Risk-Based CMC ANDA Review/ Quality Informatics in Knowledge Management

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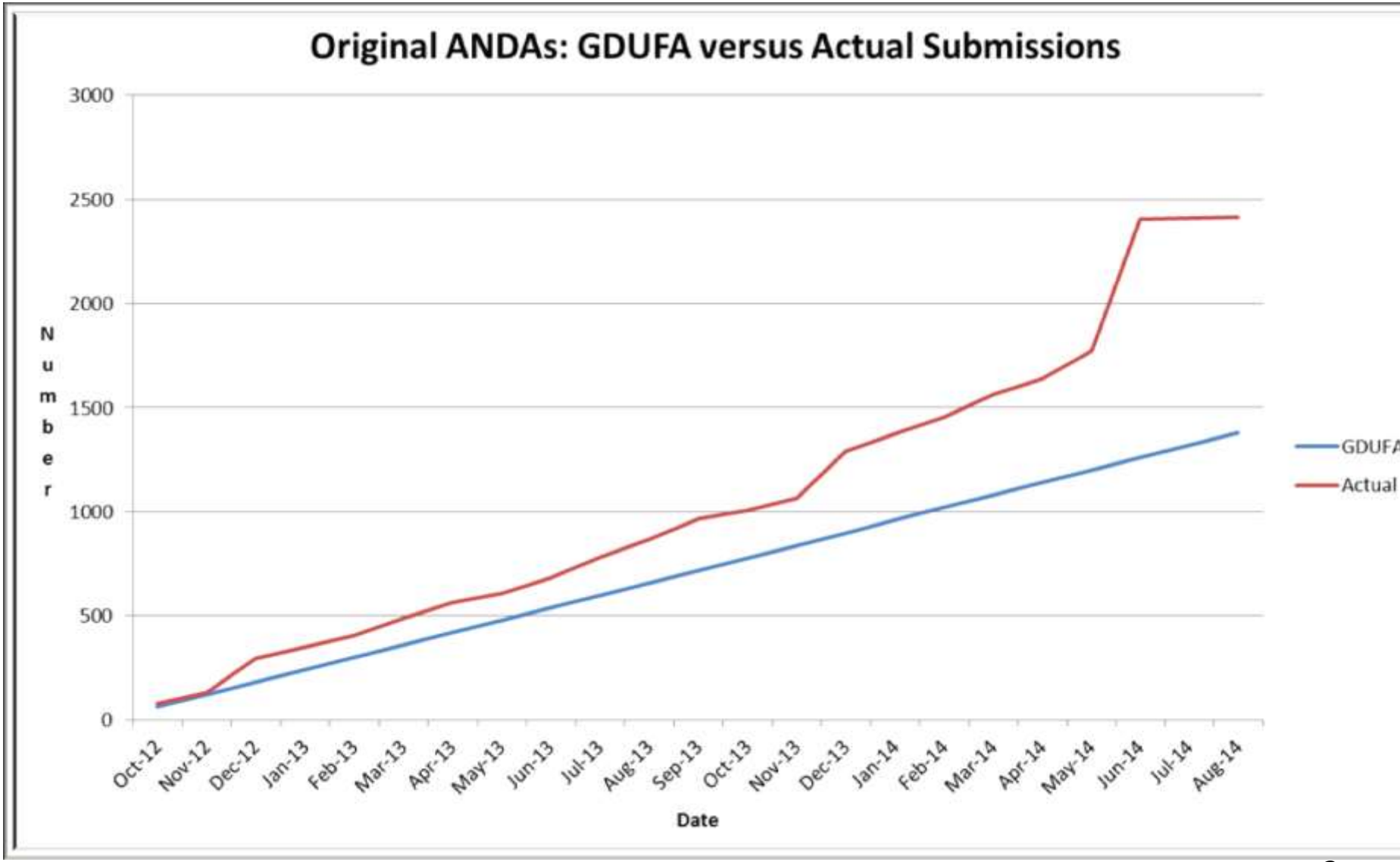
*This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

