



# Exploring Strategies for Responses to Deficiency Letters in the US and EU to Help Expedite Approval

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# What should you remember?

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Utilize approaches to avoid and prepare for potential “deficiencies”

Develop contingency plans

Regulatory oversight can help avoid unnecessary deficiencies

Keep track of “what” you say to “who” (and “what” you have committed to!)

The answer to the age-old question: How perfect should a submission be?

# So, what is a deficiency?

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It's a general term that is used to describe questions, requests for information, or request for changes received from a regulatory authority

They can occur at any time during the review of a submission  
or

They can occur at a pre-established time interval (e.g., during a centralized or mutual recognition process in the EU)

What are they not?...they are not a reason to panic!

Many times they can be avoided, and sometimes they can't be predicted

However, they must always be responded to...

# Topics to be covered

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The Gaps

The Team

The Strategy

The Nuts & Bolts

Regulatory Oversight

The Cautionary Tales

Reality

How perfect should a submission be?

# Part 1

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## The Gaps



# How do we prepare?

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## Understand regional requirements

- Regional differences should be addressed
- ICH hasn't harmoniz(s)ed everything
- CTD means format and not content

If you need to, speak with the Agency up front. But remember: anything you agree to with them is usually non-negotiable.

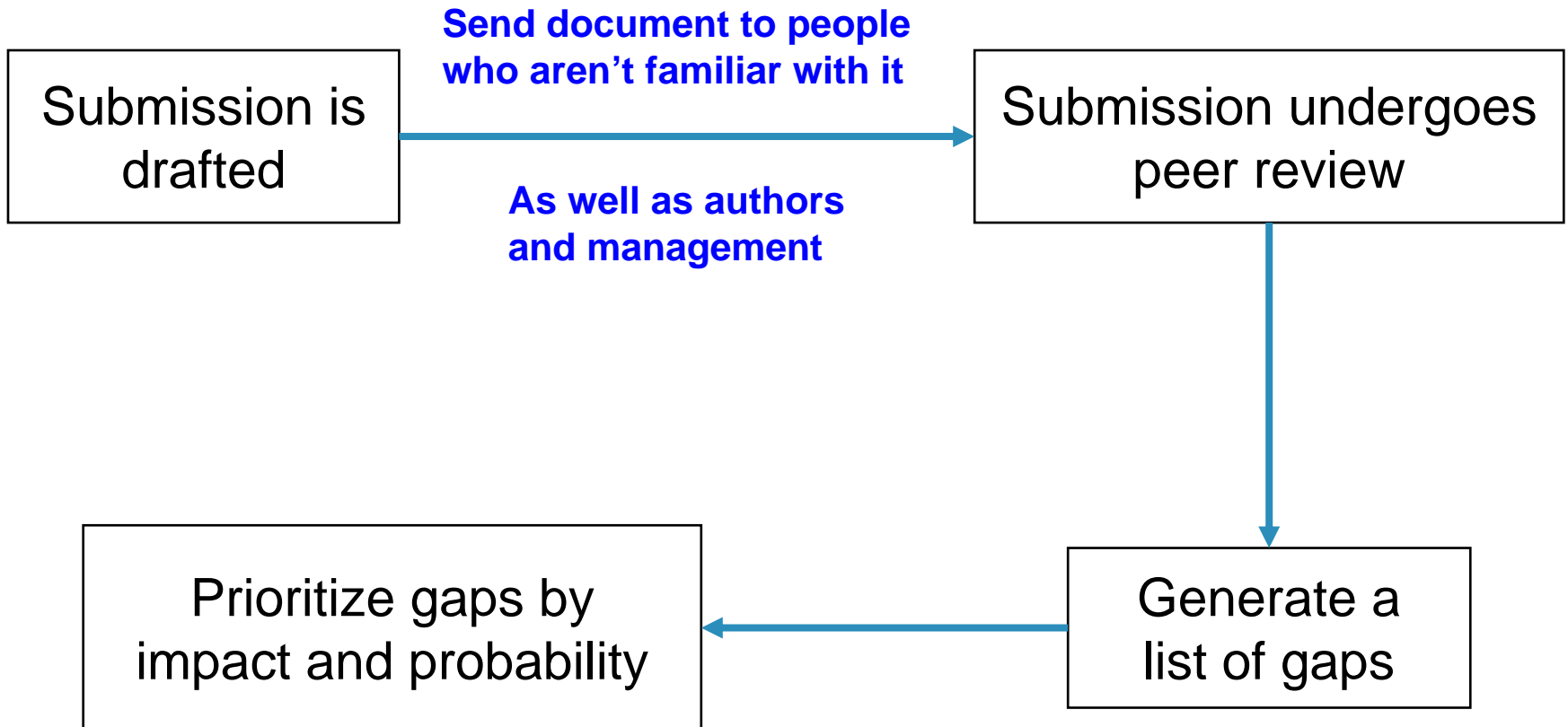
## There are opportunities to discuss potential issues

