Roundtable Session 2 – Table 3 – Recent Trends in Questions from Global Health Authorities

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Abstract:

The regulatory environment for biopharmaceuticals is complex and constantly evolving. Organizations must stay competitive, comply with regulations, reduce risks, and ensure the delivery of safe and effective medicines to patients. Harnessing Chemistry, Manufacturing, and Controls (CMC) regulatory intelligence, through understanding recent trends in questions and evolving areas of focus and concern from Global Health Authorities is crucial.

These trends often reflect the latest scientific advancements, public health challenges, and changing guidance. By leveraging CMC regulatory intelligence, companies can better anticipate regulatory expectations, streamline their development processes, and avoid potential compliance issues. Our discussion will focus on knowledge sharing and collaboration between companies to benefit from collective wisdom.

Discussion Questions:

Questions:

Global Health Authorities set the standards for drug approval. Staying updated on their evolving requirements ensures that biopharmaceutical companies can design their processes to meet these standards, reducing the risk of delays or rejections.

- In terms of recent trends in questions from global Health Authorities, which guidance and requirements have you had the most interpretation and implementation problems with, over the last 12-18 months? Without compromising confidential information, describe your experience.

Regulatory trends often highlight areas of unmet medical need or emerging health threats. By aligning their research and development efforts with these priorities, biopharmaceutical companies can focus on developing innovative therapies that are more likely to receive regulatory support and meet market demand.

- What public health challenges seem to be influencing regulatory trends?

- Describe the challenges you have encountered or expect to encounter?

- Is there clear guidance available, if not what guidance can be used to help bridge the gap?

- What is the regulatory expectation?

For companies operating in multiple regions, understanding the regulatory trends across different jurisdictions helps in harmonizing their product development and regulatory strategies, facilitating smoother global operations

- In terms of recent trends in questions from global Health Authorities, what hot topics & themes have you encountered over the last 12-18 months by geographic area?

- What have been the most challenging questions from global Health Authorities?

- What recent scientific advancements seem to be influencing global Health Authorities questions?

- What legislation seems to be influencing global Health Authorities questions? Copy and paste the discussion questions from the online program (if applicable)

Summary Using Microsoft Copilot:

- **FDA/EMA Requirements**: There were discussions on in-use stability and microbial challenge requirements, with a focus on understanding how to set up microbial challenge studies. The presence of preservatives in drugs was highlighted as critical, with alternative strategies like antimicrobial effectiveness testing (AET) being suggested if preservatives are present.
- **Germany's Extended Use Studies**: Germany requires extended use studies, such as diluting samples and holding them for 30 days. There was a consensus that this might be atypical without additional details.
- **Japan's Local Testing Requirements**: Companies face challenges with local testing requirements in Japan, including whether to set up local labs or use EU release labs. The Japanese market is considered challenging due to many pushbacks and scrutiny.
- **Biosimilars**: There are difficulties in showing local comparability with originators, with some countries being very rigorous with their specifications. Indonesia, for example, does not seem to accept scientific justifications and requires concrete, data-based specification setting.
- **Host Cell Protein (HCP) Specifications**: Discussions included the FDA's request for tightened HCP specifications and whether companies have had success removing HCP from commercial specifications.
- **Collating and Trending Queries**: Companies track questions from health authorities and prioritize some as higher priority. There was an example where incorporating feedback from one country into other filings created negative feedback from those other agencies.
- **Subvisible Particles**: Feedback on subvisible particles depends on the product and patient population. Trends can cause regulators to pay attention if there was an issue at some point.
- **Manufacturing Changes**: There were discussions on manufacturing changes, including requests for forced degradation/accelerated stability studies for frozen drug substances. Canada allows extrapolated stability.

- **Reference Standards**: There were questions about what testing should be done for reference standards, including additional characterization assays if needed.