GDUFA Metrics
Assumptions versus Reality

Assumptions: ANDA submission would not exceed the maximum of ~700/year

Reality:
FY2013 : 968 ANDAs
FY2014: > 1400 ANDAs


Original ANDAs: GDUFA versus Actual Submissions
3000
2500
2000
1500
1000
500
0
Number
Oct-12
Nov-12
Dec-12
Jan-13
Feb-13
Mar-13
Apr-13
May-13
Jun-13
Jul-13
Aug-13
Sep-13
Oct-13
Nov-13
Dec-13
Jan-14
Feb-14
Mar-14
Apr-14
May-14
Jun-14
Jul-14
Aug-14
Date
GDUFA
Actual

GDUFA Review Performance Goals

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Original ANDA	Expedite review of paragraph IV and maintain pre-GDUFA productivity		60% in 15 months	75% in 15 months	90% in 10 months
Tier 1 first major amendment	Maintain pre-GDUFA productivity		60% in 10 months	75% in 10 months	90% in 10 months
Tier 1 minor amendments (1st – 3rd)	Maintain pre-GDUFA productivity		60% in 3 months*	75% in 3 months*	90% in 3 months*
Tier 1 minor amendments (4th – 5th)	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
Tier 2 amendment	Maintain pre-GDUFA productivity		60% in 12 months	75% in 12 months	90% in 12 months
Prior approval supplements	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
ANDA, amendment, and PAS in backlog on Oct 1st, 2012	Act on 90% by end of FY 2017				
Controlled correspondences	Maintain pre-GDUFA levels		70% in four months**	70% in two months**	90% in two months**

*10 months if inspection required

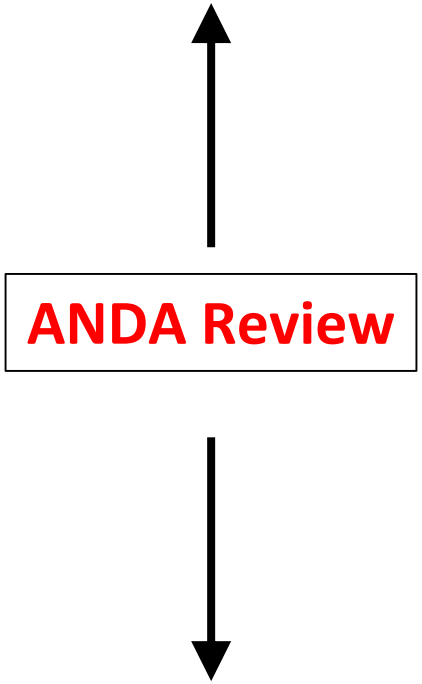
** One additional month added to goal if clinical division input required

Pharmaceutical Quality Desired State

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

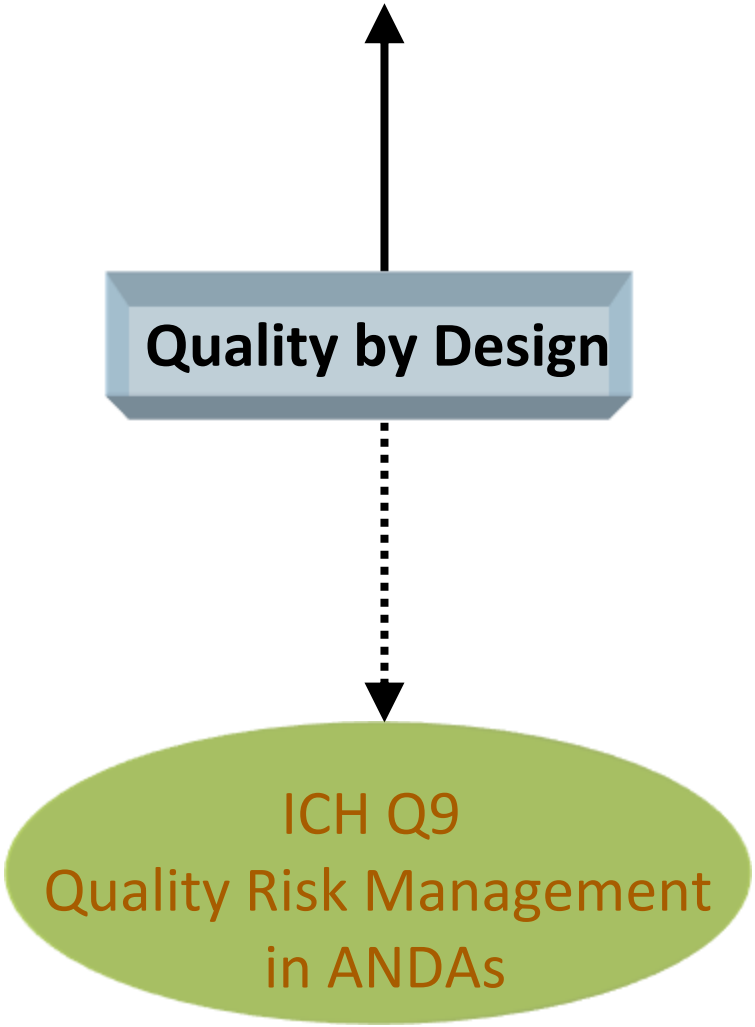
Competing Priorities?

