M. Pharm (Drug Regulatory Affairs)

I SEMESTER

Theory Papers hrs/week

I.	Drug Regulatory Affairs-I	3
II.	Drug Regulatory Affairs-II	3
III.	Pharmaceutical Jurisprudence (Forensic Pharmacy)	3
IV.	Laws related to Drug Product Design, Safety & Environment	3

Practicals hrs/week

I.	Drug Regulatory Affairs-I & II	9
II.	Pharmaceutical Jurisprudence and Laws related to Product design	9

II SEMESTER (Theory Papers)

I.	Drug Development & Approval Process	3
II.	Regulation of Clinical and Preclinical Studies	3
III.	Good Manufacturing Practices	3
IV.	Formulation Production Management	**3**

Practicals hrs/week

I.	Drug Development & Approval Process	9
II.	Formulation Production Management	9

III SEMESTER

Comprehensive Viva-voce
Seminar on Dissertation Topic (Project Work) (Introductory)

IV SEMESTER

Final Seminar on Dissertation (Results)
Dissertation

M.Pharm. I Semester

Theory	Marks	Lectures	Tutorials	Practicals
Paper - I	100	3	2	-
Paper - II	100	3	2	-
Paper – III	100	3	2	-
Paper – IV	100	3	2	-
Practicals				
Paper – I	100	-	-	9
Paper – II	100	-	-	9
Seminar	50			
Assignment	50			
Total	**700**	**12**	**8**	**18**

M.Pharm. II Semester

Theory	Marks	Lectures	Tutorials	Practicals
Paper - I	100	3	2	-
Paper - II	100	3	2	-
Paper – III	100	3	2	-
Paper – IV	100	3	2	-
Practicals				
Paper – I	100	-	-	9
Paper – II	100	-	-	9
Seminar	50			
Assignment	50			
Total	**700**	**12**	**8**	**18**

M.Pharm. III Semester

	Marks
Seminar (Pertaining to the topic of research and work plan)	50
Comprehensive viva-voce	50
Total	**100**

M.Pharm. IV Semester

	Marks
Seminar (Experimental Work, Results, Discussion and Conclusion)	50
Dissertation evaluation	200
Dissertation Viva-Voce	50
Total	**300**

PAPER I. DRUG REGULATORY AFFAIRS – I(As per USA): (Theory)
3 hrs/week

1. A detailed study of Federal Food, Drugs and Cosmetics Act of USA, restricted to human drugs, cosmetics and biotechnological products, with special emphasis on:
   a. History of drug regulation in USA.
   b. Organization and functions of FDA, including historical developments.
   c. General definitions.
   d. Adulterated & misbranded drugs/cosmetics/biotechnological products.
   e. OTC drugs, Orphan drugs, Orange Book and Fast Track Products.
   f. General penalties as applicable to drugs, cosmetics and biotechnological Products.

2. A detailed study of Federal Food, Drugs and Cosmetics Act of USA, restricted to human drugs, cosmetics and biotechnological products, with special emphasis on:
   a. General drug approval process.
   b. Investigational New Drug application (INDA).
   c. New Drug Application (NDA) and BLA.
   d. ANDA.
   e. SNDA, SUPAC and BACPAC.
   f. Post marketing surveillance.

TEXT BOOKS:

1. Guidebook for drug Regulatory submissions by Sandy Weinberg, Clayton state university, Copyright © 2009 by John Wiley & Sons, Inc. Published by John Wiley & Sons, Inc., Hoboken, New Jersey
2. Real World Drug Discovery, A Chemist's Guide to Biotech and Pharmaceutical Research by Robert M. Rydzewski Copyright _ 2008 Elsevier Ltd Elsevier The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK, Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands
3. Reliable design of medical devices / Richard C. Fries.--2nd ed Published in 2006 by CRC Press Taylor & Francis Group 6000 Broken Sound Parkway NW, Suite 300 Boca Raton, FL 33487- 2742

REFERENCES:

1. New Drug Approval Process, R.A.Guarino,4th Edition , Marcel Dekker, NY
2. New Drug Approval Process Global Challenges and Solutions RICHARD A. GUARINO., Fifth Ed. informa Healthcare
3. DRUGS From Discovery to Approval, Second Edition RICK NG, A-Bio Pharma Pte Ltd, Singapore, Copyright © 2009 Published by John Wiley & Sons, Inc., Hoboken, New Jersey
4. New Drug Development: Regulatory Paradigms for Clinical Pharmacology and Biopharmaceutics, edited by Chandrahas G. Sahajwalla
5. Drug discovery from Bedside to Wall Street Tamas Bartfai& Graham V. Lees, 2006, ElsevierInc Elsevier Academic Press, 30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
6. Drug discovery and development / edited by Mukund S. Chorghade Copyright © 2007 by John Wiley & Sons, Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

7. FDA administration enforcement manual/ Florence R. Parker, © 2005 by CRC Press LLC, CRC Press LLC, 2000 N.W. Corporate Blvd., Boca Raton, Florida 33431.(Taylor & Francis roup, the academic division of T&F Informa plc.)
8. Commercial Manual on Drugs and Cosmetics 2004, 2nd edition Published by *Commercial* Law Publishers (India) Pvt. Ltd., Dehli.
9. Good Manufacturing Practices for Pharmaceuticals, S.H. Wiling, Vol. 78, Marcel Decker.
10. Protection of Industrial Property rights by P.Das and Gokul Das
11. Websites: fda.org, wipo.int, patentlawlinks.com, hc-sc.gc.ca, ich.org
12. Marketing authorization of pharmaceutical Products with special reference to Multisource (generic) products: A manual for drug regulatory authorities WHO Division of Drug Management and Policies in Geneva from 7 to 8 April and 6 to 8 July 1998

PAPER II. DRUG REGULATORY AFFAIRS – II (Highly Regulated Markets like EU and Japan): (Theory) 3 hrs/week

1. a. Drug regulatory authorities in European Union (EU) -- Introduction, Organization and General Guidelines.
   b. Regulatory consideration for pre-clinical testing and clinical testing in EU.
2. a. Registration application for marketing approval (IND, NDA, ANDA) in EU.
   b. Drug Master Files in EU.
3. Regulatory considerations for manufacturing, packaging and labeling of pharmaceuticals in EU.
4. The WHO Guidelines – The WHO Guidelines and their relevance in international registration. The WHO certification scheme on the quality of pharmaceutical products moving in international commerce.
5. Introduction to Pharmacovigilance.

PAPER III. Pharmaceutical Jurisprudence (Forensic Pharmacy) : (Theory) 3 hrs/Week

Acts & Laws as present in Indian context with respect to Drugs & Cosmetics and Biotechnology products.

A detailed study of the following laws, including latest amendments in India :

a. The Drugs and Cosmetics Act, 1940 and Rules thereunder (Incuding Manufacturing, Distribution, Import , Export and Sales).
b. The Drugs (Prices Controls) Order, 1955.
c. The Indian Patents and Designs, Act 1970, including recent amendments.
d. Indian laws on Trade Marks and Copy Rights.
e. Drug Registration Application for marketing approval as applicable in India.
f. Labelling and advertising requirements .
g. Magic Remedies and Objectionable advertisements Act.
h. Prevention of Food Adulteration Act 1954 (5 hrs)
i. Intellectual Property Rights:
    - Protection of patients and trademarks and design and copy rights and patent system in India.

- Present status of IPR future changes expected in Indian patents.
- What may be patented
- Who may apply for patent
- Preparation of patent proposal
- Registration of patent in India and foreign countries and vice versa
- ICH guidelines for clinical trials, therapeutic drug monitoring and bioequivalence.
- Exclusive marketing rights
- Black box
- IPR and IDMA views on patents
- Human health and patent laws latent lethality

Reference:

1. Guidelines of various countries like MCA, TGA, ICH.
2. Drug and cosmetic act 1940 and rules their under
3. IPR Lecture notes
4. GLP regulation by Alen Hirsch Vol 38 Marcel Decker series
5. GMP for pharmaceuticals forth edition by S. Willing, J. Stocker Marcel Decker series 1997.
6. I.P., B.P., U.S.P. International Pharmacopoeia
7. Pharmacokinetics, Regulatory, Industrial, academic prospective by P. G. Willing and F.T.S. Tse.