Notes:

Goals for this session: Learn from difficulties for those who have had any troubles with global authorities

FDA/EMA – in-use stability; microbial challenge requirement

- Struggling to understand how to set up the microbial challenge study
    - Introducing microbes
    - Critical whether drug has preservatives or not
    - Alternative strategy if preservative is present: antimicrobial effectiveness testing (AET) – USP exists specific to this

Germany asks extended use studies – dilute sample, hold for 30 days

- Normal in-use study was performed – can product maintain good quality in IV bag for 30 days
- No requirement for microbial study
- Not usually in pharmacy manual to even allow this
- Agreement that this might be atypical without additional details

Experience with Japan (PMDA)

- Local testing requirement – do companies set up local lab in Japan, or use EU release lab to do this
    - One participant says they set up a lab in Japan
        - Analytical method transfer is completed for initial submissions
    - Post-approval change management protocol is difficult
    - Agreed that Japanese market is challenging – many pushbacks, scrutiny to unexpected portions of submissions
    - ICH Q12 – describing protocol for transfer, PACMP

What the rest of the world agencies are asking?

- What are the deficiencies so that smaller agencies can be supported with training modules
- Biosimilars - often want local comparability with originator, difficult to show this comparability
- Some countries are very rigorous with their specifications – FDA/EMA are usually more accepting of spec justifications

- Indonesia does not accept scientific justifications, must be concrete, data-based specification setting
- Even US has challenged scientific justifications, but usually will meet in the middle with sponsors
- FDA has requested tightened HCP specs, both in-process and release
    - Would FDA accept an action limit and a separate spec for HCP in BLA
    - Suggestion that simply tightening the HCP spec was sufficient
    - As more manufacturing introduced, variability increases

Have companies had success removing HCP out of commercial spec?

- Generally no
- However, one agency says they have approved products without HCP spec
- Usually not removed, but have seen it moved from release to in-process control
- Were able to remove after several years of commercial production
    - Idea that identifying problematic HCPs and characterizing product, show absence could help with removal of release testing requirement

How are companies collating and trending queries from health authorities?

- Questions are tracked; don't expect that because they received a question once, does not necessarily mean changing default strategy
    - Some get flagged as higher priority
- Regulatory groups usually do this; accessible database for rest of teams
- Is there communication with program teams?
    - Usually regulatory team will pass these questions/concerns along.
- One example where a company received comments from one country, then proceeded to incorporate it in other country filing. This ended up creating negative feedback from those other agencies.
    - Use what is reasonable in filings – not just because one agency requested it

Is anyone getting additional feedback on subvisible particles?

- Depends on the product, patient population
    - Trends can cause regulators to pay attention if there was an issue at some point
    - High conc. dose challenging subvis particles different
    - Structure specs around collecting future data
- If you find trend in methods that is not in specifications, potential risk to CQAs
    - But method was removed from spec, or was not needed
    - If inspection is performed and this occurs, need to be aware of how to present this

Raw data requests seem to have been increasing.

Request for net gross volume release spec? Has it been incorporated in release spec?

- Has not been requested by additional agencies, yet.
- Why has that been asked?
    - Want to see upper/lower limit in a release spec
    - Too much volume can present a safety risk
    - Some of the low dose products were filled in large containers; this was communicated to congress. Initially meant to reduce public funding waste, but is now interpreted as a fill volume spec.
- This is already captured by overfill, already an in-process control

Any changing perspectives/guidances for CGTP (MOA)?

- HCP, DNA, Protein A; agencies seem to be more open to technologies for "advanced technology products"
- Microbial testing common.

Manufacturing changes – CDER has requested forced deg/accelerated stability liquid state for a frozen drug substance, hard to do an accelerated stability for frozen without a phase change, never a condition in the manufacturing process. Do other agencies ask for this?

- Not aware of any.
- Commonly see it as a part of comparability package, depends on approach to the comparability program, though
- Canada does allow extrapolated stability
- During shipping – if temperature deviation causes thaws, need to qualify for the liquid state
- Cross-validation should bridge these conditions.

Stress conditions for accelerated stability/comparability

- Most currently only do temperature
- pH, oxidation requested by S. Korea
- Depends on formulation; if molecule is pH-sensitive/dependent, need to capture this
    - Need to consider degradation pathways; understand the process to understand what are the relevant degradation pathways
- If manufacturing change, do you need to do any additional testing?
    - Use a risk assessment

Filing in China

- Is additional testing necessary? Needing an ADCC cell-based assay
- Can you justify surrogate?
    - If MOAA has nothing to do with ADCC, can justify not needing
    - Not successful filing this in China; Japan can be difficult to file this.

Reference standards – what testing should be done?

- Reference standard characterization – release, lean characterization; request to add additional characterization assays if needed
- What extra tests are requested?
    - Peptide map, higher order structure