In Vitro Bioequivalence Data for a Topical Product: Chemistry Review Perspective

FDA Public Workshop

Topical Dermatological Generic Drug Products:
Overcoming Barriers to Development and Improving Patient Access

October 20th, 2017

Pahala Simamora, Ph.D.
Division of Liquid-Based Products
Office of Lifecycle Drug Products
OPQ/CDER

Disclaimer

This presentation reflects only the views of the author and should not be construed to represent FDA's views or policies.

Presentation Outline

- ANDA Review
  - Integrated Quality Assessment (IQA)
  - Risk Assessment
  - Information being reviewed
- Product Development
  - Expectation/Recommendations
  - Points/tips for consideration in topical formulation design
  - Complex Drug Products
- Acyclovir Cream Draft Guidance
- Common Deficiencies/Recommendations
  - Examples for topical semisolids
- Summary

OPQ's ANDA Review (Quality Part)

Performed via Integrated Quality Assessment (IQA)

- Team-based review that incorporates inspection
- Includes a formal risk assessment to best focus review and inspection
- Results in a single collaborative review/assessment which provides OGD a recommendation on ANDA approvability

- IQA team:
  - Drug Substance
  - Drug product
  - Process
  - Facility (including ORA investigators)
  - Microbiology
  - Biopharmaceutics
  - Others (as needed)
- Team led by
  - Application Technical Lead (ATL)
  - Regulatory Business Process Manager (RBPM)

Reviewers + Investigators → ANDA approvability and facility acceptability

Risk Assessment

- Risk Assessment is a critical component of the review process
  - Defines the scope and extent of the review
  - Risk assessment increases efficiency and effectiveness of the review by focusing on the critical areas and potential failure modes that pose risk to patients

Drug Product CQAs	Initial Risk Ranking FMECA Score	Comments	Updated Risk Ranking after Review Cycle #	Comments
CQA1				
CQA2				
CQA3				
CQA4				
CQA5				
CQA6				
CQA7				
Other CQAs				

Risk Assessment

Product Property/CQA	Initial Risk Ranking	Comments	Updated Risk Ranking	Comments
Assay (Active)	18	Meets finished product release and stability criteria. No trend.		Assay meets release and stability criteria
Assay (Volatile Solvent Content)	N/A		N/A	
Chemical Stability (All CQAs)	48	All CQAs meet product specification		All attributes meet stability specification.
Bulk Content Uniformity (BCU)	36	The API is fully dissolved in the formulation. Assay and batch uniformity is part of in-process controls. Note: please check sampling plan (locations and # of samples)		Assay meets bulk specification.
Uniformity in Containers	36	The API is fully dissolved in the formulation. Uniformity in the container is controlled.		Assay meets bulk specification
Microbial Limits	18	Microbial control is part of the finished product specification.		The USP <5l> test showed that the DP is sufficiently antimicrobial. The product is tested as per USP<61> and <62>. Results at release and stability meet criteria.
Weight Loss	18	Weight loss is controlled in finished product.		No apparent weight loss on stability.

Product Property/CQA	Initial Risk Ranking	Comments	Updated Risk Ranking	Comments
pH	27	Drug product is an emulsion and pH range should be comparable to the RLD. The pH is controlled in DP.		pH appeared to be critical for API stability in the product. The target pH is comparable to the RLD data. Also, the test results from stability study did not show any trending.
Viscosity	48	Drug product viscosity may impact drug influx through skin. Viscosity is controlled in DP.		Viscosity is comparable to RLD. Stability data also meet stability criteria, without any discernable trend. The rationale to use viscosity method was justified in response to IR#1. Both test and RLD showed comparable flow behavior.
Physical Stability (Solid state in drug product)	36	API is fully dissolved in the formulation. Note to reviewer: Please verify that the API is (and remains) dissolved in the DP throughout shelf-life.		API is soluble in the formulation. Therefore, solid state is not applicable. API solubility in the formulation is adequate. However, to ensure the DP is free from drug crystals/precipitation, the applicant is asked to provide microscopy data and include control strategy to the specification. Per IR#l, microscopy data showed no particles in the samples, remain in dissolved state.
Physical Stability (API precipitation)	32	API is fully dissolved in the formulation		API solubility in the formulation is adequate. However, to ensure the DP is free from drug crystals/precipitation, the applicant is asked to provide microscopy data and include control strategy to the specification. Per IR#l, microscopy data showed no particles in the samples, remain in dissolved state. A criterion to evaluate DS particles has been added.
Physical Stability (Phase Separation/Sedimentation)	48	The drug product is an emulsion. Phase separation is possible. Globule size in DP is controlled.		Homogeneity test to verify phase separation is included in the specification. Stability data did not show any phase separation.
API Particle Size (for suspensions)	32	API is fully dissolved in the formulation		API is fully dissolved in the cream base and its solubility is adequate in the formulation.
Particulate Size (for multi-phasic semi-solid products (e.g. emulsions (globule/droplet), etc.)	64	Drug product is an emulsion. Globule size is an important quality attribute. Globule size is controlled in the DP.		Globule size is controlled in the product. It is comparable to RLD. The globule size did not change significantly during stability study.

