MedPharm
Breaking through boundaries

20 | Aug | 2021

QMS: Industry Perspectives

One Company's Journey from R&D to 'Regulated' IVRT/IVPT Studies

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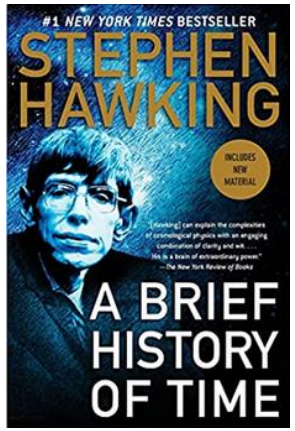
Senior Director, Performance Testing and Bioanalytical

Disclaimers

- This presentation represents the opinions of the presenter which may or may not be official policies of MedPharm, Ltd.

- Any misinterpretations of the MCU timeline are entirely the fault of the author and not Marvel Studios or the Walt Disney Company.

A brief history of time



- 13.8 bn years ago – Big Bang
- 1999 – MedPharm founded in UK, offering semisolid formulation development/ manufacturing & related *in vitro* performance testing services (IVRT, IVPT)
- 2016, May – MedPharm opens first US site (Durham, NC) with the aim of making it our center of *in vitro* performance testing
- 2016, December – Draft Guidance on Acyclovir released by FDA

This presentation

- 2019 – MedPharm's IVRT/IVPT BE study data submitted to FDA
- 2020, January – FDA comes to visit us in Durham, NC

It's May, 2016 …

- MedPharm opens US lab
  - We have three people
    - Myself (bioanalytical)
    - Jon Lenn (IVPT/all things skin)
    - A biologist
    - ~100 staff in UK for support
  - And an empty lab

- Captain America: Civil War released

May 2016 – Dec 2016

- Focused on
  - Running R&D IVPT studies
  - Transferring over 15 years' worth IVRT expertise from UK to US
  - Building other site capabilities
  - QMS
    - Supported by UK QA colleagues
    - Planning for US-QMS based around ICH Q10
    - Writing US-specific SOPs

- Timeline
  - October 2016 – A UK colleague helps us out
  - November 2016 – Doctor Strange released
  - December 2016
    - Seven US employees (~100 US+UK)
    - **Draft Guidance on Acyclovir!**

Jan 2017 - Read the guidance

Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 Office of Generic Drugs.

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 1 (May 2015).[1]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

- We support qualitative (Q1), quantitative (Q2), and physico-chemical characterization studies; out of scope for this discussion
- We also have a long history of hands-on experience with both IVRT and IVPT
  - We knew the science behind these
  - We knew how to conduct these in the lab
- So, skip ahead to Section C …

… and came to this

C. IVRT Comparison

2. Refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding considerations for retention of study drug samples and to 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, investigators are recommended to perform the IVRT validation and pivotal studies within a quality management system that is compatible with applicable principles of GLP described in 21 CFR 58. Any aspects of the quality management system that are not compatible with these GLP principles, and any aspects of GLP that are not applicable, should be identified in the relevant IVRT study protocol and final report. Retention samples should be randomly selected from the drug supplies received prior to dispensing during the IVRT study in which the test and RLD products are compared. Experimental observations that may have the potential to influence the interpretation of the study results, as well as any protocol deviations, should be reported.

- Immediately apparent that the expectations for study conduct would be very high
- But still a very good fit for our technical skills

Jan 2017 – Jun 2017
To BE or not to BE …

- We're still primarily focused on building out site laboratory capabilities and capacity
- We're also having a tough internal discussion, trying to answer this question: is it in our best interest to pursue in vitro BE work?
  - Some of the big risks
    - Inspection from regulatory authorities (FDA)

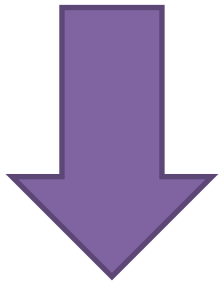
Kendall Powell

From: Kendall Powell
Sent: Tuesday, May 16, 2017 2:02 PM

[redacted] Bioequivalence studies almost always result in an FDA inspection, as in BE studies the only data are those generated by the bioanalytical lab. If the in vitro option as described in the acyclovir guidance is offered by MedPharm, the US site WILL be audited by the FDA after our first study is completed and filed with the agency. FDA here does not certify labs beforehand. FDA comes to visit and makes sure you did the study right after the fact. If they come in and have findings, this can lead to lab closures and companies going out of business if things are not done properly. I've seen it happen more than once. We must do this right if we're going to do it, else the risk is extremely high.

