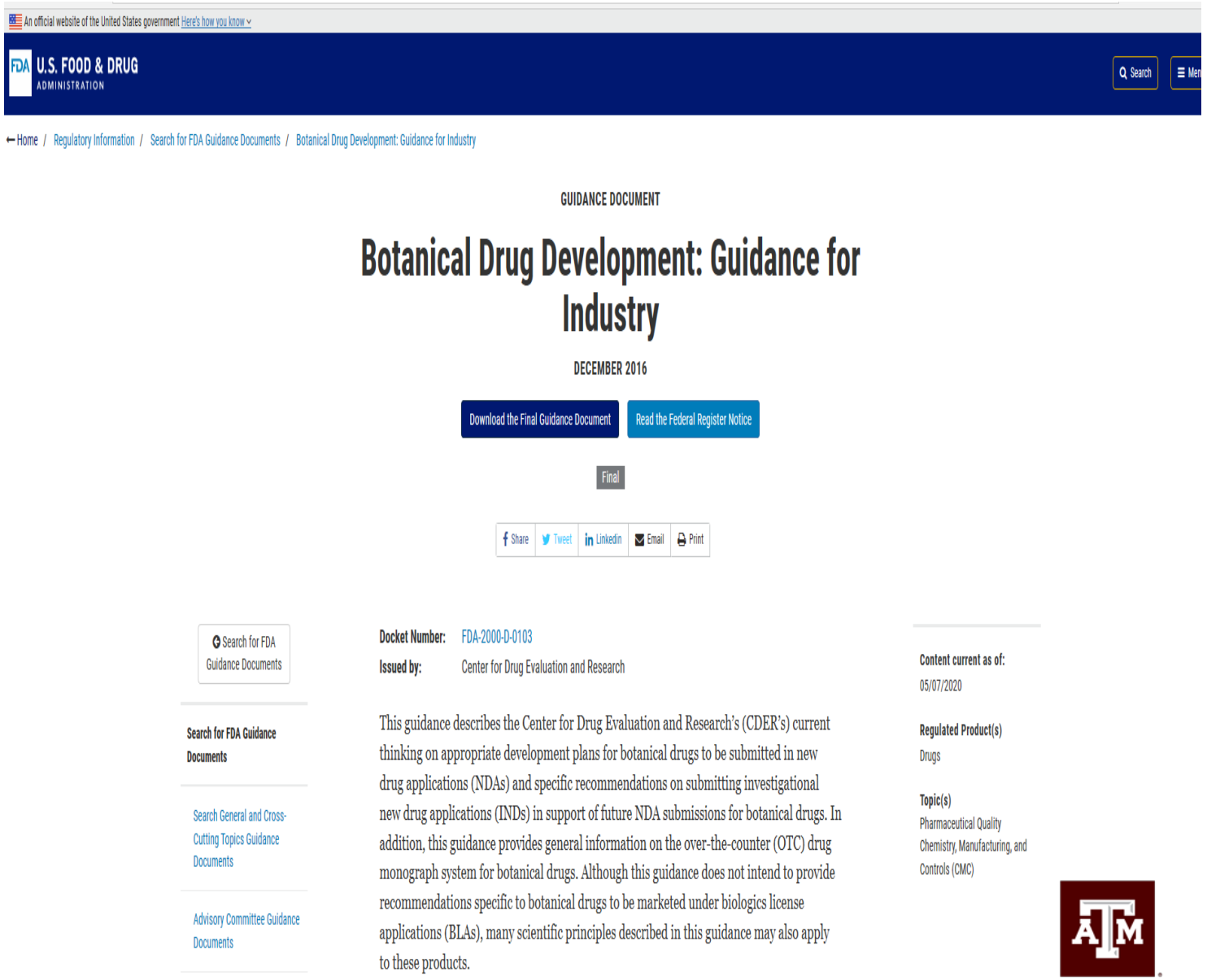
Drugs and Drug Products/Delivery Technologies that are fairly well studied through science – Lagging behind in submissions or approvals

- Some examples (Pubmed.Gov accessed on 05-30-2020)
  - Oral delivery of proteins – 1963-2020 > 7000 manuscripts
  - Oral delivery of insulin – 1972 – 2020 > 1700 manuscripts
  - Herbal drugs – 1947-2020 >56000 manuscripts
    - *Two products approved so far; Sinecatechins, Veregen® and crofelemer, Mytesi™*
  - Over 150 approved brand products where there are no generic products

Paw-Paw: Explanation of Clusters in PCA Scores Plot







Selection of Excipients

- Well known excipients
  - Monograph
  - IIG List for adult products (http:/www.accessdata.fda.gov/scripts/cder/iig/index.cfm)
  - Documented human use in the proposed level
  - GRAS
- New excipients (Battery of tests needed) (http://www.fda.gov/cder/guidance/5544fnl.cfm)

PHARMACEUTICAL CGMPS FOR THE 21ST CENTURY — A RISK-BASED APPROACH FINAL REPORT

EXECUTIVE SUMMARY — KEY ACCOMPLISHMENTS

In August 2002, the Food and Drug Administration (FDA or the Agency) announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality — to bring a 21st century focus to this critical FDA responsibility. The initiative, which this final report describes in detail, was intended to modernize FDA's regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines. As part of this initiative, both the pharmaceutical, as well as the chemistry, manufacturing, and controls (CMC) regulatory programs were evaluated with the following objectives in mind.

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- Encourage implementation of risk-based approaches that focus both industry and Agency attention on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
and/or
Communications Staff, HFV-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place,
Rockville, MD 20855
(Tel) 301-827-3800
http://www.fda.gov/cvm/guidance/published.html

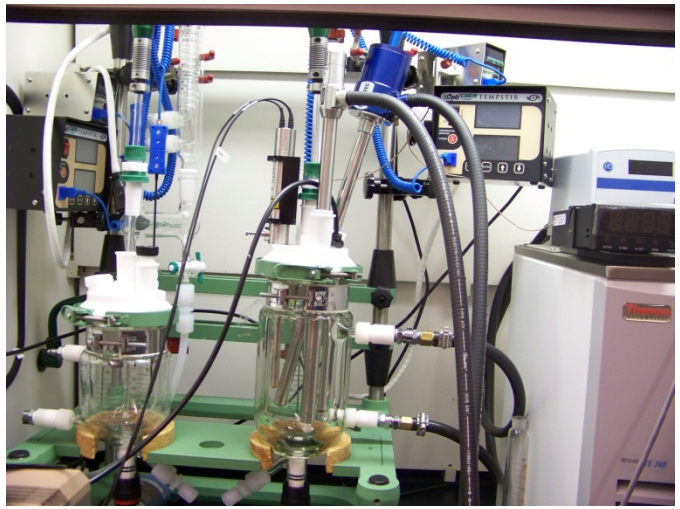
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)
September 2004
Pharmaceutical CGMPs