- EOP2
- Pre-NDA
- Request for Scientific Advice

Prepare the submission and then...

# Preparation process put simply

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# Paper responses to gaps

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Gap = Difference between what you need and what you have

Once gaps are prioritized there are three options:

- Ignore them (may not be good for your company)
- Remediate them (\$\$ and time)
- Prepare to respond to questions (sometimes your best option)

Draft responses can be in the form of a white paper, or a spreadsheet

- Purpose is to outline the issue and the strategy
- First response to a potential question
- Follow up responses
- Identify the line you can't cross

The focus should be on gaps identified as most critical

# An example of documenting strategy options

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**Issue**: Acceptance criteria for assay does not meet EU requirements (95-105%); proposed limits are 93.0-106.0%

**Strategy**: Justify limits in 3.2.P.5.6 (justification of specifications). Refer to batch release and stability data. **Caution**: Limited data supports tighter limits.

**Primary Challenge**: Propose that an additional 30 lots of product be tested, stability data for the first three commercial lots be obtained, then adjust limits if statistical evaluation justifies it.

**Secondary Challenge**: Propose a tighter limit of 94.0-106.0%

**Final Proposal**: Willing to accept release limit of 95.0-105.0%. The lower shelf-life limit cannot be increased above 94.0%.

# Business impact of gaps

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In situations where older products require changes to dossiers, business decisions play a bigger role

You might have many dossiers that are not up to today's standards

- There may be resistance to correct this
  - It costs money, takes time and uses resources
- If you want to keep a product on the market, someone has to make the decision to do this
  - Push it back to commercial groups and project management

Business groups need to decide if a market is truly needed for products that require too much remediation

Is there enough money to be made?