Jan 2017 – Jun 2017
To BE or not to BE …

- Some of the big risks (continued)
  - Possibility of study rejection by regulatory authorities (FDA)
  - Financial burden/risk to MedPharm



$ ○ Adapt/build QMS for US site (SOPs, validate/calibrate equipment, etc.)

$ ○ We're going to need more people to handle overhead (QA, QC, study directors, etc)

$ ○ Then we have to maintain these systems & personnel

$ ○ And make a profit after we do all this

Jan 2017 – Jun 2017
To BE or not to BE …

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- May 2017
  - Decided in earnest to pursue in vitro BE work
  - Our UK colleagues are funny
  - Guardians Vol. 2

Kendall Powell

From: Christian Hoenig
Sent: Tuesday, May 23, 2017 11:48 AM

Hi Kendall,

Thanks for the feedback, it is much appreciated. Please feedback if/when these studies are performed as to the resource usage and whether the price is appropriate.

What is this FDA that you speak of?

Thanks,

Christian

- Jul 2017
  - Full time QA person hired for US site
    - US Employee #15
    - >20 yr. large pharma GxP experience
    - Will lead the effort to build the US QMS
  - Spiderman: Homecoming

Aug – Dec 2017 – Get organized and close the gaps

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- Our new QA guy hatches a plan
  - Fully assess the Draft Acyclovir Guidance from a compliance perspective
  - Identify all areas where we still have gaps & fill 'em
  - Plan it like a project

Assess the Draft Acyclovir Guidance

- 21 CFR
  - 58 (Good Laboratory Practice for Nonclinical Laboratory Studies)
  - 320.36 (Requirements for Maintenance of Records of Bioequivalence Testing
  - 320.38 (Retention of Bioavailability Samples)
  - 320.63 (Retention of Bioequivalence Samples)
- ICH
  - Q2 (R1) (Validation of Analytical Procedures)
  - E6 (Good Clinical Practice)
- Guidance for Industry
  - ANDA Submissions – Refuse-to-Receive Standards
  - Handling and Retention of BA and BE Testing Samples
  - Bioanalytical Method Validation

Key
QMS related
BE related
Analytical related

Assess the Draft Acyclovir Guidance

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	Context
• 21 CFR	
○ 58 (Good Laboratory Practice for Nonclinical Laboratory Studies)	○ "applicable principles"
○ 320.36 (Requirements for Maintenance of Records of Bioequivalence Testing	○ "maintenance of records"
○ 320.38 (Retention of Bioavailability Samples)	○ "retention of study drug samples"
○ 320.63 (Retention of Bioequivalence Samples)	○ "retention of study drug samples"
• ICH	
○ Q2 (R1) (Validation of Analytical Procedures)	○ Analytical
○ E6 (Good Clinical Practice)	○ "retention of study records and data"
• Guidance for Industry	
○ ANDA Submissions – Refuse-to-Receive Standards	○ Q1/Q2 sameness
○ Handling and Retention of BA and BE Testing Samples	○ "retention of study drug samples"
○ Bioanalytical Method Validation	○ Analytical

"Applicable principles" of 21 CFR 58 (GLPs)

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PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

Subpart A—General Provisions

Sec.
58.1 Scope.
58.3 Definitions.
58.10 Applicability to studies performed under grants and contracts.
58.15 Inspection of a testing facility.

Subpart B—Organization and Personnel

58.29 Personnel.
58.31 Testing facility management.
58.33 Study director.
58.35 Quality assurance unit.

Subpart C—Facilities

58.41 General.
~~58.43 Animal care facilities.~~
~~58.45 Animal supply facilities.~~
58.47 Facilities for handling test and control articles.
58.49 Laboratory operation areas.
58.51 Specimen and data storage facilities.

Subpart D—Equipment

58.61 Equipment design.
58.63 Maintenance and calibration of equipment.

Subpart E—Testing Facilities Operation

58.81 Standard operating procedures.
58.83 Reagents and solutions.
~~58.90 Animal care.~~

Subpart F—Test and Control Articles

58.105 Test and control article characterization.
58.107 Test and control article handling.
~~58.113 Mixture of articles with carriers.~~

Subpart G—Protocol for and Conduct of a Nonclinical Laboratory Study

58.120 Protocol.
58.130 Conduct of a nonclinical laboratory study.

Subparts H–I [Reserved]

Subpart J—Records and Reports

58.185 Reporting of nonclinical laboratory study results.
58.190 Storage and retrieval of records and data.
58.195 Retention of records.