ANDA Review (Quality Part)

Information provided in Module 3

- **Drug Substance**
  - S1 General information
  - S2 Manufacture
  - S3 Characterization
  - S4 Control of DS
  - S5 Reference standards/materials
  - S6 Container Closure System
  - S7 Stability
- **Drug Product**
  - P1 Description/Composition of DP
  - P2 Pharmaceutical Development
  - P3 Manufacture
  - P4 Control of Excipients
  - P5 Control of DP
  - P6 Reference standards/materials
  - P7 Container Closure System
  - P8 Stability

Please ensure the information is complete and accurate

Product Development

Expectation/Recommendations:

- Conduct risk-based approach to product development
- Demonstrate product understanding and process understanding
- Establish Quality Target Product Profile (QTPP)
- Identify Critical Quality Attributes (CQAs)
- Identification of potential failure modes and mitigation of risk factors
  - Formulation design
    - Material attributes ⟹ Critical material attributes (CMAs)
    - Process parameters ⟹ Critical process parameters (CPPs)
  - Product/process understanding and optimization

Example of QTPP of a generic X Cream USP, N%

QTPP Element	Target	Justification
Dosage form	Cream	Pharmaceutical equivalence requirement: Same dosage form
Route of administration	Topical	Pharmaceutical equivalence requirement: Same route administration
Dosage strength	N% w/w	Pharmaceutical equivalence requirement: Same strength
Stability	At least 24-month shelf-life at room temperature.	Equivalent to or better than RLD shelf-life, pharmaceutical equivalence requirement.
Drug product quality attributes	Physical Attributes: rheological behavior, drug particle size, oil globule size, pH, in vitro release test	Pharmaceutical equivalence requirement: Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality)
	Identification	
	Assay	
	Homogeneity and Tube Uniformity	
	Degradation products/Residual Solvent	
	Preservatives Content	
	Microbial Limits	
Container closure system	Identical primary packaging to RLD	Match RLD and for patient acceptability
Package Integrity	No failure	Needed for stability, clinical effectiveness and safety
Administration	Concurrence with RLD labeling	Information provided in the RLD labeling

- Information regarding the RLD
- Sources: Labeling, Literature, patents, etc.
- Information collected: dosage form, strength, active and inactive ingredients, dose and administration, CCS, storage conditions, etc.

Example of CQAs of generic X Cream USP, N%

CQA	Target	Justification
Identification*	Positive for Active	Needed for clinical effectiveness
Assay	90 – 110%	Needed for clinical effectiveness
Impurities	Impurity A: NMT 0.2% Impurity B: NMT 0.2% Any individual unknown: NMT 0.2% Total Impurities: NMT 0.5%	Needed for safety
Homogeneity and Tube Uniformity	Top, middle and bottom of three containers, nine assay values should be within 90.0% to 110.0% label claim and RSD is not more than 5%	Needed for clinical effectiveness
Physical Attributes Rheological behavior particle size, pH, in vitro release test Oil globule size	Match RLD	Needed for clinical effectiveness and patient acceptability To demonstrate similar arrangement of matter to RLD (Q3)
In Vitro Release Test	Match RLD	In-vitro Surrogate used to guide BE
Microbial Limits	Meet USP <61>	Needed for safety
Residual Solvents*	Meet USP <467>	Needed for safety

*Formulation and process variables are unlikely to impact this CQA. Therefore, the CQA will not be discussed in detail in PDR.