## Part 2

## The Team

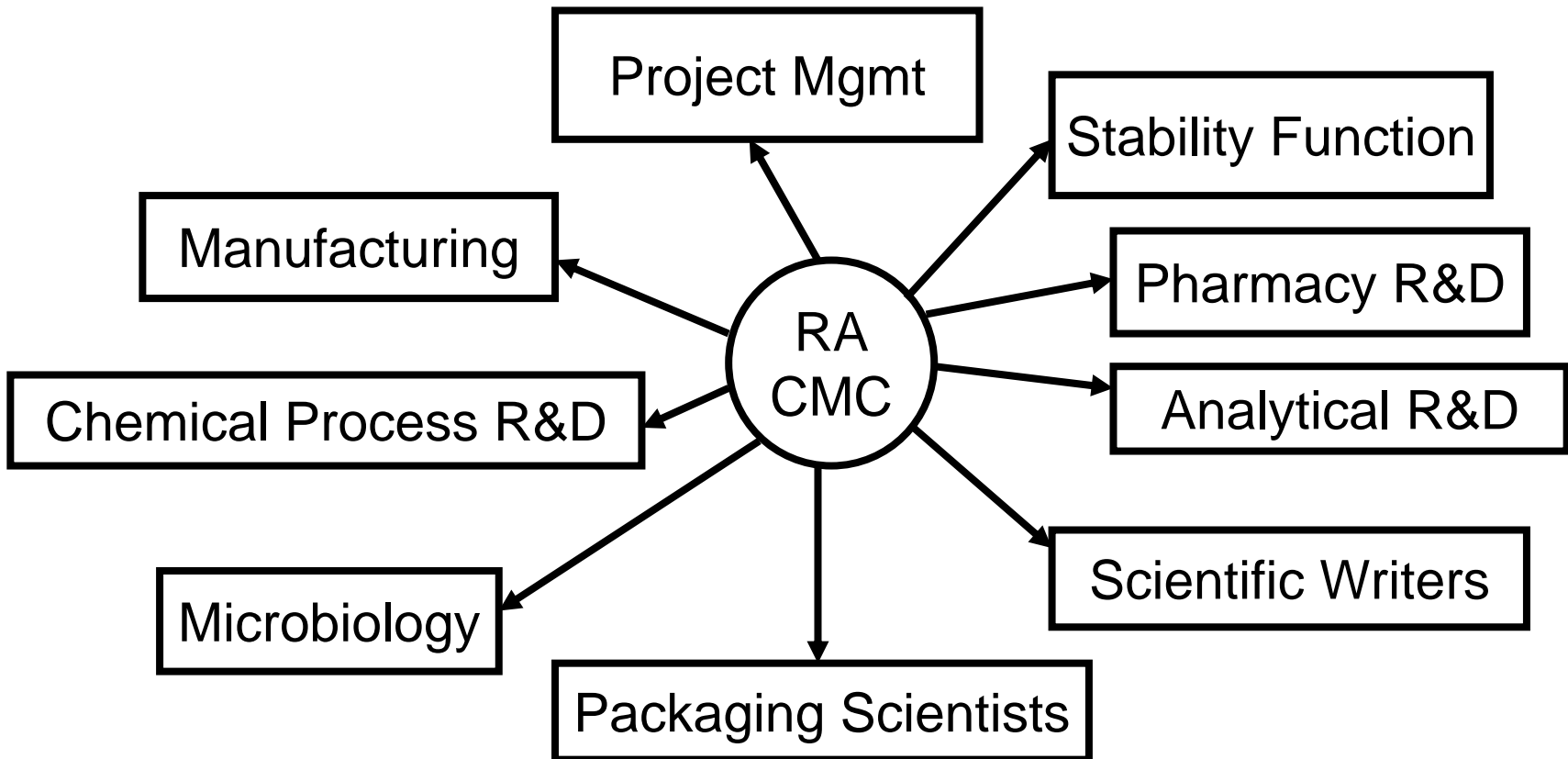


# TEAMWORK

**Because it takes a whole group of you to cover for that one lazy  
guy who takes 3 hour lunches**

# There's no I in team

It is imperative to maintain continuity with the team that contributed to the work



# The experts

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The experts that created the dossier are your most valuable asset

It is important to use these experts to draft responses to the gaps. It takes time, but it's worthwhile to do this up front.

- Use your gap analysis to prioritize
- Gain buy in from the team and management on the responses and the strategy
- Especially valuable since experts aren't always a constant

You need access to these experts...and they need to know that their assistance may be needed

# Communication

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Many times you can at least estimate when questions will start coming in

Let the team know when you anticipate needing their help (a guess is better than a surprise)

- In some cases this will be easier (MRP, CP)
- In other cases, it's out of your control (National filings, NDAs)

It's helpful to have a central contact or contacts in R&D to rely on

Remember –

- Keep the lines of communication open
- Listen to your experts
- Keep to your strategy, but remain flexible

# Part 3

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## The Strategy



*(Let the Wookiee Win)*

# So, what's the strategy?

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There is no “one size fits all” or “works every time” strategy for preparing for deficiencies

What usually won't work is reacting with no planning

There are many different approaches in the practice of regulatory affairs

Decide what you are most comfortable with...

**Cautious**: Provide lots of information to avoid deficiencies and delays

**Pragmatist**: Based on risk assessment, minimize data for low risk items

**Saver**: Don't provide all your arguments up front, save some for the responses

# You have what you have

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Many times you go in with what you have

- Prepare for the questions through gap analysis
- Understand your constraints and limitations (business, process, etc.)

Plan for multiple fall back positions, because sometimes the first one doesn't work

- Important when discussing specifications
- Can become part of your CMC agreement (FDA)

# The challenge

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You have to ask, when is it appropriate to challenge a question or a request

- During an MRP, questions should focus on safety concerns. Sometimes questions and requests that aren't, should be challenged.
- The business sometimes drives our responses and our strategy
- In order to get an approval, we may commit to things that aren't ideal

Sometimes you accept divergence early to gain approval. Adjust later as needed, if possible