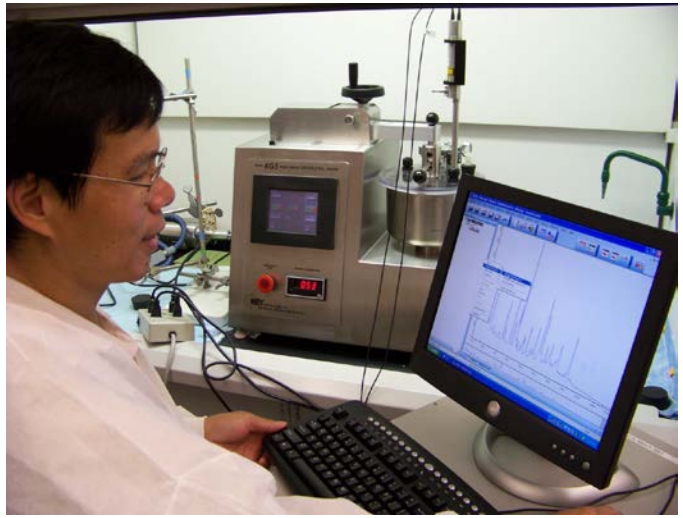
DPQR/FDA Publications

Characterization

Process/formulation variables
Mechanistic evaluations

- J. Pharm. Sci. 2005, 94 (7), 1589-1597
- Int. J. Pharm. 306, 56-70, 2005.
- J. Pharm. Sci. 2005, 94 (10), 2301-2313
- AIChE Proceedings P-235 Paper 684d, p 1-3, 2006
- J. Pharm. Sci. 96(6): 1451-67, 2007
- Conf Proc 2007 AIChE, 2007. Paper 648f. P-246. ISBN: 978-08169-1022-9.
- J. Pharm. Sci., 2008, 97 (12), 5328-40.
- Int. J. Pharmaceutics., 2008, 353 (1-2), 187-94.
- J. Pharm., and Biomed. Analysis, 2008,
- *J. Pharm. Sci.*, 97(10):4485-97, 2008
- Int. J. of Pharm., Sept. 2008.
- AAPSPharmSciTech, 9(1):250-258, 2008.
- Eur J Pharm Biopharm: 70: 226-33, 2008.
- AIChE Pub. No. P-255. ISBN: 978-0-8169-1050-2.
- J Pharm. Sci., 2009. DOI 10.1002/jps.21646
- Pharm. Develop. And Tech. 2009 accepted.
- DDIP, 2009 accepted
- Int. J. Pharm. 2009, Accepted for publication.
- AAPSPharSciTech., 10(2), 500-4, 2009.
- Eur. J. Pharm. Sci., 2011, 44(1-2), 93-102
- 2012, J. Pharm. Sci., accepted for publication
- Int J Pharm. 2012 Jul 31;436(1-2):582-592

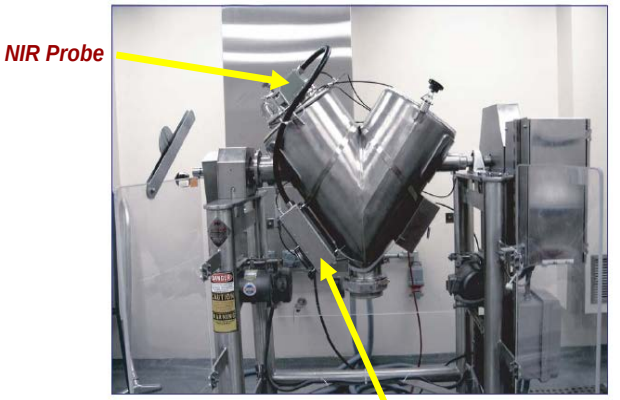




Publications:

PAT & QbD

- Pharm. Manuf. May: 28-33, 2005.
- AAPS PharmSciTech, 2005
- European Pharmaceutical Review 3, 46-48, 2004.
- AIChE Proceedings P-235 668d, p 1-7, 2006
- Proceedings of 2005 Joint Stats Meetings American Statistical Association, Feb, 2006
- Chem. Eng. Comm. 194:760-79, 2007
- *J. Pharm. Sci.*, 2007, 343(1-2), pp. 148-58.
- Int. J. Pharm., 2007, 343 (1-2): 148-58.
- J. Pharm. Sci., 96, 3390-3401, 2007
- J. Pharm. Sci., 2008, Accepted for publication. DOI 10.1002/jps.
- Applied Spectroscopy, 63(1): 1-15, 2009.
- Journal of Pharmaceutical & Biopharmaceutical Analysis, 49 : 48-54, 2009.
- J Pharm Biomed Anal, 48, 1-7, 2008.
- AAPS Journal, 2010, accepted
- J. Pharm. Sci., (2009), 98(8), 2784-2798
- J. Pharm. Sci., (2009), 98(3), 1155-1166
- Applied Spectroscopy, (2009), 63(1): 1-15
- AIChE Pub. No. P-255. ISBN: 978-0-8169-1050-2
- Int. J. Pharm., 8;372(1-2):39-48, 2009
- J. Pharm. Sci., (2010) Mar;99(3):1516-34.
- AAPS Journal, (2010), accepted for publication
- J. Pharm. Sci., 2010, Accepted
- Int. J. Pharm., 2011, Accepted
- AAPSPharmScieTech, 2011, accepted
- J. Pharm. Sci. (2011), 100(5), 1969-1986
- Int. J. Pharm. (2011), 405, 63-78
- AAPSPharmScieTech (2011), 12(1), 262-267
- Pharm. Dev. and Technol., 2011, 16(6), 549-76
- Int. J. Pharm., 2012, Oct 31;419(1-2):52-9
- Int J Pharm. 2012 Feb 28;423(2):543-53
- J. Pharm. Sci., 2012 Apr;101(4):1450-61
- Journal of Molecular Structure. 2012, accepted for publication
- New York: Springer, 2012. in-press



Quality, design space and regulation

- Quality Product – Dr. Janet Woodcock

A high quality drug product as a product free of contamination and reproducibly delivering the therapeutic benefit promised in the label

