Challenges and Opportunities in Animal Health Regulatory Affairs

A Compilation of Industry Roundtable Discussions

Oct. 20, 2017

KANSAS STATE UNIVERSITY | Olathe

22201 W. Innovation Drive
Olathe, KS 66062

olathe.k-state.edu

Overview

On Sept. 21, 2017, officials at the Food and Drug Administration's Center for Veterinary Medicine (CVM) met with 130 professionals from animal health companies from across the U.S. to discuss the challenges and opportunities in the current animal health regulatory process.

The meeting, "The Future Vision of FDA's Center for Veterinary Medicine: Opportunities and Challenges in the Regulatory Process," was the first in a series of regulatory affairs seminars at the Kansas State University Olathe campus in Olathe, Kansas. The goal of this first seminar was to expand the dialog between the animal health industry and the CVM in order to identify areas for improvement in the regulatory process by both industry and the CVM. This will ensure mutual goals can be met relating to the safe and effective delivery of animal drugs.

The 130 animal health professionals participated in small roundtable discussions about how industry and the CVM could improve the current regulatory affairs process. Groups looked at the areas of bioequivalence study design, data quality, global approvals and the supply chain. Group members discussed the challenges that exist in each topic when it comes to both discovery and generic drugs in the animal health arena, and identified opportunities and potential solutions for these challenges.

This document outlines those identified challenges and opportunities. Both the CVM and industry can use the information provided to enhance current practices and recommendations. The CVM has committed to using the information for continued process improvement and is looking to industry for leadership to work on the identified industry challenges and opportunities. Kansas State University is willing to convene industry in partnership with appropriate animal health regulatory organizations for this purpose and looks forward to a continued dialogue on how to move forward.

Industry participation

The following organizations participated in the roundtable discussions:

AlcheraBio LLC
Animal Health Institute
Aratana Therapeutics
Arther Consulting LLC
Bayer Animal Health
Bergt Consulting Inc.
Bimeda Inc.
Boehringer Ingelheim Animal Health
Brakke Consulting Inc.
Cardinal Health Regulatory Sciences
Ceva Animal Health
Connect Veterinary Consulting
Dechra
DeSoto Investments LLC
Elanco Animal Health
Herschel J. Gaddy and Associates
Huvepharma Inc.
Integrated Animal Health
Kansas State University
Kindred Biosciences Inc.
Likarda LLC
Midwest Veterinary Services Inc.
MRIGlobal
Norbrook Inc.
Novus International
Nutsch Consulting Inc.
One Medicine Consulting
Parnell
Pegasus Laboratories Inc.
Phibro Animal Health Corporation
Piedmont Animal Health
Prelude Dynamics
ProPharma Group
QAS
Scout Bio Inc.
Sparhawk Laboratories Inc.
Tri-Source Pharma
University of Missouri-Kansas City
Virbac Corporation
WPD and Associates LLC
Zoetis

Bioequivalence study design challenges

Group objective: Identify the challenges in bioequivalence study design for industry and the FDA CVM.

Industry challenges

- Multiple species on label
- Reviewer consistency
- Time = Money
- Weight range required for single tablet administration
- Uniformity of product formulation
- Animal models are so variable it is difficult to achieve bioequivalence – species, source
- Demonstration that test animals are healthy prior to dosing
- Having sufficient animal numbers to prove bioequivalence
- Clinical practice experience "Are you getting what you think/label claims?"
- Are bioequivalent products going in vivo?
- Lack of efficacy studies
- Not all dosage forms treated equal (bio-waver, injectable, etc.)
- When drug sponsors results are not consistent with guidance; timing/communication challenge for industry
- Administering equivalence/consistency across many species and dosage forms
- If generic has improved on innovators product
- Reviewer variability (some "nit-picky" reviewers)
- Consistency between review teams/cycles
- Reactivation of Dev after EMP insp. resolution
- Not understanding import/export restrictions for clinical materials; delays affect animal readiness and analytical expiry
- Understand/track "new" requirements
- Cannot predict schedule approval→BE schedule lost CRD managements
- Expiration of bio-challenge/RLNAD biowaver
- Lack of knowledge between approved and unapproved generics
- Tech
- QbR
- Dissolution testing
- Incentive for stakeholders to pursue generics (ANADAS)
- Variability of PK data
- Competition with human generics and compounded drugs
- Expanding experimental methodologies for study design requires resources for process/method validation
- Cannot find the reference label product
- Chasing the science