# The commitments

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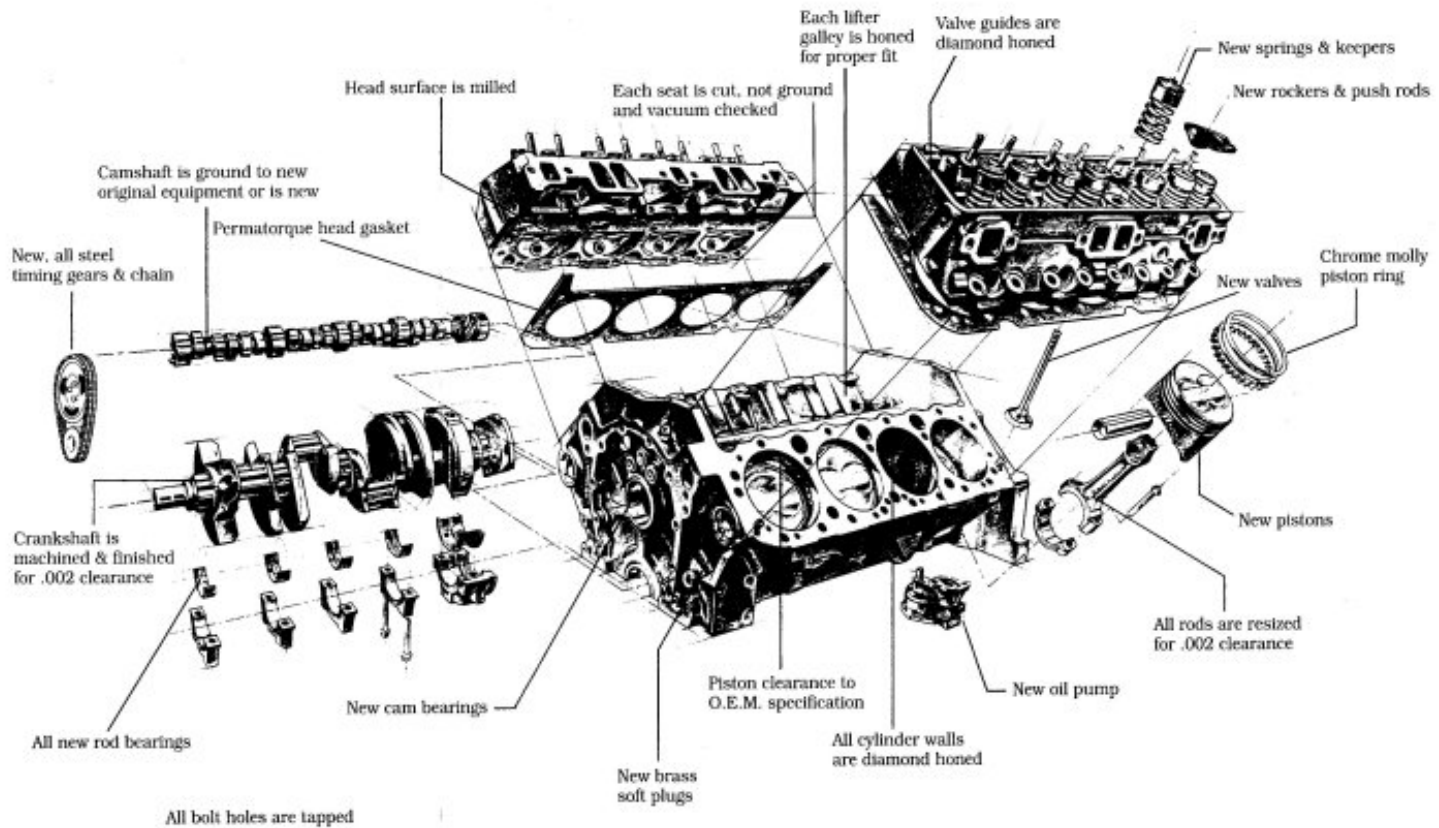
Sometimes you can make a commitment in the face of a question.  
This can be:

- timeline driven
- data driven

To handle the commitments you're making, you need very good documentation and supply chain systems

# Part 4

## The Nuts & Bolts



# The nuts and bolts of dealing with deficiencies

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First thing you do when you get a question is dissect it

What are they asking?

- Be sure you answer the question
- Don't give more than is asked for

Don't take questions at face value, there can be translational issues

- Go back to your in-country affiliates and ask for guidance
- If the opportunity avails itself, go back to the authorities for clarification

# The nuts and bolts of dealing with deficiencies

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How do you generate a response?