Free of contamination: CGMP focus

Reproducibly delivering the therapeutic benefit promised in the label

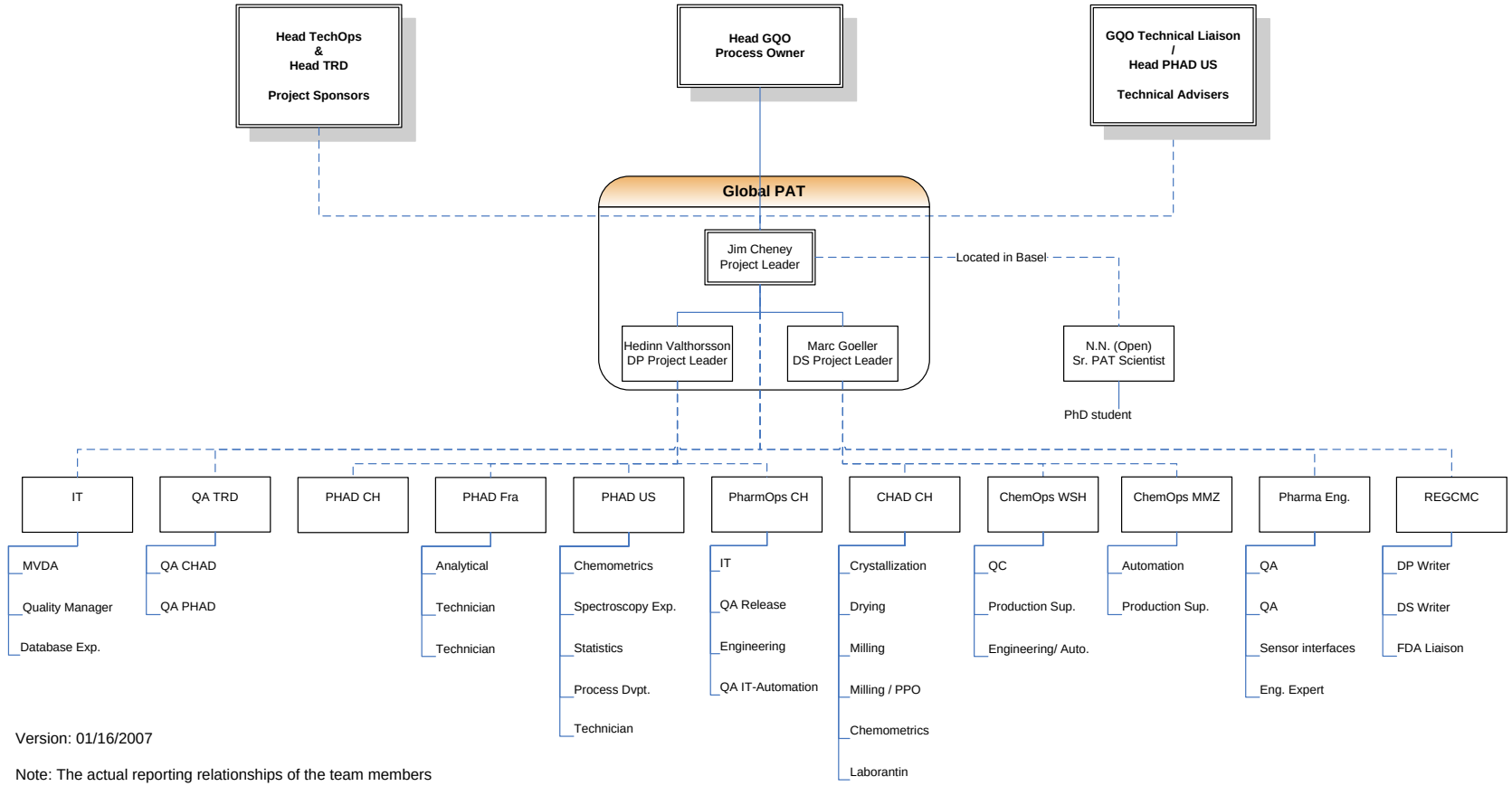
Without extensive regulatory oversight

- Design space – The multidimensional combination and interaction of input variables (eg. Material attributes) and process parameters that have been demonstrated to provide assurance of quality. *Working within the design space is not considered as a change.*

Guidance for Industry, CDER/CBER, Rev 2, Nov 2009

… and a Team

- Without a cross functional team, a QbD project can not succeed… thus a BIG thank you to all our team members!

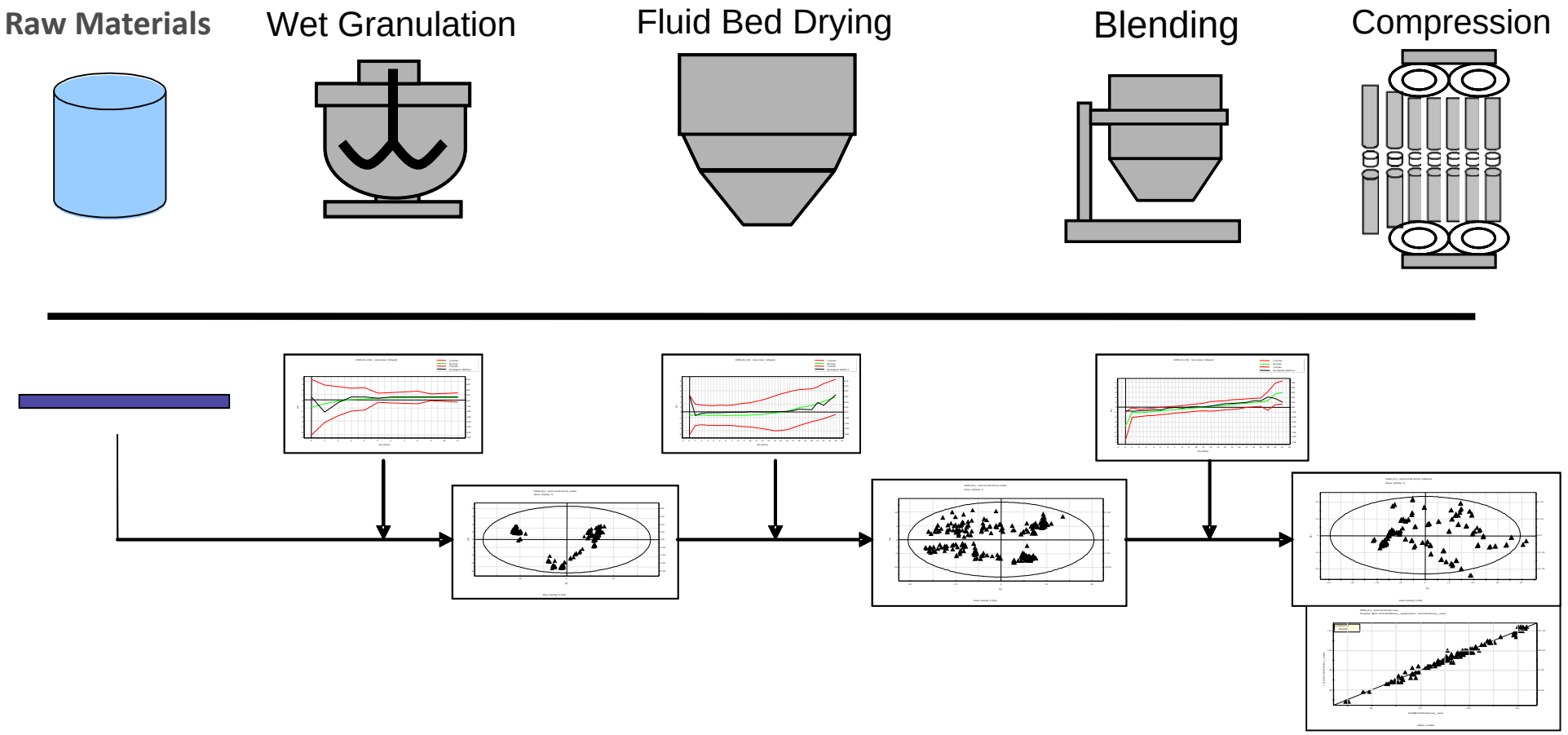


Version: 01/16/2007

Note: The actual reporting relationships of the team members are within the line functions/countries that employ them.