Subpart K—Disqualification of Testing Facilities

58.200 Purpose.
58.202 Grounds for disqualification.
58.204 Notice of and opportunity for hearing on proposed disqualification.
58.206 Final order on disqualification.
58.210 Actions upon disqualification.
58.213 Public disclosure of information regarding disqualification.
58.215 Alternative or additional actions to disqualification.
58.217 Suspension or termination of a testing facility by a sponsor.
58.219 Reinstatement of a disqualified testing facility.

Example - 58.35 Quality Assurance Unit

- You need an *independent* QAU that will
  - Maintain a master schedule & copies of protocols
  - Inspect studies
  - Submit status reports
  - Ensure no deviations from SOPs
  - Review the final report
  - Sign an inspection summary in the report →

QUALITY ASSURANCE STATEMENT

Study Number: [redacted]

Study Title: *In vitro* testing of the Sponsor's [redacted] formulations compared to the [redacted] *In vitro* skin permeation pivotal experiment

Study Director: [redacted]

This study was audited and inspected by MedPharm Quality Assurance periodically during the study. Reports from these audits and inspections were given to the Study Director (SD) and Management as required by FDA Good Laboratory Practice Regulation.

Study Phase	Date Inspected	Date Reported to SD	Date Reported to Management
Study Plan Review	04March2019	04March2019	05March2019
Skin Integrity and Dosing	13March2019	15March2019	08April2019
Data Audit	29Apr-06May2019	07May2019	07May2019
Draft Report Audit	07May-08May2019	08May2019	10May2019

The reported results accurately reflect the raw data generated during the study.

Signed By: [redacted] Date: 31 May 2019

[redacted]

QA Manager

Other QAU Considerations

- GLPs are a nice guide for QA responsibilities on a per study basis
- Building a strong QAU takes more than this, including concepts such as
  - Change control
  - Deviation investigations
  - Corrective and preventative action
  - Continuous improvement

Section 2: Change Control Plan

(List key actions required and identify responsible person, e.g. Lab Manager, Department Head or Contractor. This section should contain reference to appropriate validation or test activities as defined in individual equipment or system SOPs)

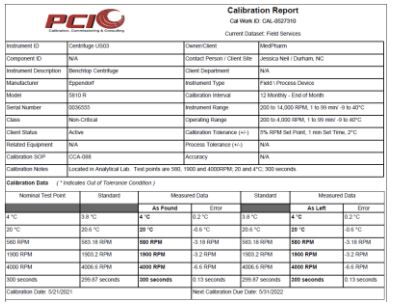
No.	Action	Task Owner	Target Completion Date *(must be prior to proposed completion date)*
1.	Complete all necessary URS	JN	01Dec2019
2.	Order all new equipment	JN	31Dec2019
3.	Install all new equipment. Validate/qualify as necesary	JN	31Jan2020
4.	SOP written/revised as necessary	KP	28Feb2020
5.	Employee training updated as necessary	KP	28Feb2020
6.	Relocate existing equipment. Validate/Qualify as necessary	KP	28Feb2020

Example - 58.63 Mainteneance and calibration of equipment

- Equipment
  - Inspected/cleaned/maintained and tested/calibrated/standardized
  - SOPs to cover equipment
  - Records of the above activities

Example - 58.63 Mainteneance and calibration of equipment

Complexity	Simple	Simple	Complex
Impact	No impact on study data	May affect study data	Directly affects study data
SOP?	No	Yes	Yes
Calibrate or qualify?	No	Yes - calibrate	Yes – IQ/OQ/PQ
Documentation	Listed in equipment log	+ certificate	+ lots



"Applicable principles" of 21 CFR 58 (GLPs)