CVM challenges

- Data quality/integrity
- Legal ramifications due to regulation decisions
- Interpretation of new designs that may fall outside of "guidelines"
- Figure out a way to accept BE study for products purchased in another country
- Interpretation on bioequivalence of a product in different forms (tablet vs liquid)
- Avoid over regulating/scope creep → Utility based approach to review
- Streamline Q&R template for BE protocol submission (not incomplete /non-concurrent)
- Look for ways to improve
- Training large numbers of new hires
- TL do more complete review of reviewer comments
- Balance company interests
- Data
- Technology
- Dissolution testing
- Balance BE studies vs NADA – Does BE always = safety and efficacy
- Perception in market that generics are not as effective
- OTC generics vs approved drug generics
- Off label drug use
- Compounding
- Acknowledge alternative methodologies – beyond traditional test guidelines
- Clarify opportunities for suitability position
- Better communicate the increase of the requirements
- Variability of reviewers
- Define list generally recognized API
- Bridge animal data for humans and animals to be used for approvals (where CVM are examples)

Bioequivalence study design opportunities

Group objective: Identify the opportunities in bioequivalence study design for industry and the FDA CVM.

Industry opportunities

- Embrace QBR and improve
- Continue to collaborate with CVM on BE issues
- Increase communication through meetings and informal email communications
- More proactive communication with regulatory agency while developing protocol
- Use of Bio-E studies to investigate/justify different dosage forms (tablet – vs liquid)
- Library/database for good study design
- Examples and question based reviews
- Form coalition/forum where anonymous questions can be proposed
- Be more proactive and provide solutions/suggestions
- Sponsor better education on requirements (rookie)
- Improve quality/completeness of submissions
- More proactive discussions between AHI and GADA
- Biomarker equivalencies – Demonstrate equivalency response (part for drugs without linear PD relationship or alternate approach for highly variable drugs)
- Provide feedback
- Change in thinking
- Educate public and stakeholders on potential use of BE opportunities- for efficiency in review of designs
- Decrease in large animal studies?
- Modify existing applications; can BE designs be used?
- Present alternative data for consideration
- Collaborate to develop alternatives and/or adjunct approval process proposal
- Design alternate study methods that are reproducible and reliable
- Devise better modeling/analytical systems
- Better understand CVM requirement to harmonize bioequivalence of pioneer formula
- Harmonization – bridging analytical methods, requirements- mutual recognition
- Other avenues to demonstrate alignment vs. bioequivalence

Bioequivalence study design opportunities cont.