Quality Monitoring

MVDA Modeling Strategy



Full Scale Design Space Confirmation
Lab Scale to Manufacturing Scale

25 Liter Gral

Lab Scale Dryer

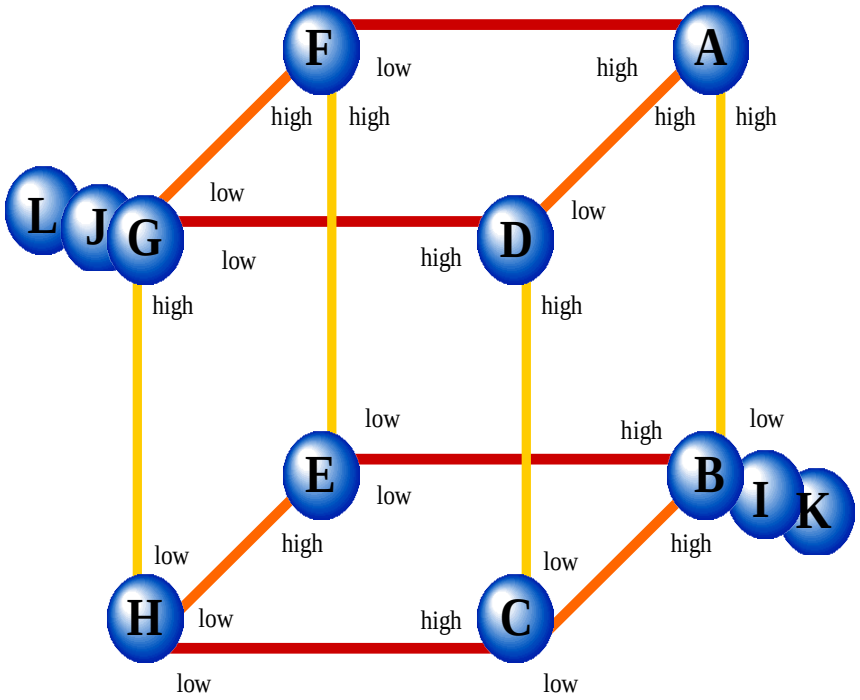
600 Liter Gral

Manufacturing Scale Dryer

DOE for Full-scale DP Design Space Confirmation

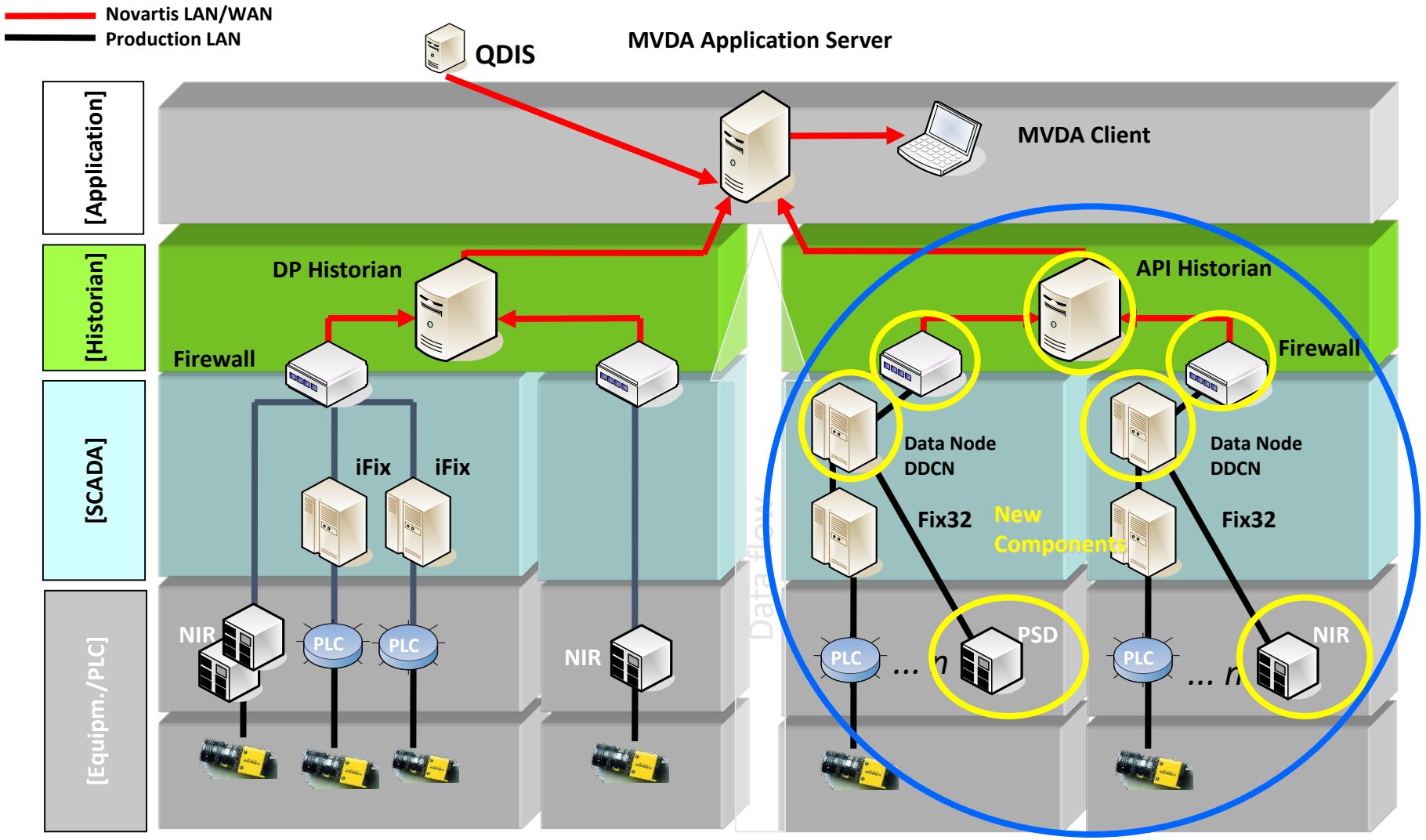
2^3 factorial DoE design

Variable 1:□ Water amount (WA)
Variable 2:□Granulation time (GT)
Variable 3:□Air Volume Dryer (AF)

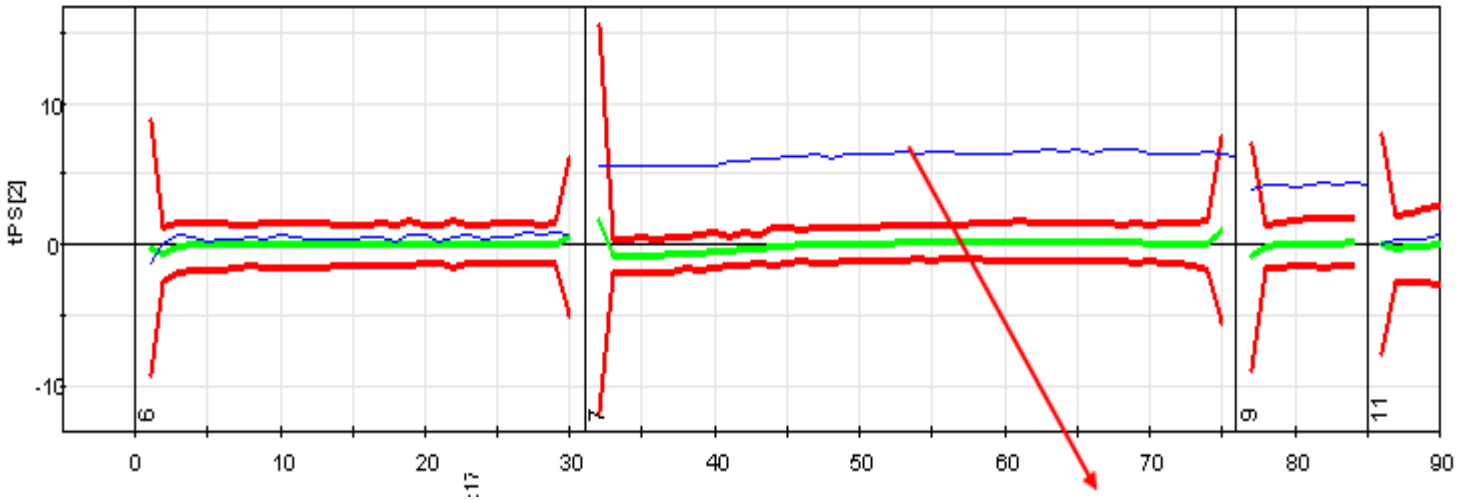


a 2^3 full factorial design for Exjade® 500mg (8 batches A-H) Tablets and
to complete that DoE for Exjade® 125mg(2 batches K-L), 250mg (2 batches I-J)
using a bracketing approach encompassing two batches each at extreme values