CQAs for Generic Topical Products

- Comprehensive testing of multiple lots of RLD product
- Fresh lots and aged lots at or close to expiry
- Mean value and variability of all quality attributes for the RLD
- Identification and quantification of inactive ingredients
  - reverse engineering to obtain Q1/Q2 formula
- Physical attributes:
  - appearance, color, odor, pH, rheological behavior, particle size, globule size, etc.
- Chemical attributes:
  - drug polymorphic form, assay, impurity profile, homogeneity, etc.
- Release rates (IVRT/IVPT)

Identification of Potential Failure Modes and Mitigation of Risk Factors

Formulation Component	Potential Risk	Potential Impact on Drug Product CQAs	Action Plan
Drug Substance	Particle size or morphology change	Shift in content uniformity, drug release and dermal distribution of the drug.	Micronized drug substance with identical solid state form to the RLD from a qualified source is used for the drug product manufacturing and particle size is measured as part of drug substance release testing with a tight limit of D90 of not more than 10 µm. Drug concentration in the cream preparation needs to be monitored to ensure homogeneity of drug distribution in the drug product matrix.
White Petrolatum	Viscosity variation	Shift in viscosity	White petrolatum from a qualified source is used for the drug product manufacturing. Consistency is measured as part of every white petrolatum lot via release testing using more stringent limits than USP limits to ensure product viscosity closely matching that of the RLD.
Propylene Glycol	Unidentified	--	--
Methyl and Propyl Paraben	Possible chemical instability of preservatives in the cream	Shift in preservative content in the cream	The antimicrobial properties of the drug product are studied during product development stage through antimicrobial effectiveness test. Based on the results from these microbial studies, set an adequate lower limit of preservative content for drug product release and stability specifications to reduce the risk of microbial contamination.
Purified Water	Increased water activity and bacteria growth potential	Drug product microbial limit	Quality system, cGMP

Components of Topical Drug Products

Component Functionality	Component description	Example
Emollient/ stiffening agent/ ointment base	Main structure-fom1ing materials for semisolid dosage form Based on their composition and physical characteristics, the USP classifies ointment bases as hydrocarbon bases (oleaginous bases), absorption bases, water-removable bases, and water-soluble bases.	Carnauba wax, Cetyl alcohol, Cetyl ester wax, Emulsifying wax, Hydrous lanolin, Lanolin, Lanolin alcohols, Microcrystalline wax, Paraffin, Petrolatum, Polyethylene glycol, Stearic acid, Stearyl alcohol, White wax, Yellow wax
Emulsifying agent/ solubilizing agent	Surfactants used to reduce the interfacial tension to stabilize emulsions and to improve the wetting and solubility of hydrophobic materials	Polysorbate 20, Polysorbate 80, Polysorbate 60, Poloxamer, Emulsifying wax, Sorbitan monostearate, Sorbitan monooleate, Sodium Lauryl) sulfate, Propylene glycol monostearate, Diethylene glycol monoethyl ether, Docusate sodium
Humectant (polyols)	Promotes the retention of water in the system	Glycerin, Propylene glycol, Polyethylene glycol, Sorbitol solution, 1,2,6 Hexanetriol
Thickening/ gelling agent	Increases viscosity Main structure-fom1ing materials for gels	Carbomer, Methyl cellulose, Sodium carboxyl methyl cellulose, Carrageenan, Colloidal silicon dioxide, Guar gum, Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose, Gelatin, Polyethylene oxide, Alginic acid, Sodium alginate, Fumed silica
Preservative	Prevent microbial growth	Benzoic acid, Propyl paraben, Methyl paraben, Imidurea, Sorbic acid, Potassium sorbate, Benzalkonium chloride, Phenyl mercuric acetate, Chlorobutanol, Phenoxyethanol
Permeation enhancer	Increases the permeation by promoting the diffusion, partitioning, or the drug solubility of an active ingredient through the stratum corneum	Propylene glycol, Ethanol, Isopropyl Alcohol, Oleic acid, Polyethylene glycol
Chelating agent	Binds metal ions to minimize metal-catalyzed degradation and to enhance the preservative effect	Ethylene diamine tetraacetate
Antioxidant	To minimize oxidative deterioration	Butylated hydroxyanisole, Butylated hydroxytoluene
Acidifying/ Alkalizing/ buffering agent	Maintain a proper pH for the dosage form	Butylated hydroxyanisole, Butylated hydroxytoluene Citric acid, Phosphoric acid, Sodium hydroxide, Monobasic sodium Phosphate, Trolamine
Vehicle/ solvent	Facilitate the dispersion and/or dissolution of API	Purified water, Hexylene glycol, Propylene glycol, Oleyl alcohol, Propylene carbonate, Mineral oil