CVM opportunities

- Consider scientific justification for imperfect situations
- Meet with sponsors and engage issues
- Continue embracing novel study design
- In vitro approach
- Embrace designs other than PK levels
- Better alignment with agencies in other countries
- Library/database for good study design
- Examples and question based reviews
- Assure we are focusing on both regulatory issues AND science (when good science doesn't neatly comply with guidance/regs)
- Finalize publish BE guidelines
- Publish requirements for BE design for highly variable drugs
- Publish metrics on 1st cycle review and common deficiencies
- Defined path to get to clinical end point BE
- Increased number of generic approvals
- Flexibility on 80-125% requirement → scientific justification
- Demonstrate compliance with USP vet compounding mimeograph or establish OTC vet mimeograph system based on human model
- Meet with industry
- Harmonize
- Look at other countries – hybrid generics- dosage form changes- regimen changes
- Novel/new methods of analysis
- Educate public and stakeholders on potential use of BE opportunities- for efficiency in review of designs
- Decrease in large animal studies?
- Modify existing applications; can BE designs be used?
- Consider if there would be an alternative and/or adjunct testing/clinical outcome to blood levels
- Alignment between reviewers/consistency
- Collaboration with industry to enhance technical understanding of alternate methods available
- Better communication to understand the science behind study
- Rethink use of bioequivalence in combo products
- Optimize old pioneer formula dossiers (RLNAD)
- Utility based approach to data requirements; extend simple solution approach of bioavailable to other dosage forms (i.e. immediate dissolve tablets)
- Develop better guidelines for multiple species products
- Change in thinking
- If bioequivalence in one species why show in all?
    - Can you get just one species?

Data quality challenges

Group objective: Identify the challenges in data quality for industry and the FDA CVM.

Industry challenges

- Share data (your IP) with industry; better for animals
- Adopt, improve and prove data capture techniques
- Understanding what FDA CVM wants; different reviewers want different formats
- Standardizing formatting requirements
- Reviewers do not always know what "Raw Data" represents or is
- Source data is at times not what is needed since they might not be readable or understood
- Lack of understanding of CVMs expectations
- Finding/maintaining the relevant skill sets
- Lack of training opportunities
- Moving target
- Continuation of Part II compliance (x 2)
- Difficulty in implementing EDC due to:
    - Resources
    - Lack of clear expectations
    - Various EDC systems with different capabilities
- Multiple data formats/requirements, due to multiple DROs and multiple agencies
- Cost of advancing technologies
- Timeline to submission
- Number of personnel
- Lack of training
- Site non-compliance
- Cannot be there all the time
- Cost
- CMO/API manufacturing- How do you control the Quality Culture at another facility?
- Inability to submit to an incomplete letter until everything is ready -- ex. Sometimes can answer 80% in one week and 20% in 6 months
- Collaborative relationships that facilitate communication and synergy with FDA and CROs etc.
- Shifting CRO Landscape – managing changes, acquisitions
- Incomplete letters due to data quality issues increases development timeline
- University investigators and facilities performing "novel" testing
- Difference in quality between multiple contributors in same submission
- More specific re: data quality issues; study type, similar in nature or one off type study
- EDC – multiple systems .xml format – interpretation of data
- VMF: Incomplete – Why? Provide more detail
- Sponsor and VMF collaborate over incomplete issues? What kind of authorization does CVM need between sponsor and VMF holder to share info?
- What will auditor look at paper or EDC
- Where is highest confidence level?
- How to maintain and support integrity of data
- Inconsistency in data presentation and review change in expectations over time, USP updates
- Time delay in setting up CVM meeting
- Be more assertive -- Industry -- more communication, quicker and easier
- Unforeseen changes at the supplier level
- Different standards for human/animal (ex. packaging)
- Expense associated with having alternate suppliers
- Suppliers limited human/animal mfrs.
- Oversight diverse CMO network
- Implementation of global changes
    - Differences in requirements, timing, inspections
    - Communicating within structure of CVM

Data quality challenges cont.