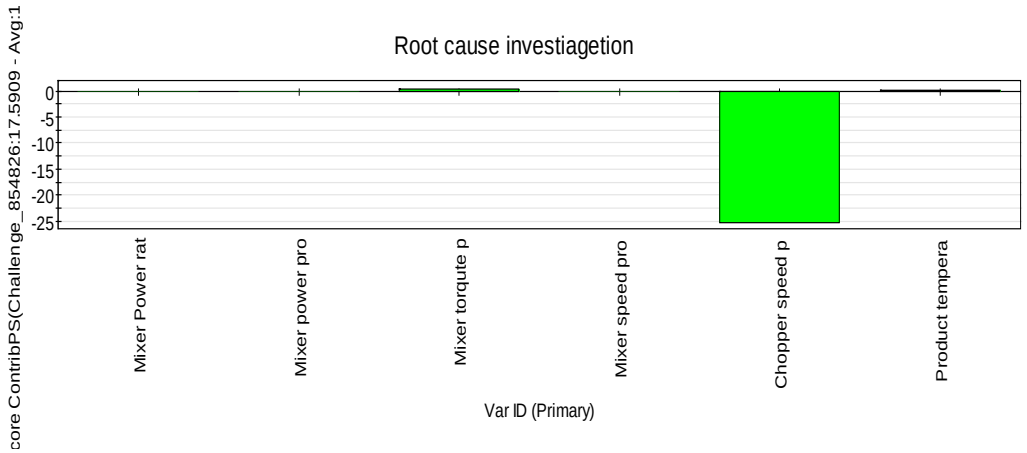
Quality Monitoring
IT/Automation infrastructure supporting MVDA



Quality Monitoring
Observation Level / Failure detection

- 

Root cause is traceable



QbD Pilot Project Timelines (actual) *Regulatory Activity*

- DS submission
  - **EMA: Filed 3Oct2008 Approved 05Jan2010**
    - Response Filed 5Oct2009, PAI 17-21Mar2009
  - **FDA: Filed 3Oct2008**
    - Responses Filed 30Jan2009, 13Oct2009, 5Feb2010, 28Apr2010
    - Complete Non-Approvable Response Letter Received 18Feb2010
      - Response planned for 2Q2011
    - PAI 5-9July2010 – Approval Recommended
- DP submission
  - **EMA: Filed 13Mar2009 RTRT Approved 13Jan2010**
    - Response Filed 5Oct2009
    - PAI 24-28Aug2009
  - **FDA: Filed 2Apr2009 Approved 17Dec2010**
    - Responses Filed 13Nov2009, 9Mar2010, 23Apr2010, 21June2010
    - PAI 28-June through 2-July-2010

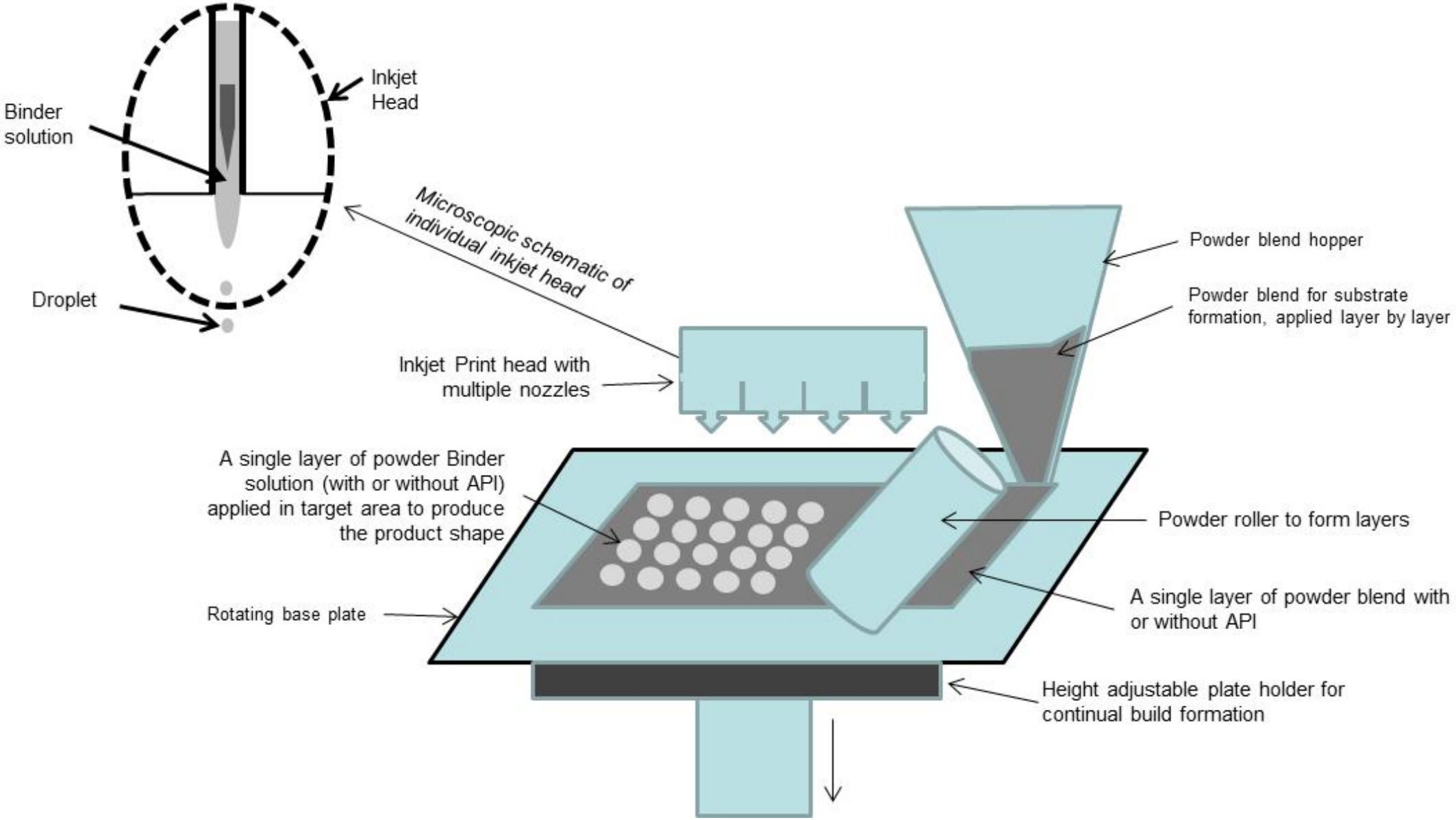
C. Balducci, Novartis AIChE 2011

Top reasons of FDA Product recalls (2013 to June 2019)

