Let’s Start At The Very Beginning... Building a Quality Dossier

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Let's start at the very beginning...
A very good place to start!
Agenda

• What is a Quality Dossier and How Do I Build One?
  – Content?
  – Style?
What is a “Quality" Dossier?

• Is it the CMC Section (Module 3) content?
• Is it a well-written submission (style)?
• Is it a combination of the two?

Let’s Explore This....
Content
Content – What do we need for CMC?

• Build Quality into the Product from the Very Beginning

• Assure Patient Safety

• Provide Phase Appropriate Information and Detail
What is the Target Product Profile?

The answers to these questions can drive very different risk profiles and development programs...
Tip #1

Think holistically about the product, indication and administration route – and the potential risks/concerns to patients
Two Examples to Think About...

**Same product...**

**Product “X”**
- Anti-angiogenic Monoclonal Antibody
  - Inhibition of vasculogenesis
  - Intravitreal
  - Age-related macular degeneration

**Product “X”**
- Anti-angiogenic Monoclonal Antibody
  - Inhibition of vasculogenesis
  - Intravenous
  - Cancer

*With potentially very different risk profiles*
Assure Patient Safety is at the Forefront!

Specifications might need to consider the following:

**Oncology Indication**

Specifications

- Endotoxin NMT 5 EU/kg/hr
- Impurities
  - Aggregates < 5.0%
    - IV administration, immunosuppressed patient population

**Arthritis Indication**

Specifications

- Endotoxin NMT 5 EU/kg/hr
- Impurities
  - Aggregates < 2.0%
    - Intravenous administration, patient population is not immunosuppressed/is immunoactive; aggregate levels correlate with increased adverse events
How do You Build an Appropriate Level of Detail?

Provide sufficient detail for established conditions

Ensure the appropriate level of detail to effectively manage change control

Utilize the pharmaceutical development sections to tell the story

Provide data and figures
What is the Appropriate Level of Detail?

Content (and level of detail) should evolve just as the product does...

Example - S.4.3 Validation of Analytical Procedures

• Phase 1
  — Methods are not validated; eg, fit for purpose
  — Platform methods

• Phase 2
  — Some analytical methods may have preliminary method validation

• Phase 3
  — Methods are validated or close to final validation

• Licensure/Post-Licensure
  — Analytical methods are validated
Tip #2

Ensure that the appropriate amount of information is provided.
It takes considerable effort to update submissions – especially globally. If you have been asked for specific information several times then start including it the first time.
Style
A Well-Written Document Displays Substance with Style

• My purpose in public address and in speech is really encapsulated in three C’s: **clear, concise, correct**. No overblowing rhetoric or anything like that. As simple as possible: clear, concise, correct.
  — *Bob Sheppard*

• Clutter is the disease of American writing. We are a society strangling in **unnecessary words, circular constructions, pompous fills and meaningless jargon**.
  — *William Zinnsser, ‘On Writing Well’*

• Good writing is an aliveness that keeps the reader reading from one paragraph to the next, and it’s not a question of gimmicks to “personalize” the author. It’s a question of using the English language in a way that will achieve **the greatest clarity and strength**.
  — *William Zinnsser, ‘On Writing Well’*

• Literature is the art of writing something that will be read twice; **journalism what will be grasped at once**.
  — *Cyril Connolly*

• Science is **organized** knowledge.
  — *Herbert Spencer*
Style – What do we need for CMC?

An Effective CMC Document.....

- Strategic: Is designed to achieve specific goals
- Persuasive: Makes clear and effective arguments
- Consistent: Follows a shared set of principles
- Easy to read: Is well-organized and easy to read
Tip #3

Ensure that your document is well-written and organized.
Documents are visual objects...

Maybe our reviewers don’t understand because they can’t see what we are trying to tell them.
Important Writing Techniques to Use

• **Bottom Line on Top (BLOT)**
  – Put the Key Message/Takeaway at the top!
  – Just say no to BLOB (Bottom Line on Bottom)
  – Use Topic Sentences for Paragraphs

• **Chunk**
  – Separate – or chunk- content into visible patterns
  – Use titles to separate content for readability
  – BLOT each subsection/chunk

• **Claims, Reasons, Evidence**
  – Use C, R, E to **strategically** get your point across!
Tip #4

Ensure that you have a justification and data to support a claim.

And

Ensure that the justification is clearly written (see Tip #3).
Let's start at the very beginning...

A very good place to start!

When you read you begin with A, B, C
When you sing you begin with Do, Re, Mi
When you write a quality regulatory submission you lay out C, R, E
Claims, Reasons, Evidence...

• **Claims**
  - A Sentence asserting something that may be true or false and needs support.
  - The claim is **BLOT**.

• **Reasons**
  - Statements that give your readers cause to accept your claim.
  - A reason answers the question “why” and has an implicit or explicit “because”.

• **Evidence**
  - Irrefutable facts or data on which you base your reasons.
  - Evidence to answer the question “How do you know?”.
Claims, Reasons, Evidence... A fictitious example

Claim

- Doodlemab is expected to be a potent and tumor-specific antibody that (1) will attack Doodle-expressing tumor cells, while (2) having decreased off target effects such as skin rash due to limited binding to normal tissue.

Reasons

- The antibody binds to a Doodle epitope unique to a Doodle-expressing tumor cells. This specific epitope is a characteristic of tumor cells with the Doodle deletion mutant or tumor cells with activated wild-type Doodles. In these tumor cells, the antibody is internalized, and then intracellular enzymes release the toxin leading to inhibition of microtubule function, the disruption of critical cellular processes, and cell death.

- In contrast, the epitope allows limited binding to normal tissues expressing non-activated, wild-type Doodle. Therefore, the epitope is largely inaccessible when Doodle is expressed at normal physiological levels. This property limits the effects of the toxin on normal tissues while allowing a high degree of activity on Doodle-overexpressing tumor cells.

Evidence

- Both preclinical studies and Phase 1 human trials demonstrate the relative tumor specificity of the Doodlemab antibody. The preliminary clinical data are summarized below in Table 2.
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It is not content over style or style over content...
It is content written WITH style!!!!
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