Many excipients used in topical drug products have dual or multiple functionalities

Chang et al., AAPS Journal, 16(1), 41-52, 2013.

Points to Consider in Topical Formulation Design (1/2)

Area	Consideration	Comment
• Drug Substance	• Quality of API and adequate DMF • Residual solvents • Physical state of API, e.g., melting point (liquid, low melting point, or high melting drug), micronized drug. polymorphs, etc. • Solubility of API in hydrophobic and hydrophilic vehicles • Cost and availability issue	• The selection of an API source is a central part of generic drug formulation development. Pay attention to the impurities which are not present in the RLD and residual solvents which are not listed in the ICH Q3C. • Preformulation data are critical for generic formulation and process development. This data may include API's physical state, particle size, morphic form, solubility properties, sensitivity to light, moisture or air, and degradation pathway.
• Excipients	• Compendial material vs. non-compendial material	• Compendial excipients usually are preferred; non-compendial materials are acceptable with justifications.
	• Residual solvents	• The firm is required to provide residual solvent data and test specifications to demonstrate that its drug product is in compliance with USP <467> requirements.
	• Physical state of excipients, e.g., melting point (liquid, low melting point or high melting excipient)	• Excipient compatibility study using a binary mixture is desired to ensure the drug product stability prior to the drug product development However, in many cases, homogenous mixing of the selected excipient and the API is impossible. Different excipient compatibility study design can be used.
	• Excipient compatibility	• Generally, the excipients used in the RLD are presumed compatible with the drug substance. The formulator should be aware that different vendors or grades may contain different impurities, which in turn may trigger the drug degradation.
	• Hydrophilic-lipophilic balance (HLB) and type of emulsifier	• It is prudent to keep the type of emulsifier(s), hydrophilic-lipophilic balance (HLB) of emulsifier and solvent to emulsifier ratio similar to those of the RLD, if the test formula is different from the RLD.
	• Functionality	• Excipients used in topical formulation can have emollient and hydrating effects and make the skin softer, smoother, and firmer.
• Physicochemical properties of drug product	• Target product profile such as dosage form, viscosity, pH, strength. release profile, in vitro permeation rate, homogeneity, etc.	• Characterization of the RLD in terms of product attributes and stability profile is essential for the generic drug development. • Quality target product profile and critical quality attributes need to be identified as a part of quality by design.

Chang et al., AAPS Journal, 16(1), 41-52, 2013.

Points to Consider in Topical Formulation Design (2/2)

Area	Consideration	Comment
• Container closure system	• Selection of container closure system as close to that of the RLD as possible. Package compatibility	• Material of construct for the selected container closure system should be similar to that of the RLD. It is prudent to conducta preliminary stability study using the final formula to demonstrate package compatibility in the formulation development stage.
• Chemical stability	• Consistency for chemical properties of the drug product over time	• The goal, if possible is to maintain assay value as close to 100% label claim and impurity level as close to 0% throughout the shelf-life period.
• Physical stability	• Consistency for physical properties of the drug product over time	• The goal, if possible is to maintain physical properties of the drug product throughout the shelf-life period. Potential problems include separation of phases, syneresis, pH change, specific gravity change, viscosity change, homogeneity of dosage form, etc.
• Manufacturability and scalability	• Process equipment • Process parameters, such as agitation, rate, mixing time, temperature, etc.	• Appropriate process equipment and process parameters need to be identified as a part of quality by design. • Based on the past scale-up experience of the same type of formulation and process as well as engineering principles, the commercial size scale up and equipment changes should he justified.
• Preservative efficacy	• Selection of preservatives • Optimization of • preservative concentration • Minimum acceptable limit of preservatives	• The minimum acceptable limit of preservatives in a drug product must he demonstrated by performing a microbial challenge assay as specified in USP <51>.
• Patient's acceptance	• Consistency of the preparation • Sensory perception before, during and after application	• Patient's acceptance is the key for a successful drug product commercialization in a competitive marketplace. A test panel evaluating the consistency, washability, cosmetic feel, and rub-in properties of topica.l drug products can be used to identify a commercially viable drug product.