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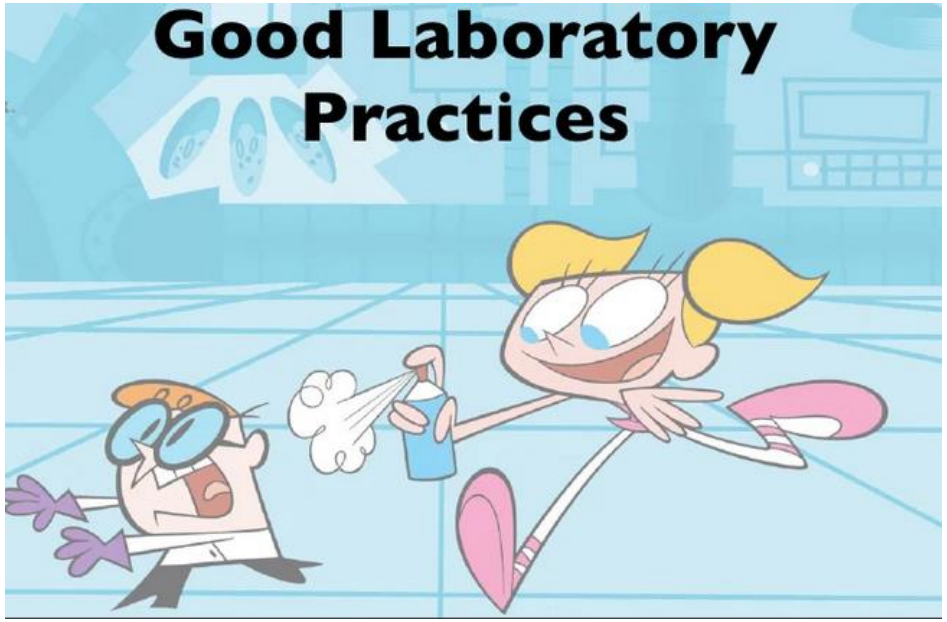
- Is this in vitro BE work technically GLP?
  - We decided the answer to that question was largely irrelevant.
  - GLPs provide great starting point for performing a *well controlled study* under a strong QMS, some of the key points of which are to
    - Ensure patient safety
    - Prevent fraud
    - Provide data integrity
    - Allow study to be reconstructed
    - Encourage labs to work in a similar fashion



"Give people enough guidance to make the decisions you want them to make. Don't tell them what to do but encourage them to do what is best."
Jimmy Johnson, football coach & commentator

Other Compliance Notes

- Went through same process with all other mentioned regs & guidance documents

- What else did we think about?
  - 21CFR11 – Electronic Records; Electronic Signatures
    - It's not specifically cited in AG, but we thought important
    - Our approach: when in doubt, go paper
      (Also, fully compliant systems are $$$)

> (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

  - Analytical Guidances – our *opinion*
    - Neither cited guidance is a *perfect* fit
    - ICHQ2R1 general intent is for very few samples with known concentrations using a very narrow calibration range (e.g., assay methods)
    - FDA BMV G general intent for large numbers of samples with unknown concentrations using wider calibration ranges (e.g., plasma PK methods); it's a good *framework* even for methods supporting IVRT

The Gaps

- Primarily SOPs (lab operations and QA) and equipment qualification
- A few examples

Task
Water Baths
Stir Plates
IR Camera
Incubators & Ovens
Skin Integrity Meter
Fridges & Freezers
LCMS
HPLC
Analytical Validation
Small Measurement Instruments SOP

Manage it

MedPharm

Task	Dept.	Resource (Hours)	6-Nov-17	13-Nov-17	20-Nov-17	27-Nov-17	4-Dec-17	11-Dec-17	18-Dec-17	25-Dec-17	1-Jan-18	8-Jan-18	15-Jan-18
Water Baths	PT	73 hrs											
Water Bath SOP	PT	17 hrs			4	10			3				
Draft Water Bath SOP	PT	16 hrs											
Review Water Bath SOP	M	1 hr											
Issue Water Bath SOP	M	0 hrs											
Water Bath Qualification	PT	48 hrs		4	8	10	8	8	10				
Write Water Bath Qualification Plan	PT	8 hrs											
Water Bath PQ	PT	40 hrs											
Water Bath Qualification report	PT/QA	8 hrs									3	3	2
Write Water Bath PQ report	PT	8 hrs											
Review Water Bath PQ report	QA	0 hrs											

This isn't fast or cheap

- Personnel – heads of three departments & their staff
- Time – initial estimate was in excess of 750 hours *excluding* QA SOPs and audits
- Timelines – aiming for completion ~ Feb 2018 

Task	Dept	Resource (Hours)
Water Bath SOP	PT	17 hrs
Water Bath Qualification	PT	48 hrs
Water Bath Qualification report	PT/QA	8 hrs
Stir Plate SOP	PT	17 hrs
Stir Plate Qualification	PT	48 hrs
Stir Plate Qualification report	PT/QA	16 hrs
IR Camera Calibration	PT	4 hrs
IR Camera SOP	PT	17 hrs
Incubator & Oven SOP	PT	33 hrs
Incubator & Oven Qualification	PT	37 hrs
Incubator & Oven Qualification Report	PT/QA	12 hrs
MedFlux Qualification	PT	56 hrs
HTX Plate Reader SOP	PT	9 hrs
HTX Plate Reader Qualification	PT	16 hrs
Fridge & Freezers Qualification	A	18 hrs
LCMS Qualification SOP	A	33 hrs
LCMS Qualification	A	32 hrs
HPLC Qualification SOP	A	9 hrs
HPLC Qualification	A	32 hrs
Analytical Validation SOP	A	17 hrs
Water Purification SOP	A	21 hrs
Water Purification Qualification	A	16 hrs
TurboVaP Qualification	A	16 hrs
Small Measurement Instruments SOP	TC	74 hrs