Total Recalls – 10,284

- Class 1 recalls - 1139
- Class 2 recalls – 8034
- Class 3 recalls – 1070
- Unclassified – 40

- cGMP issues – 905
- Microbial contamination – 741
- Stability – 606
- Degradation – 339
- Particulates – 302
- Data integrity – 266
- Dissolution – 198
- Super-potent – 116
- Potency failures – 106


Inkjet Head
Binder solution
Droplet
Microscopic schematic of individual inkjet head
Powder blend hopper
Powder blend for substrate formation, applied layer by layer
Inkjet Print head with multiple nozzles
A single layer of powder Binder solution (with or without API) applied in target area to produce the product shape
Powder roller to form layers
Rotating base plate
A single layer of powder blend with or without API
Height adjustable plate holder for continual build formation

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ADR-12945; No of Pages 12

Advanced Drug Delivery Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

A new chapter in pharmaceutical manufacturing: 3D-printed drug products☆,☆☆

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ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form 27 February 2016
Accepted 7 March 2016
Available online xxxx

Keywords:
3D printing technology
3D printed drug products
On-demand manufacturing
Personalization

ABSTRACT

FDA recently approved a 3D-printed drug product in August 2015, which is indicative of a new chapter for pharmaceutical manufacturing. This review article summarizes progress with 3D printed drug products and discusses process development for solid oral dosage forms.

3D printing is a layer-by-layer process capable of producing 3D drug products from digital designs. Traditional pharmaceutical processes, such as tablet compression, have been used for decades with established regulatory pathways. These processes are well understood, but antiquated in terms of process capability and manufacturing flexibility. 3D printing, as a platform technology, has competitive advantages for complex products, personalized products, and products made on-demand. These advantages create opportunities for improving the safety, efficacy, and accessibility of medicines.

Although 3D printing differs from traditional manufacturing processes for solid oral dosage forms, risk-based process development is feasible. This review highlights how product and process understanding can facilitate the development of a control strategy for different 3D printing methods.

Overall, the authors believe that the recent approval of a 3D printed drug product will stimulate continual innovation in pharmaceutical manufacturing technology. FDA encourages the development of advanced manufacturing technologies, including 3D-printing, using science- and risk-based approaches.

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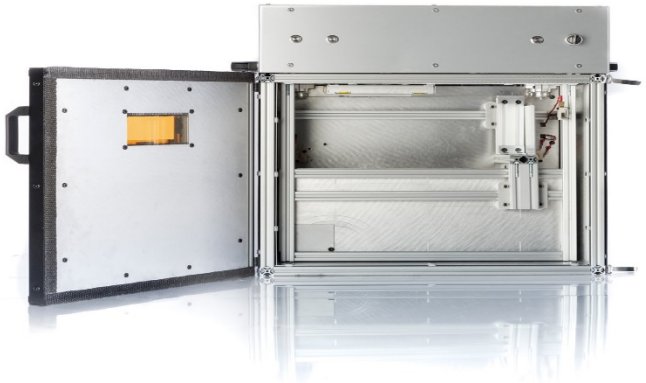
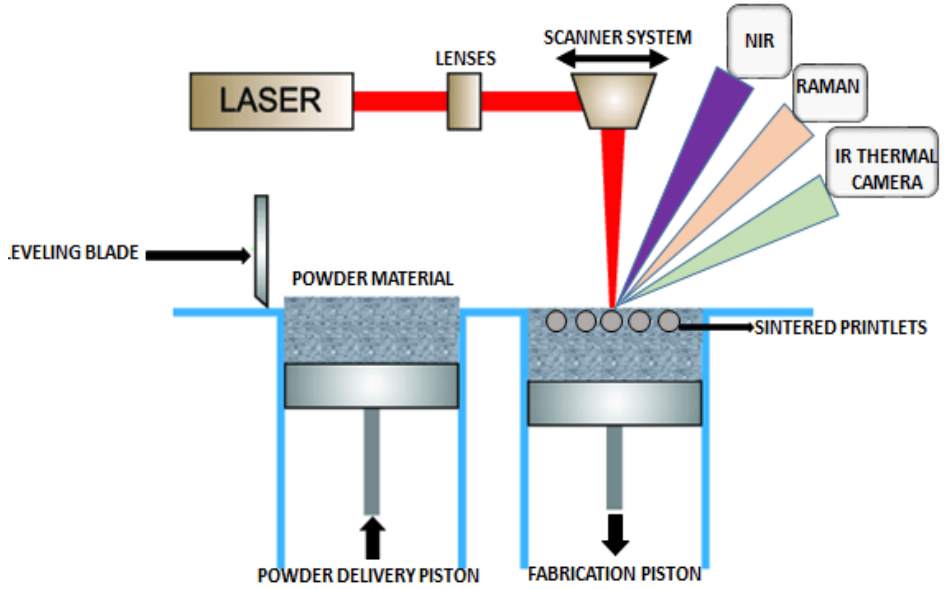
3D Printing - Selective Laser Sintering (SLS)





1. Barakh Ali SF, Mohamed EM, Ozkan T, Kuttolamadom MA, Khan MA, Asadi A, Rahman Z. Understanding the effects of formulation and process variables on the printlets quality manufactured by selective laser sintering 3D printing. Int J Pharm. 2019;570:118651.

Defects - Very different from compressed tablet defects

- Banding: ripples on a part's sides caused by vibration in the x-y plane during printing
- Leaning: off-axis parts caused by drift in the x-y plane during printing
- Warping: part distortion caused by thermal expansion or contraction
- Stringing: wisps of filament caused by filament elongation during an extruder's off phase
- Collapse: loss of porosity caused by sagging layers or excessive mass/energy input
- Residuals: unbound powder or uncrosslinked monomer caused by incomplete printing

Be prepared for a several new type of products – IR, ER, DR, Combinations, Precision Medicines – Possibility of real-time monitoring, feed-back control loops, continuous manufacturing

What should we call the product - Nomenclature

- Is this a tablet?
- Is this a lozenge?
- Is this an ODT?
- Is this a triturate?
- Is this a wafer?
- Is this a 3D tablet?
- How do we protect the novelty of the product?