- Don't waste time, send the comments out as soon as you can
- Go back to your strategy and planning documents
- Draft a first version as a strawman. Can make everyone's life easier.
- Share the burden with your R&D colleagues. You're not alone.

Have a clearly defined process for drafting responses, setting strategy, getting responses reviewed and approved

Define what the roles and responsibilities are up front.

If you can, discuss your draft responses with reviewers. It may help clarify what they're looking for.

# The nuts and bolts of dealing with deficiencies

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There are occasions when you can politely say “no” to a request

- You are asked for mixing times for miscible liquids
- You are asked to set tighter than ICH limits for impurities for a low dose drug
- You are asked to replace LOD with GC residual solvents test for a drug dosed at the sub-mg level

Fully understand up front what you’re willing to give in on

- Again, know your limitations (business and process)
- Make sure there is buy in from your commercial organization

# The nuts and bolts of dealing with deficiencies

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Keep track of what you've said to who

- Having a database of responses allows you to answer similar questions from other Agencies
- Look at trends in questions: countries, reviewers, divisions.
- Allows you to prepare better dossiers to avoid the same old questions

# Part 5

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## Regulatory Oversight



# Regulatory Oversight

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One key purpose of a Regulatory Affairs group is to minimize regulatory burden

Responses to deficiencies should be designed to do this as much as possible

A Regulatory Affairs organization has the advantage of an historical perspective

Having this oversight function drives consistency in approach and philosophy

# Regulatory Oversight

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The responsibilities of Regulatory Affairs are to:

- Help design strategies
- Act as a focal point
- Be the voice of the company's interests to the regulators
- Understand the regulations and interpret them

# Part 6

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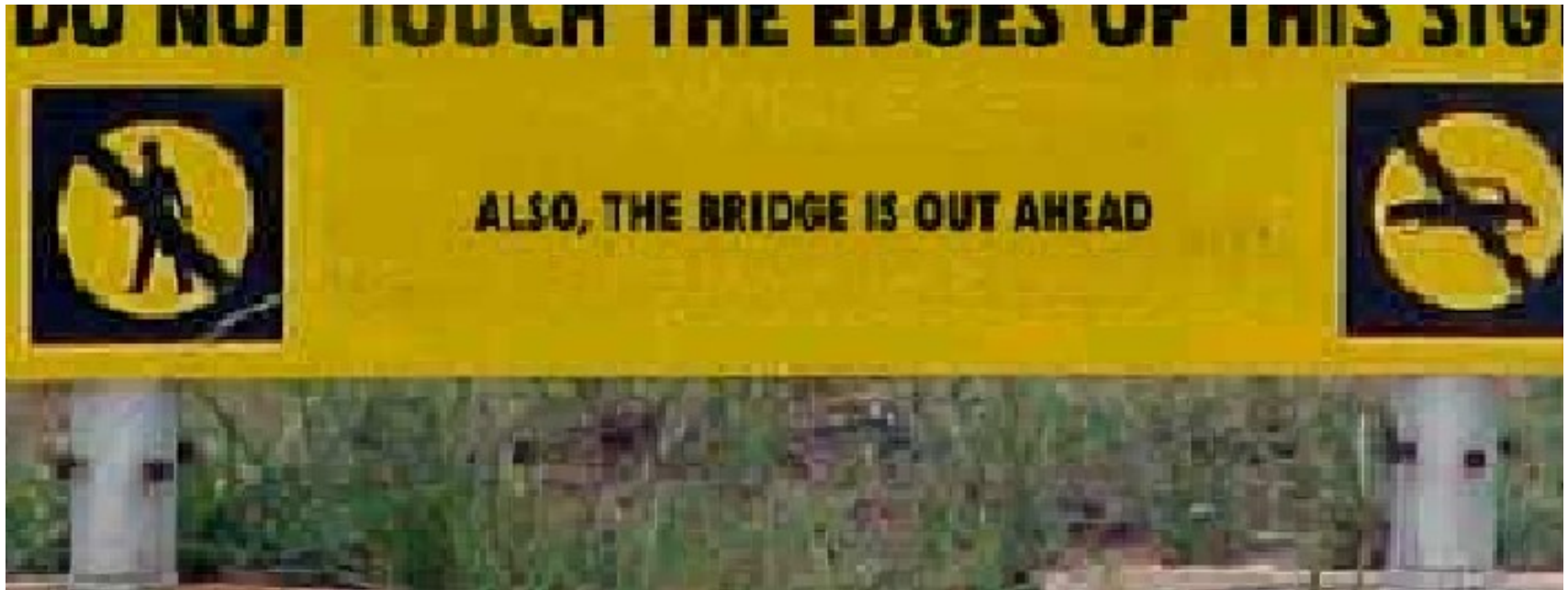
## The Cautionary Tales