ANDA Backlog and GDUFA Goals



Expectation of QbD Elements Submitted in ANDAs
Highly Detailed Assessment of QbD in Reviews

ICH Q8 (Pharmaceutical Development)
Guidance for Industry (Process Analytical Technology)



Preliminary Hazard Analysis (PHA)

Semi-Quantitative Risk Analysis Based Upon Probability and Severity (Quality) Perspective.

Rates Risk on Formulation /Process Variables on specific CQAs

Probability / Severity	Low Probability (1)	Medium Probability (2)	High Probability (3)
Low Severity (1)	Low	Low	Medium
Medium Severity (2)	Low	Medium	High
High Severity (3)	Medium	High	High

Preliminary Risk Assessment of ANDA xxxx using the PHA Approach

Product Quality (CQAs and BE) Impacted	Hazards			
	Drug Substance Inherent Properties	Formulation Variables and Excipient CMAs	Manufacture Process Steps and Process Parameters	Container Closure System
Assay	Low	Low	Low	Low
Content Uniformity	High	High	High	Low
Dissolution	Low	Low	Low	Low
Degradation Products	Low	Low	Low	Low
Bioequivalence	Low	Medium	Medium	Low

Performed PHA Risk Analysis "Manually" for ~100 ANDAs for Staff Prior to Formal Review

Semi-Quantitative Risk Analysis Based Upon Probability and Severity (Quality) Perspective

Rates Risk on Formulation / Process Variables on Specific CQAs

Preliminary Hazard Analysis (PHA)

Highly dependent on risk assessors prior knowledge
Regulatory risk assessment tool may be problematic

Other Possible Approaches

Risk Ranking Team (Christine Moore) had developed a quantitative and objective system using Failure Modes, Effects and Criticality Analysis (FMECA)

Risk priority number (RPN) is calculated for each failure mode for each drug product CQA using severity, probability and detectability of failure and used to rank risk.

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

Focus on Patient Risk Due to the Severity of Harm

Making Risk Assessment More Objective

- FMECA was chosen due to its objectivity.

- Algorithm scores based upon sound scientific principles and modified for initial risk profiling using cross-validation studies with PHA

	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	PHA
CQA1	02	s1	d1	o2s1d1	low
CQA2	01	s2	d1	01s2d1	low
CQA3	01	s1	d2	o1s1d2	low
CQA4	01	s1	d2	o1s1d2	low
CQA5	01	s1	d1	o1s1d1	low
CQA6	02	s1	d1	o2s1d1	low

	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	PHA
CQA1	05	s4	D1	o5s4d1	high
CQA2	01	S2	D1	01s2d1	low
CQA3	03	S5	D2	O3s5d2	medium
CQA4	02	S3	D2	O2s3d2	medium
CQA5	02	S2	D3	O2s2d3	medium
CQA6	05	S5	d1	o5s5d1	low

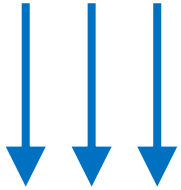
- Algorithm will be continuously improved and updated based upon additional information gathered