CVM challenges

- Don't confuse process quality with data quality (science)
- Review data at site (visit at the site) rather that submitting raw data
- People who review protocol have different ideas/priorities vs people who review report data
- More internal communication could be beneficial for more consistency
- Statisticians prefer different files vs. other reviewers who may want html or some other human readable files (e.g. PDF)
- Electronic data capture
- Lack of understanding of limitations and restrictions related to EDC
    - Proprietary software
    - Validity of paper data when e-data is available and is the actual source data
- Inconsistencies between review groups and centers
- Is there a need to reassess part 1?
- Volume and Quality of Data – Electronic Capture and resources to QC review
- Global and internal harmonization
- Personnel numbers
- Correct training for inspectors
- Focus on some meta-data issues aren't really issues → on equip timing matching up for sequencing ex: HPLC
- Become a "catch phrase" of blame
- CVM only allows 3 file types – so have to convert and provide "read me" files to explain
- Data quality
- Use internal process to determent "refuse to file" sooner
- Part II compliance EDC
- More specific regarding data quality issues; study type, similar in nature or one off type study
- EDC – multiple systems .xml format – interpretation of data
- Guide EDC vendors on Part II and CVM requirements for submission
- Different standards for human/animal (e.g. packaging)
- Import – inconsistency at the port
- Resources, number of applications → M&A
- Evolving/emerging technologies (API & DP)
    - Can't get guidance out fast enough
    - How to communicate alternate pathways to approval and change in thinking
- Increase of CMOs → more to inspect
- Internal communication/consistency between review teams →pioneer→generic
- Managing when to use regulatory discretion in cases of supply chain interruptions

Data quality opportunities

Group objective: Identify the opportunities in data quality for industry and the FDA CVM.

Industry opportunities

- Industry needs more consistency "final output" vs "new data"
- Because you can, should you?
- Explain the key by key
    - EDC data
    - Timestamps etc.
- Mission critical data set – spot on critical vs "extras" = not so important
- EDC audit trail, field vs CRF
- Food animal data collection more difficult than companion
- Data integrity is difficult in the lab setting (benchtop)
    - Part II compliance
- No agreement regarding formatting standardization
- Will it be beneficial to standardize – considering small companies/human industry?
- Avoid bias against biopharma (e.g. use excel sheet)
- Early/timely engagement with CVM to define file-specific requirements
- Continue engagement in industry relations organization
- Use of electronic-capture systems
- Data capture software – improvement and Part II compliant electronic data integrity
- Embracing EDC
- Auditing more and being present (monitoring)
- Add times/steps for QC data review – before final report → concurrent review – plan for it
- Build/plan better for your data management
- To get early feedback
- Lessons learned
- Plan better/realistically for QC and monitoring reviews
- Involve QASR earlier (i.e. protocol review)
- Use e-submitter
- Communicate more frequently with FDA
    - Formal meetings and informal (email etc.)
- Focus on problem areas identified by CVM
- Push for better data quality from academia
- EDC efficiency and more continuous monitoring
- Time delay in setting up CVM meeting
- Be more assertive -- Industry more communication quicker easier
- Alternate suppliers
- Apply quality by design parameters
- Work with USP, contribute to drug subst. monographs, AHI, GADA register multiple sources of API (decreases risk factor for sponsors →causes increase in work for CVM and industry increased costs); Implications → labeling 100
- Increase frequency audits of 3rd party mfgs → risk based approach
- Robust quality agreements linked to change management process

Data quality opportunities cont.