Aug – Dec 2017 Summary

- Aug-Oct 2017
  - Assess Acyclovir Guidance
  - ID the gaps
  - Plan it like a project

- Sep 2017 - Key IVRT paper

International Journal of Pharmaceutics 535 (2018) 217–227

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Research paper

A comprehensive approach to qualify and validate the essential parameters of an in vitro release test (IVRT) method for acyclovir cream, 5%

Katrin I. Tiffner[a], Isadore Kanfer[b,c,*], Thomas Augustin[a], Reingard Raml[a], Sam G. Raney[d], Frank Sinner[a]

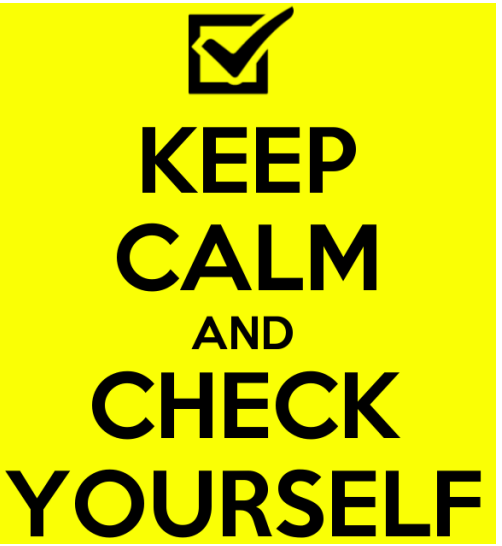
[a] Joanneum Research Forschungsgesellschaft mbH, Health – Institute for Biomedicine and Health Sciences, Neue Stiftingtalstr. 2, 8010 Graz, Austria
[b] Rhodes University, Faculty of Pharmacy, Artillery Road, Grahamstown 6140, South Africa
[c] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada
[d] Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, U.S. FDA, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

- Nov 2017
  - We're in progress on SOP/qualification activities
  - Thor: Ragnarok

- Dec 2017
  - We hit 19 US employees (> 100 US+UK)
  - Third party vendors employed for some qualification work ($)

2018

- Feb 2018
  - Behind schedule – initial resource & timeline estimates were low
  - We hired a third party to come in and audit us ($)
    - Good independent stress test of developed QMS
    - May find additional gaps you failed to identify
    - Only items found were known to still be "in progress"
  - Black Panther
- Apr 2018
  - All key systems now have SOPs and are qualified
  - Avengers: Infinity War
  - We're in the method development phase of a BE study
- Oct 2018 – EMA releases draft guidance on topical products
- Dec 2018 – 27 US employees (> 100 US+UK)



- Avengers: Endgame

- MedPharm: Endgame
  - MedPharm study data submitted to FDA

- Dec 2019 – 41 US employees (> 100 US+UK)

Jan 2020

- Remember this?

Kendall Powell

From: Kendall Powell
Sent: Tuesday, May 16, 2017 2:02 PM

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- Jan 2020: FDA comes to visit MedPharm

Jan 2020 … Well???

MedPharm

Establishment Inspection Report
MP Pharma Services Inc., dba MedPharm, US
Durham, NC 27703

FEI: 3012291107
EI Start: 1/27/2020
EI End: 1/31/2020

1 Summary

This was an FY2020 analytical BIMO program inspection conducted by [redacted] from the Office of Study Integrity and Surveillance (OSIS) under Compliance Program 7348.004, FACTS assignment [redacted] observed the inspection for training purposes. The current surveillance inspection covered the following submission: [redacted]

We inspected MP Pharma Services Inc., Durham, NC dba MedPharm US. The inspection covered method validation and sample analysis activities conducted by MP Pharma Services Inc., Durham, NC.

At the conclusion of the inspection, we did not issue Form FDA 483 to MP Pharma Services Inc., Durham, NC and there were no discussion items. We did not encounter refusals. This Establishment Inspection Report (EIR) was written by [redacted].

TL;DR

It worked!

Summary

- It's a risk
  - Is it worth it for you?
    - $ vs $
    - Inspections
  - If you do it, do it right

- Assess
  - Acyclovir Guidance
    - Context is key
  - Yourself
    - Find your gaps
    - Plan/manage like a project
    - You need the right people!
    - External audit

Contains Nonbinding Recommendations

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Acknowledgements