Initial ANDA Profiling Algorithms for Expanded to Other Dosage Forms

- Delayed/Modified Release Solid Orals
- Topical Dosage Forms (Creams Ointments, Lotions)
- Oral Solutions/Suspensions
- Injections
- Ophthalmics
- Nasal Sprays

Risk Management: Formalized in ANDA Review Second Quarter of 2014

Drug Product CQAs	Initial Risk Ranking FMECA Score	Comments	Updated Risk Ranking after Review Cycle #	Comments
CQA1				
CQA2				
CQA3				
CQA4				
CQA5				
Other CQAs				



Similar Approach Later Formalized in NDA Review

Future State

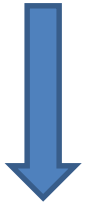
Dashboard for Drug Product Quality

A Quality Informatics Tool for Lifecyle Risk and Knowledge Management

Quality Informatics for Lifecyle Risk/Knowledge Management

Current Reviews: Independent "Narratives" of NDA/ANDAs. Administrative Record for "Expert" Basis of Decision

Narratives: Difficult to Retrospectively Mine Across Our Repertoire of 1000s of Approved Drug Products *(OPQ Mission)*



Need a Tool/ Metric to Quickly Capture Drug Product Quality

Not All Products (multiple versions of Generics/Brand) have "Same Risk"

Oversight (Inspection/Supplements) should be Commensurate with Risk.

Conceptual Dissection of ANDA Quality Review

Product Standards/Methods

"Universal Standards"
"Often Dosage Form Based"
"Specific Aspects of Formulation Process Design"

USP <905>
Content Uniformity Standards

Failure Modes/Risk Mitigations

Relatively Straightforward to Capture In NDA/ANDAs for Lifecycle Management

Segregation Risk Potential
Blending Process Understanding
Material Properties
Sampling Scheme

Relatively Straightforward to Capture In NDA/ANDAs for Lifecycle Management

Difficult to Effectively Capture for Lifecycle Management

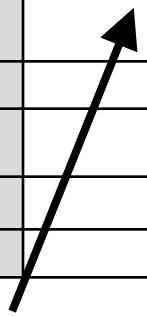
Drug Product CQAs	Initial Risk Ranking
CQA1	Minimal Discussion of Risk Mitigation
CQA2	Limited Discussion of Risk Mitigation
CQA3	Critical Evaluation to Ensure Risk is Mitigated

Decrease Probability of Occurrence (O)
Formulation Design/ Process Design

Increase Probability of Detection (D) of
Product Failures Prior to Batch Release

Formalized Risk Mitigation

Drug Product CQAs	Initial Risk Ranking FMECA Score	Comments	Updated Risk Ranking after Review Cycle #	Comments
CQA1				
CQA2				
CQA3				
CQA4				
CQA5				
Other CQAs				



"Objective" Initial FMECA Risk Scoring Algorithm in Place

Prospectively Flags Risks (Approximate Starting Point)

Standardized Risk Mitigation Menu

- **Formalized as Structured Descriptors for each Sub-discipline (OLDP/ONDP/Biopharm/OPF)**
- **Semi-Quantitative Score for Relative Product Quality Risk Ranking Following Approval**

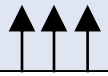
Quality Dashboard Based upon Drug Product Risk Mitigation

CQA	Universal Sources of Variability	Risk Mitigation Strategies	Explanatory Comments
Content Uniformity	Raw Materials (DS, Excipients,CCS)/Formulation	OLDP/ONDP Drop Down Menu Similar API and Excipient PS Similar API and Excipient Bulk Densities Adsorption of API onto Carrier Excipient Other	
	Manufacturing Process/Equipment/Environment	OPF Drop Down Menu Process design Scale-up plan Other	
	Measurement System	OPF Drop Down Menu PAT Monitoring for Tablet Uniformity Extensive Stratified Sampling (100 Units) Other	
Dissolution	Raw Materials (DS, Excipients,CCS)/Formulation	OLDP/ONDP Drop Down Menu	
	Manufacturing Process/Equipment/Environment	OPF Drop Down Menu	
	Measurement System	ONDP-Biopharm Drop Down Menu	
Chemical Stability	Raw Materials (DS, Excipients,CCS)/Formulation	OLDP/ONDP Drop Down Menu	
	Manufacturing Process/Equipment/Environment	OPF Drop Down Menu	
	Measurement System	OLDP/ONDP Drop Down Menu	