CVM opportunities

- Define different mechanisms used to collect data → drives quality
- Consistency of Reviewer (expertise varies)
    - How to be expert enough
    - Quickly enough
    - Personal experiences trump training
- (20-60 day) review/turnaround for simple revisions (CRFs\forms changes more detailed protocol)
    - EDC vs. paper acceptance
- Inconsistency challenges with reviewers; will CVM accept SEND?
    - If not SEND, CDISC?
    - Of not, some standard?
    - Standardized office document?
- Share best practices
    - Continue SQAs
    - Real-time database of general incomplete items
    - Update data quality webinar
- Continue active participation in industry – relations organizations, eg. AHI, GADA
- Use e-submitter as a mechanism to guide for more consistent data submissions
- Complete revision of GLP registrations
- Utilize data from multiple sources (literature, other companies)
- Consistent expectations of data requirement
    - Review process more harmonized (table of contents)
- Data quality review at beginning – to provide early feedback; Will work with you on minor fixable issues
- Embracing of EDC
- Opportunity to decrease risk by having informal review – Especially for new types or for templates
    - Adoption of template like- send data from human side
    - Standard for exchange of non-clinical data
- Further split up of submission to have time for QC
- Communicate quality issues – specifics
- Provide example workshop
- Define requirements for electronic raw data
- Provide QASR expectations/checklist
- Identify where most of the issues are coming from
- Prioritize data requests
- Involve QASR earlier i.e. protocol review
- Use e-submitter
- Top 10 list or comprehensive reviewers' checklist with can be shared with industry
- Standards for monitoring/quality
- Educate industry on what the challenges are
- Forum with EDC companies
- Guide EDC vendors on Part II and CVM requirements
- Let us know of changes/expectations before they happen
- Review VMF before it is referenced
- Update GFI 83 too gray/high level
- Define increased focus on "hot" topics particularly on older products. Product hasn't changed why an increased focus?
- Stay current on EDC programs; be proactive instead of reactive to changing technologies. More opportunities are becoming available.
- Mutual recognition between major countries
- Disconnect between CVM reviewer and guidance authors
- Sharing information
- Simplify guidance's/consolidate, retire outdated guidance's
- Improve review times with inspections, regulatory discretion
- Consistency at ports (import)
- Locally based (country) auditors/inspectors
- Inspection classification database updated
    - Update it more often/timely manner
- Database for establishment registrations –links to other establishment databases (food, devices, etc.)
- Schedule foreign PAI's in more timely manner (30 day pre-submission notice)
- More collaboration w/ inspection agencies of foreign gov.; more mutual recognition (like EMA initiative)

Global approvals challenges

Group objective: Identify the challenges in the global approvals process for industry and the FDA CVM.

Industry challenges

- Communication with international agencies
- Language/logistics
- Different species/pathogens
- Different standards (LATAM)
- Formatting of documents
- Component acceptability is not equal between regions GRAS - different specs
- Privacy requirements for different countries/regions
- Customs issues sending study materials
- Restrictive foreign policies (e.g. Brazil)
- Rapidly evolving regulatory requirements of different foreign entities getting more difficult
- Lack of internationally accepted GLP certification of CROs
- Dealing with inconsistencies and raw data requirements
- Multiple language documentation
- Difference in electronic system
- Data translation
- Having a CVM checklist will make the process a much smother process to share with stakeholders
- Consistency of data quality between submissions
- Protection of IP
- Educate CVM on new scientific developments
- Registry for clinical trials management for spontaneous disease
- No harmonized guidance for GCP/clinical OECD (additional work); increased complexity, ambiguity overall
- Acceptability of EU generated data
- Data validity/acceptance
- Global studies are more complex (cost/communication)
- Study design challenges/hurdles
- Managing specific requirements
- Understanding marker/cultural differences
- Non-drugs could require registration
- Drug approval vs. market usage
- Managing reg. approval and post-market approval requirements for all countries
- Smaller companies tend to seek approval in other countries with less stringent requirements
- Sharing info between companies
- Labeling requirements
- Time, cost, repeated efforts to go to market
- Afford bridging opportunities of global product
- Potential lack of expertise of personnel in global regulations
- Communication between country R&D centers
- Due to lean practices, difficult to have bandwidth to address global challenges

Global approvals challenges cont.