Chang et al., AAPS Journal, 16(1), 41-52, 2013.

What is a "Complex" Drug Product

- Complex Drug Products are defined[3] as those with:
  - **Complex active ingredients**
    - peptides, polymeric compounds, complex mixtures of APIs, etc.
  - **Complex formulations**
    - liposomes, colloids
  - **Complex routes of delivery**
    - locally acting drugs
  - **Complex dosage forms**
    - transdermals, metered dose inhalers, extended release injectables, etc.
  - **Complex drug-device combination products**
    - auto injectors, metered dose inhalers
  - **Other products where complexity or uncertainty concerning the approval pathway** or possible alternative approach would benefit from early scientific engagement

[3] Source: *GDUFA II Commitment Letter* accessible on www.fda.gov at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex Topical Generic Products

- Topical products can be “complex” in multiple ways
  - Complex formulation:
    - e.g., a foam, gel, cream, etc.
  - Complex route of delivery:
    - e.g., locally acting; topical dermatological
  - Complex dosage form:
    - e.g., a topical patch
  - Complex drug-device combination products:
    - e.g., a topical solution in a metered dose pump

Complex Topical Drug Products

- As the complexity of a formulation, dosage form, drug product, route of administration, site of action and/or the mechanism of action increases so do the potential failure modes for bioequivalence and therapeutic equivalence

- With a sufficient **product and process understanding**, relevant complexities can be identified and addressed systematically for the generic drug product

Product Understanding

- **Product quality characterization can describe:**
  - The composition of the drug product
  - How critical is the composition of inactive ingredients?
  - How critical is the grade of each inactive ingredient?
  - The phase states and arrangement of matter
  - Drug diffusion within the dosage form
  - Drug partitioning from the dosage form into the skin
  - How critical is the inertness of the container closure system (e.g. are there adsorption/absorption issues)?
  - How critical are the product dispensing stresses/forces?
  - Drug delivery & bioavailability at the target site
  - Skin (de)hydration, irritation or damage
  - Metamorphosis of the dosage form on the skin

Process Understanding

- How critical is the sequence of mixing?
- How critical are mixing rates and durations?
- How critical are temperatures and rates of change?
- How critical are the orifice diameters, tube lengths, pressures, etc. during transfer, holding, packaging?
- Etc.

Draft Guidance on Acyclovir Cream-*In Vitro* Option

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

A. The test and RLD products are qualitatively (Q1) and quantitatively (Q2) the same...

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization... [Q3 properties]*

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT)... using an appropriately validated IVRT method

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT)... using an appropriately validated IVPT method

* Reviewed by OPQ/OLDP

Draft Guidance on Acyclovir Cream-*In Vitro* Option

B. **Physical and Structural Comparison**

- Lots of test and RLD products evaluated in IVRT study should be the same as those evaluated in IVPT study.
  - These lots should be included among those used in Q3 evaluation
- The influence of any differences in container closures between test and RLD products, which may influence the physicochemical properties of the cream when dispensed, should be considered in the design of the studies
- Perform in a manner compatible with applicable principles of GLP

Draft Guidance on Acyclovir Cream-*In Vitro* Option

Physical and Structural Comparison:

- Assessment of appearance
- Analysis of acyclovir polymorphic form in the drug product
- Analysis of particle size distribution and crystal habit
- Analysis of the rheological behavior
- Analysis of specific gravity, water activity, pH and any other potentially relevant physical and structural similarity characterizations