"Each Sub-Office will have a Drop-Down menu of "Common" Risk Mitigation *DESCRIPTORS* Relevant to each CQA

***Descriptor*: Structured Knowledge of Formulation/Process Design and/or Control Strategy**

CQA	Universal Sources of Variability	Risk Mitigation Strategies	Explanatory Comments	Risk Profile
Content Uniformity	Raw Materials (DS, Excipients,CCS)/Formulation	OLDP/ONDP Drop Down Menu		
	Manufacturing Process/Equipment/Environment	OPF Drop Down Menu		
	Measurement System	OPF Drop Down Menu		
Dissolution	Raw Materials (DS, Excipients,CCS)/Formulation	OLDP/ONDP Drop Down Menu		
	Manufacturing Process/Equipment/Environment	OPF Drop Down Menu		
	Measurement System	ONDP-Biopharm Drop Down Menu		
Chemical Stability	Raw Materials (DS, Excipients,CCS)/Formulation	OLDP/ONDP Drop Down Menu		
	Manufacturing Process/Equipment/Environment	OPF Drop Down Menu		
	Measurement System	OLDP/ONDP Drop Down Menu		



Updated Risk Profile Score (Semi-Quantitative)

f(Quality Risk)= ((Initial Risk (i), Design Risk Mitigation Power (a), Process Risk Mitigation Power (b), Measurement Risk Mitigation Power (c))

Quality Dashboard: Structured Descriptors of Risk Mitigation Strategies Implemented Capture State of Quality Risk Approved NDAs/ANDAs

Same Drug Product

ANDA x

CQA	Initial Risk	Universal Source of Variability	Risk Mitigation Strategy	Residual Risk Remaining
Content Uniformity	High	Product Design	No strategies demonstrated	Medium (High)
		Process	No strategies demonstrated	
		Measurement	Traditional CU USP <905>	

ANDA y

CQA	Initial Risk	Universal Source of Variability	Risk Mitigation Strategy	Residual Risk Remaining
Content Uniformity	High	Product Design	Similar API and Excipient PS for Blending Unit Operation	Medium
		Process	No Strategies Demonstrated	
		Measurement	Traditional CU USP <905>	

NDA

CQA	Initial Risk	Universal Source of Variability	Risk Mitigation Strategy	Residual Risk Remaining
Content Uniformity	High	Product Design	Similar API and Excipient PS for Blending Unit Operation	Low
		Process	CPPs well understood and controlled	
		Measurement	Stratified Sampling Maintained During Commercialization	

Increasing Level of Monitoring Scrutiny

Supplements And Manufacturing Surveillance

Potential Tool to Readily Capture Drug Product Risk Across Our Repertoire of Approved Drug Products

1. **Highly Structured (using Fundamental Knowledge Descriptors) Assessment of Formulation/Process Development and Control Strategy (Measurement)**

2. **Rank Relative Product Risks ANDA/NDAs**

3. **Guide Supplement Risk Evaluation**
   (Living Document based upon Supplements Approved in Product Life Cycle)

4. **Input for Surveillance Risk Model = f (Facility Risk, g (Quality Risk))**

g(Quality Risk)= ((Initial Risk (i), Design Risk Mitigation Power (a), Process Risk Mitigation Power (b), Measurement Risk Mitigation Power (c))

i= 1,2,3 a,b,c= 0,1,2,3

Conclusion

Formal risk assessment is a natural progression of the FDA 21st Century Quality Initiative

Formal risk management approaches is being used in ANDA review to ensure that all high risk areas receive appropriate scrutiny to ensure the availability of high quality generics.

Formal risk management will also streamline the review for lower risk areas to ensure review timelines under GDUFA

Formalized Structured Risk Mitigation Dashboard:

- Tool for Lifecycle Management (Supplement Risk Evaluation)

- Tool for Picture of “Quality’ of Drug Product Inventory

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Dashboard

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OPPQ: Shanaz Read
I/O: Thomas O'Conner, Sau Lee
OS: Cindy Cho
OTR: Michael Trehy

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