CVM challenges

- Differences in regulations (may have to change standards)
- Communication with international agencies
- Language/logistics
- Different species/pathogens
- Different standards (LATAM)
- CVM has NIH mentality. Hard to accept things that didn't come from U.S. Are we really the "gold" standard? Or just a different" standard?
- How does CM determine "acceptability"/"safety" of a drug?
- Are we really making something safer or imposing requirements because they are available? What is the added value to safety, efficacy? (Post approval requirements) Broaching requirements. Changing standards – moving target!
- FDA vs. "Others" (Regulatory Agencies): FDA has to "pre-approve' other to accept their data. Resource challenge. What is criteria?
- Acceptance of protocols and action plans that is/are collaborated by multiple regions
- When we get to mutual recognition; how do we broaden to other regions?
- Procedural differences in pivotal study parameters
    - Statutory requirements more stringent than other countries
    - Harmonization takes time and effort
    - International relations
- Consistency between reviewers
- Ambiguous feedback
- Speed of review/feedback
- On tip of new science advancements
- OECD vs FDA GLP; Dual inspection (how to manage diplomatically), mapping regulations (eg. Chemical quality)
- Bureaucracy
    - Funding and resources
    - Differences/variation in standards
    - Be more global/aware
    - Acceptability of EU generated data
- Resources available to begin harmonization
- Negotiating balance among nations
- Industry utilizing eDc for global studies
- Different regulatory requirements
- Vet practices discrepancies for animal studies
- Legal landscape for CVM
- Global electronic submission of raw data (data format)
- Access to global data/dossiers

Global approvals opportunities

Group objective: Identify the opportunities in the global approvals process for industry and the FDA CVM.

Industry opportunities

- Collaboration within and between agencies and with other agencies
    - Split up sections to review EMA? Resource savings
    - Done before with Canada and Australia
    - Learnings across countries
- Streamlines for industry (more work collaboration up front but faster on back end)
- Harmonization in standards (x3)
- QBR format different than other regions. How can we work to develop a globally acceptable format?
- API – If approved CDER vs CVM for human use should be acceptable for vet. Decreases need for manpower. If under import alert for human use, is it really unacceptable for vet use? Can it be evaluated? Case by case evaluation required
- Acceptance of protocols and action plans that is are collaborated by multiple regions
- Engage key agencies earlier to gain scientific advice with implement
- EDC allows for easier submissions in different countries
- Better management of resources
- Matrix international requirements for better study design. List of all essential items for a study submission
- R&D best practices group form all companies in industry
- Collective group to "lobby" CVM when appropriate or present common concerns
- Use of human data to benefit vet market
- Conservation of resources (e.g. money, time) global learning decreased complexity (e.g. VICH TAS)
- Sponsor collaboration (between regions)
- Reps/managers per region working on global study design
- AHI organizations in Europe? Collaboration?
- Incentive to explore new opportunities
    - Risk: Reward
    - Can take increased risk because reward in multiple countries is greater
- Broaden impact of drug; extend use of drug to small markets/countries
- Acquire as much information from existing studies as possible – collaboration between companies
- Less studies, time to approval and overall cost
- Communicate global strategy and gain global endorsement
- Industry to adopt a single dossier approach
- Remove legal aspect from the regulatory solution
- Industry support development and interaction with FDA personnel dedicated to global registrations

Global approvals opportunities cont.

CVM opportunities

- Collaboration within and between agencies and with other agencies
    - Split up sections to review EMA? Resource savings
    - Done before with Canada and Australia
    - Learnings across countries
- Streamlines for industry (more work collaboration up front but faster on back end)
- Harmonization in standards
- FDA inspection notice – prior notice for foreign inspection vs "unannounced" in US.
- API – If approved CDER vs CVM for human use should be acceptable for vet. Decreases need for manpower. If under import alert for human use, is it really unacceptable for vet use? Can it be evaluated? Case by case evaluation required
- Acceptance of protocols and action plans that is are collaborated by multiple regions
- When we get to mutual recognition, how do we broaden to other regions?
- RCC program to expand to other regions/countries
    - Abbreviated approval on products on products approved in other countries with established safety/efficacy
    - Global dossier format
- Utilize resources internationally by accepting reviews/inspections/approval form other agencies
- Continue effort in aligning with other regulatory agencies
- Coping with international data
- Shifting requirements/prefer to stay consistent
- Auditing international API manufacturing
- Opportunity for sharing of knowledge and collaboration
- Recognition of CEPs of APIs
- Finalize reciprocity with EMA (major) international regulatory bodies
- Bridging data
- Set standards
    - Harmonization
    - Incorporation
    - Cooperation – protection for IP between countries
    - Trust with other regulatory agencies to facilitate drugs coming into US from other countries
        - Why re-review previous approvals?
- Who are stakeholders that can dialogue with CVM?
- Harmonization across agencies globally
    - Cost
    - Philosophy
    - National regulations
    - Trust
    - Electronic submission tool
- Streamline process for acceptance of products
- Education on EMA standards, approvals, etc. so communication/collaboration etc. is easier
- Harmonization creates efficiency and reduces resource redundancies (money/people/time)
- Shorten review cycles by leveraging data from other countries
- Harmonization/alignment
    - Regulatory requirements
    - Quality standards
    - Test guidelines/guidance
- Recognize guidelines and approaches of other countries
- Be global player
    - Increase knowledge of disease not present U.S. currently
- Set requirements – goal post always movers
- FDA be a global leader in global communications and harmonize those communications