Technical Considerations for Additive Manufactured Devices

Draft Guidance for Industry and Food and Drug Administration Staff

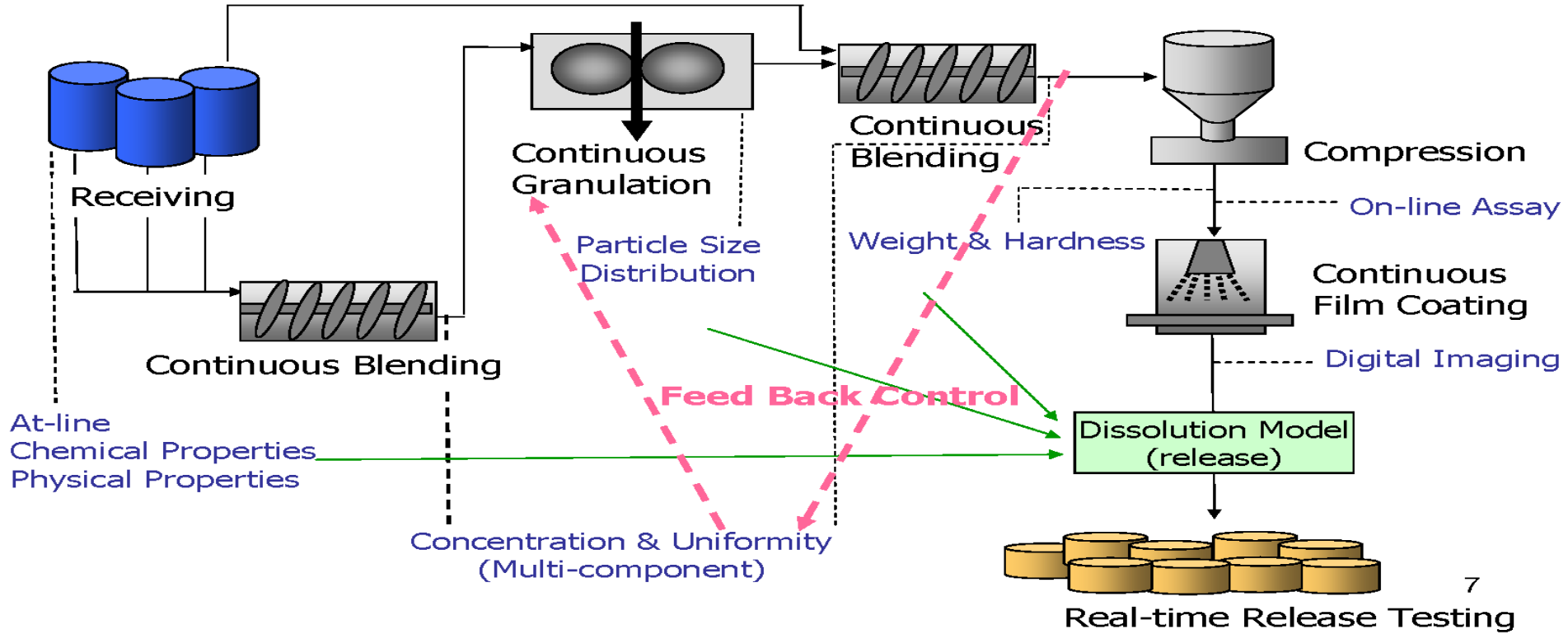
This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

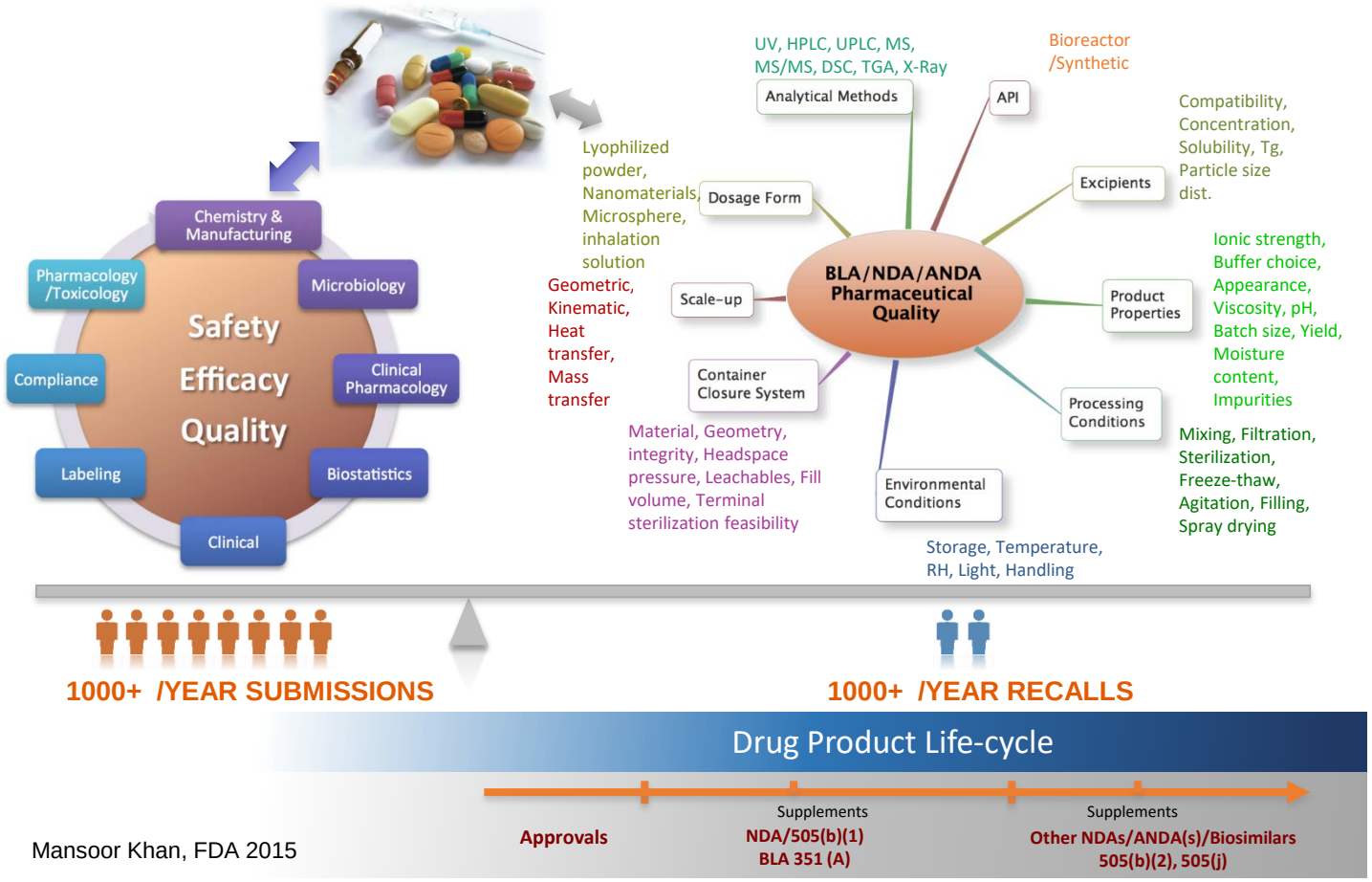
FDA has developed this draft guidance to provide FDA's initial thinking on technical considerations specific to devices using additive manufacturing, the broad category of manufacturing encompassing 3-dimensional (3D) printing. Additive manufacturing (AM) is a process that builds an object by iteratively building 2-dimensional (2D) layers and joining each to the layer below, allowing device manufacturers to rapidly alter designs without the need for retooling and to create complex devices built as a single piece. Rapid technological advancements and increased availability of AM fabrication equipment are encouraging increased investment in the technology and its increased use in medical devices. The purpose of this guidance is to outline technical considerations associated with AM processes, and recommendations for testing and characterization for devices that include at least one AM fabrication step.