Draft Guidance on Acyclovir Cream

- The draft guidance is very comprehensive and provides clear criteria and tests for evaluation and comparison
  - Q1/Q2
  - Q3 properties → Risk Identification/mitigation
  - IVRT Risk Mitigation → Product/Process Understanding
  - IVPT

ANDA Review (Quality Part) - Recap

Information provided in Module 3

- Drug Substance
  - S1 General information
  - S2 Manufacture
  - S3 Characterization
  - S4 Control of DS
  - S5 Reference standards/materials
  - S6 Container Closure System
  - S7 Stability
- Drug Product
  - P1 Description/Composition of DP
  - P2 Pharmaceutical Development
  - P3 Manufacture
  - P4 Control of Excipients
  - P5 Control of DP
  - P6 Reference standards/materials
  - P7 Container Closure System
  - P8 Stability

- *Product development information resided in P2 section*
- *Please ensure the information is complete and accurate*

Common Deficiencies* – Some Examples

Observation	Recommendations
Drug Substance (raw material) • API is said to exhibit no polymorphism but literature reports indicate otherwise • Polymorph characterization is missing or incomplete • Solubility data is not provided • Hygroscopicity is indicated but no supporting data is provided	Complete information on the physicochemical properties/CQAs of the API that may impact DP quality, performance, patient safety and/or efficacy should be provided. • PSD • Polymorphism • Hygroscopicity • Solubility (e.g., as a function of pH or % of co-solvents) • Melting point • etc.

*References which discuss extensively common deficiencies in ANDAs are provided in slides 31-33

Observation	Recommendations
Drug Product Appearance - Incomplete appearance description	More detailed description should be provided, e.g. free of lumps, free of foreign matter, homogeneous consistency, no phase separation, etc. Description (of finished product) should be part of the appearance test, e.g. package appearance (inner and outer wall) to check for seal integrity and any discoloring of inner wall as well as label evaluation

Observation	Recommendations
Drug Product CQAs (example Q3 properties) are missing or incomplete or not controlled	A comprehensive, comparative quality attribute evaluation of both the RLD and the generic drug candidate should be included. Ideally, an evaluation of three separate lots of the RLD with different expiry dates (i.e. a fresh lot and lots close to expiry) is recommended to provide a complete understanding of the variability of each quality attributes for the RLD. These Q3 attributes may include the following: pH, globule size, drug particle size, rheological behavior, drug polymorphic form and in vitro release rate, etc.

Observation	Recommendations
Drug Product Thermal cycling data is missing	Thermal cycling studies should be included as a part of stability studies to assess any impact of transportation temperature conditions on the quality of dermatologic drug products. Two storage orientations (i.e. horizontal or inverted vertical and upright vertical) are also recommended for the exhibit batches to support the ANDA filing (per *Guidance for Industry, ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers, May 2014)*

Observation	Recommendations
Drug Product Q3 attributes are missing or incomplete	A comprehensive, comparative quality attribute evaluation of both the RLD and the generic drug candidate should be included. Ideally, an evaluation of three separate lots of the RLD with different expiry dates (i.e. a fresh lot and lots close to expiry) is recommended to provide a complete understanding of the variability of each quality attributes for the RLD. These Q3 attributes may include the following: pH, globule size, drug particle size, rheological behavior, drug polymorphic form and in vitro release rate, etc.

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Summary/Conclusions:

- ANDA review is conducted via an integrated quality assessment process (IQA) involving multiple disciplines
- Risk assessment is utilized to define the scope and extent of the IQA
  - Improves efficiency and effectiveness by focusing the review on the critical areas and potential failure modes that pose risks to patients
- Risk-based approach to product development is recommended
- The Agency has been providing clear information to support high quality ANDA, e.g.,
  - Detailed criteria and tests for the in vitro option in the case of the development of the generic version of acyclovir cream
  - Multiple articles and presentations on common ANDA deficiencies
- It is important that the information provided in the ANDA is complete, accurate and of high quality in order to achieve 1st cycle approval

Acknowledgements

- Susan Rosencrance, Ph.D.
- Bing Cai, Ph.D.
- Sam Raney, Ph.D.
- Richard Chang, Ph.D.