Supply chain challenges

Group objective: Identify the challenges in the supply chain for industry and the FDA CVM.

Industry challenges

- Lack of transparency between supplier and customer
- Lack of transparency of resolution
- Changes in import requirements without notification
- Unclear import picture
- Inconsistency
- VM are small customers to supplier
- Dual inspections
- Distribution systems immature in smaller entities
- Develop SOPs to capture best practices, institutional knowledge and experience
- Identifying quality CMO's
- Resolving DMF/deficiencies when they don't have access to DMF?
- Import alert
- GMP status
- Understanding without seeing
- International supplier education
- Minimize risk by looking forward and developing a backup plan
- Tracking new innovation to NADA is too costly in general
- Not predictable, fully functional plant gets a 483 and a new application can't be submitted
- Explaining to CEOs etc. the realities and time-frame of regulatory interactions
- Human health companies see too much risk in sharing their toxicology data –risk to their approval/product
- Limited facilities who will work on animal health drugs (sterile, purification)
- Lack of understanding of customs around importation requirements leads to blocks at the border
- Shared risk
- Motivation
- Resources (oversight, CMO selection) and people
- Compounders
- Reducing trial and error with CMOs
- Qualification/Selection of CMOs
    - COG's
    - Business

Supply chain challenges cont.

CVM challenges

- Supply chain interruption can impact multiple registrations (impact animal health)
- Drug shortages
- Increased reliance on foreign suppliers (increased foreign inspections)
- Dual inspections
- Distribution systems immature in smaller entities
- Understanding by manufacturer
    - Final intermediate
    - Starting material
- Are there standardized requirements documents for customs interactions?
- "Cross talk" is needed in the process between the pre-approval and post- approval phases to provide continuity
- Make the ORA person to call very obvious
- Harmonization of requirements on
    - Inspection process
    - Approval process
    - Regulations and guidelines
- Risk/benefits to eliminate or prevent drug shortages
- Understanding without seeing
- International supplier education
- Resource issues – need more resources/people
- Compromising/proactive –vs- reactive
- Negotiation with Brazil H.A. on manufacturing of Animal Health drugs with Human Health Drugs
- Define legal market for unapproved drugs
- Human health regulations in place but not animal health
- Massive time sink for FDA when supply chain interruptions happen
- Providing timely inspections overseas
- Understanding supply chain challenges for industry
- Lack of time to be flexible on review or to communicate decision making process clearer especially between 60 day and full cycle review
- Provision of better guidance on dissolution requirements (and anything else that gets discussed with every company separately)
- Consider for the next quarterly meeting. Companies can provide case studies
- Shared cost; appropriate cost
- Resources
- Completeness (all available CMOs)
- Political issues/global harmonization
- Enforcement of CMO requirements

Supply chain opportunities

Group objective: Identify the opportunities in the supply chain for industry and the FDA CVM.