Continuous Manufacturing

Example of Continuous Manufacturing with On-line Monitoring

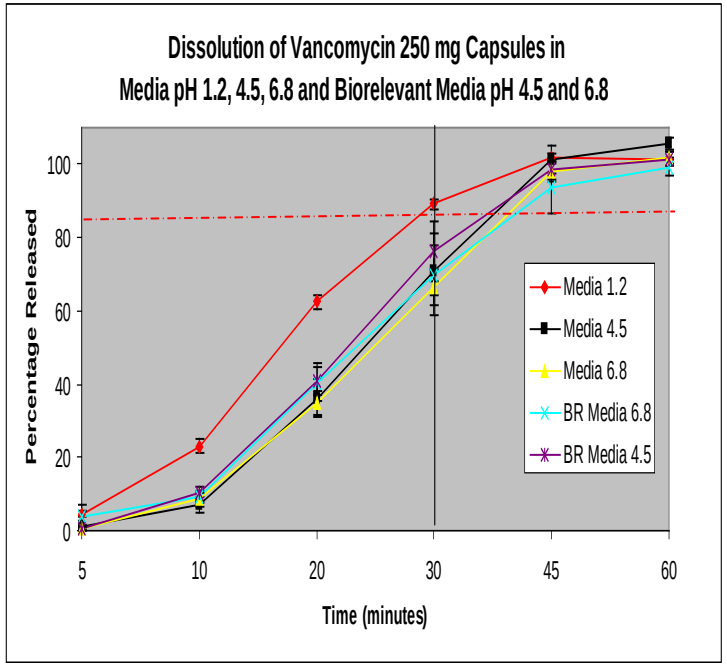


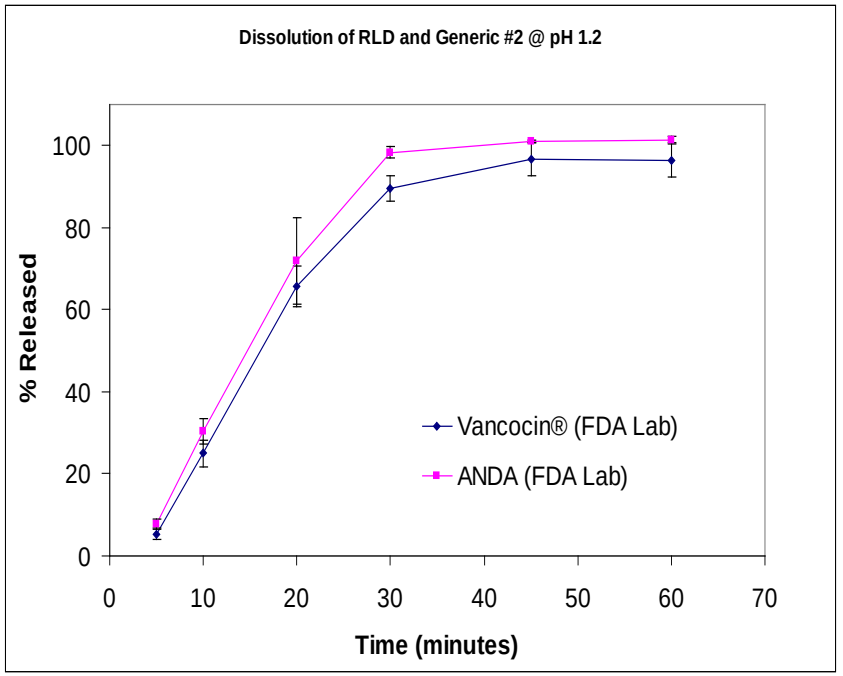
Pharmaceutical/Biopharmaceutical Drug Products



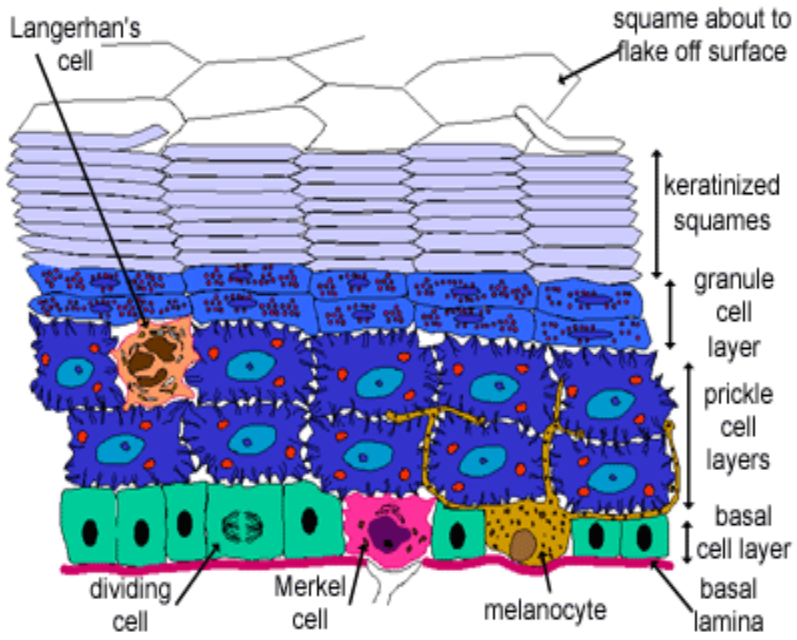
Mansoor Khan, FDA 2015

Dissolution of Vancomycin (from generic product approvals)





Acyclovir cream - HSV-1 in skin



Formulation	Qty. of drug permeated at 24 h (µg/cm²)	Flux (µg/cm²·h)	Drug retained in epidermis (mean thickness 71.2 µm), DRE	
			µg/cm²	µg/ml*
Zovirax® (pH 7.92)	12.04±1.10	0.78±0.06	2.20±0.34	308.4±47.9
F-12 (pH 5.11)	19.41±1.53**	1.22±0.12**	2.91±0.43	408.4±60.8
F-13 (pH 6.75)	17.89±1.99*	1.14±0.13*	3.42±0.49	497.7±68.3
F-14 (pH 8.43)	16.25±2.24	1.07±0.15	2.16±0.41	303.7±57.2

Physicochemical characteristics (Structural sameness, Q3) and *In vitro* performance tests – Additionally they are Q1 and Q2

- pH
- Spreadability (Yield stress)
- Viscosity at low, medium and high shear rates
- Particle size and distribution
- Content uniformity (top, middle and bottom)
- Drug concentration in aqueous phase
- Drug release rate
- Drug retention in epidermis (DRE) at the end of *in vitro* permeation study

International Journal of Pharmaceutics

Volume 475, Issues 1–2, 20 November 2014, Pages 110–122

Development of performance matrix for generic product equivalence of acyclovir topical creams

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doi:10.1016/j.ijpharm.2014.07.034

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Abstract

The effect of process variability on physicochemical characteristics and in vitro performance of qualitatively (Q1) and quantitatively (Q2) equivalent generic acyclovir topical dermatological creams was investigated to develop a matrix of standards for

Conclusions

- Continue developing strong science-based policies, and defend their actions through science and communication
- Utilize internal and external resources to promote innovative products and manufacturing – Publicize the impact of changes
- Understand and connect the past recalls with modernization of pharmaceutical manufacturing – A goal of reduction of recalls should be of mutual interest to FDA, Industry, Academia, and the patients
- QBD with MVSPC could be a solution to inspectional challenges
- Recognize and promote the advances in science in OLDP and OGD in addition to other offices