# Part 6

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## The Cautionary Tales



# And now, the cautionary tales

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When a company first sees a set of questions, it may not seem that a question is quality related.

- It could be embedded within a group of safety or clinical questions
- The quicker this is realized, the better

You need to fully understand the ramifications of agreements made in the heat of the moment.

- Think outside the box
- Consider the precedent you may be setting
- Look down the road
- If not, you might pay later

## And now, the cautionary tales

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When you submit a supplement, especially to FDA, consider that you risk opening the entire NDA up for scrutiny

Always know your threshold for keeping your reputation intact

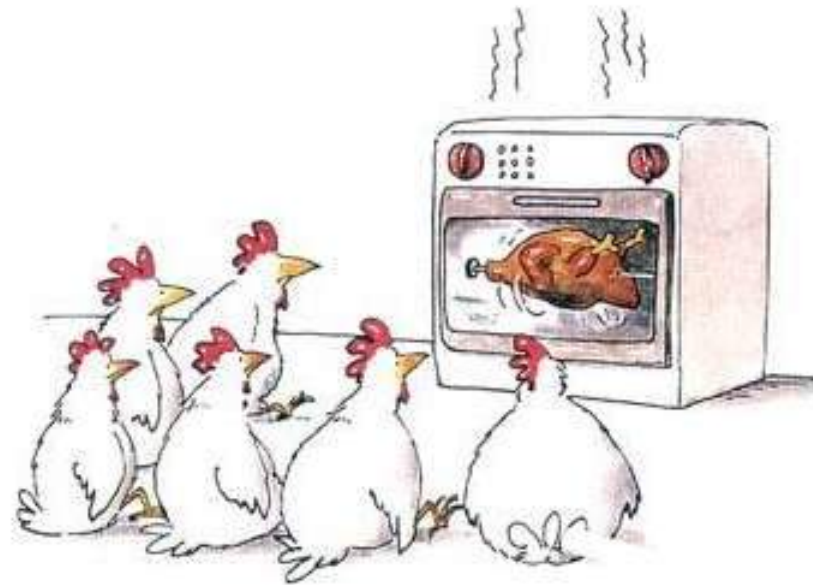
- The red face test is an important exercise

While you might want to minimize the information submitted, never minimize it to the point where you get a RTF

# Part 7

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## Reality



REALITY-TV

# The reality of the situation

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Sometimes you're just plain lucky and they ask nothing

- All that work and not a single question?
- That's always better than the alternative!

Sometimes questions seem to come out of left field.

- You can't plan for these
- You need flexible and quick response systems

As an example, Germany has reopened some pre-1968 applications and is applying today's standards. This requires a corporate strategy to address.

# The reality of the situation

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Remember, people have short memories.

- Things you agreed to a year ago may be forgotten when the questions come in
- You need to remind people what they've agreed to

Know when you can cut your losses.

Many companies these days want global submissions.

- This minimizes the variability from region to region
- Ask yourself if this minimization will cause too many deficiencies
- As much as you don't want to have multiple specs, you might need to

# The reality of the situation

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When questions come, remember your against a deadline.

- You have the agencies working on a clock
- Your sales and marketing groups are breathing down your necks
- Your management wants to hit their objectives
- All this must be balanced with what is right for the business and the future of the product
- Know when you can cut your losses!

Deficiencies on already marketed products can be more problematic

- A failure to get approval can significantly hurt an existing business

# Part 8

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So, how perfect should a submission be?



# How perfect should a submission be?

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So, what is the answer to this age-old question?

1. Perfect?
2. Perfect enough?
3. Nobody's perfect?

A submission should contain the data needed per regional requirements and experience of your Regulatory group

You must understand your gaps and be prepared to address them

Nobody's perfect, but that's no excuse for not being as prepared as humanly possible

# Acknowledgements

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