Industry opportunities

- Audit the facilities early and often
- Beware of issues that have been encountered with suppliers– don't use if you have other options
- Become more of a partner with your supplier on the technical submission to help assure FDA's concerns are being addressed
- CTD format for VMF/DMF helps point out what may be missing
- Audit open part of DMF – early
- Even if not in CTD
    - List of information required –share with your suppliers
- Making sure your suppliers are aware of the requirements
    - USP – heavy metals vs. elemental impurities
- Collaborating with USP, PDA, etc. early to make sure we understand and can communicate to suppliers what requirements are
- Vendor quality metrics are required
    - What metrics would be applicable to qualify a broker?
- Sponsor broker
    - Harmonize documentation requirements with multiple brokers
- Utilize expertise of 3rd party vendors for drug listing
- Cases of months long holdups= Outside of controlled conditions = Loss of product
- Limited ability to influence suppliers
- Educating our suppliers/supply chain in regulatory aspects
- Educate 3rd party suppliers on what we expect from them with regard to paperwork for submission/inspection readiness
- When API supplier has a 483 allow sponsor to submit dossier while the 483 is resolved to review in parallel
- Explaining to the FDA that these issues aren't due to lack of effort by sponsors
- Industry can encourage CVM to spend time influencing international/overseas manufacturers
- Preferred supplier list
- Better communication among supply chain
- Supplier auditing
- Improve supplier audit process
- Relationship building
- Flexibility with vendors and approval on individual case basis
- Make decisions based on science – not regulation
- Medically Necessary Vet. Drugs- Seeking changes to supply chain
- Add a Q/A session in the initial 30-day evaluation period
- Develop/find back up supplier in case a problem occurs with 1st supplier
- Come to CVM with a solution and scientific justification

Supply chain opportunities cont.

CVM opportunities

- Using Memorandum of Understanding from other country for facility – utilize more effectively
    - Need to understand the country to country requirements/focus to make sure concerns are captured from each division/country
- 2 Phase CMC Process
    - Reduce risk if submit DMF in Phase 1
- ORA has been more prospective in doing on-site reviews earlier on in the review process
- If you are involved enough to know FDA is inspecting for something at a location - you can alert the investigator that you have an additional item at that facility and would they look at it
- Adopt EPA process for access to data toxicology with appropriate compensation to the original sponsor
- Having a notification process if a change is identified esp. from a supplier (out of sponsor control)
- Allow iterations for changes if there are minor issue; have a stop clock equivalent to make small changes/provide answers as informal mechanism
- Other agencies allow more changes in drug substance as long as drug product is same as FDA
- Bring back end review amendments
- Is timing of review more important than approval? It feels like 180 day is sacred
- Any modification of the process to avoid incomplete and then an additional 12 months to achieve approval
- Come up with a different process to track statistics of a time line – ADUFA reduced timeline from SOD to 180 day times 3 is a long time
- Limited ability to influence suppliers
- Educating our suppliers/ supply chain in regulatory aspects
- Educate our 3rd party suppliers on what we expect of them with regard to paperwork for submission/inspection readiness
- When API supplier has a 483 allow sponsor to submit dossier while the 483 is resolved to review in parallel
- Explaining to the FDA that these issues aren't due to lack of effort by sponsors
- Industry can encourage CVM to spend time influencing international/overseas manufacturers
- Increased communication with sponsor and FDA inspector
- Differentiate impact of 483 within facility
- Fast track for communication
- Flexible approach to input of OAI Inspectors
    - Reactivation of INADA (shorter)
    - Expedited review of secondary sources
    - Allow for multiple raw material sources (initially!)
- Separating data integrity concerns from API/Product quality
- CVM expectations of CMOs
    - FDA inspection early
    - Quality of agreement
    - Designated sponsor oversight contact
- Plan for CMC plan – Concurrence
    - Broker
    - Monetary consequence
    - Risk mitigation
- Selection process
- Shared data bank (DMF, Cost repository)
- Audit sharing globally
- Pre-approval of CMO (Credit Score)