PAPER VI. LAWS RELATED TO DRUG PRODUCT DESIGN, SAFETY & ENVIRONMENT: (Theory) 3 hrs/week

A detailed study of the laws affecting drug product design, manufacture and distribution in India (with latest amendments) :

a. Industrial Development and Regulation Act 1951.
b. The Environmental Protection Act
c. Consumer Protection Act
d. Law of Torts
e. Law of Contracts
f. Monopolistic & Restrictive Trade Practices Act
g. Auditing of manufacturing facilities by International regulatory agencies.
h. The ISO 9000 series of quality systems standards.

I – Semester

(PRACTICALS)

PAPER I. DRUG REGULATORY AFFAIRS – I & II **9 hrs/ week**

Based on the contents of the theory Paper I and II including mock inspections, auditing and document/ report writing and evaluation of reports. Preparation of dossiers for filing.

PAPER II. . LAWS RELATED TO DRUG PRODUCT DESIGN, SAFETY & ENVIRONMENT 9 hrs/ week

Based on the contents of the theory Paper III and IV
Preapration of Documents/reports, Writing, auditing and inspection and evaluation. Preparation of dossiers for filing.

II – Semester

PAPER I DRUG DEVELOPMENT &APPROVAL PROCESS : 3hrs/week

1. **Drug development stages:** target selection, pre-clinical development and clinical development.
2. **New Drug approval process:**

A. National drug regulatory requirements, national drug policy, Drugs and Cosmetics Act and its amendments, Overview of schedules, details of schedule M, Schedule Y.

B. FDA guidelines on IND, new drug approvals (NDA), ANDA approvals. European regulatory agency, types of filing process (Centralized, de-centralized, RMS countries).

3. **Generic drugs and Drug product approval:**
   Generic and product development (Orange book), SUPAC changes and understanding on 505 (b) (2) applications launch, post-launch and life cycle management
4. **Drug development in industry:**
   Company organization, Setup of drug development in large, medium, small and virtual pharmaceutical companies, interdisciplinary project teams and interactions.
5. **Property Rights :**

A. Types of IP, definition, scope, objectives Patents, types, contents of patent, claims and types of claims, key terminology used in patents (Application, examiner, prior art, priority, specifications, provisional and non-provisional applications, claims, applicant, assignee, inventor, anticipation, obviousness, infringement and invalidation). Patent information and research.

B. Indian patent act and post 1995 amendments, US and European patent act.

C. Trademarks, copyrights, design International conventions, GATT, WTO, TRIPS, Paris convention and patent cooperation treaty.

TEXT BOOKS:

1. New Drug Approval Process, R.A.Guarino,4th Edition , Marcel Dekker, NY
2. New Drug Approval Process Global Challenges and Solutions RICHARD A.GUARINO., Fifth Ed. informa Healthcare
3. DRUGS From Discovery to Approval, Second Edition RICK NG, A-Bio Pharma Pte Ltd, Singapore, Copyright © 2009 Published by John Wiley & Sons, Inc., Hoboken, New Jersey
4. New Drug Development: Regulatory Paradigms for Clinical Pharmacology and
5. Biopharmaceutics, edited by Chandrahas G. Sahajwalla Published by Informa Healthcare
6. Drug discovery from Bedside to Wall Street Tamas Bartfai& Graham V. Lees, 2006,ElsevierInc Elsevier Academic Press, 30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
7. Drug discovery and development / edited by Mukund S. Chorghade Copyright © 2007 by John Wiley & Sons, Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

REFERENCES:

1. New drug development Design methodology and, analysis by J. Rick Turner , 2007, WILEYINTERSCIENCE A John Wiley & Sons, Inc., Publication Published by John Wiley & Sons, Inc., Hoboken, New Jersey
2. Drug-like Properties: Concepts,Structure Design and Methods:from ADME to Toxicity Optimization, Edward H. Kerns and Li Di, Copyright © 2008, Elsevier Inc, Academic Press is an imprint of Elsevier , 30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
3. FDA administration enforcement manual/ Florence R. Parker, © 2005 by CRC Press LLC, CRC Press LLC, 2000 N.W. Corporate Blvd., Boca Raton, Florida 33431.(Taylor & Francis Group, the academic division of T&F Informa plc.)
4. Commercial Manual on Drugs and Cosmetics 2004, 2nd edition Published by *Commercial* Law Publishers (India) Pvt. Ltd., Delhi.
5. Drugs and Cosmetics act by Vijay Malik Publisher: Eastern Book Company
6. Protection of Industrial Property rights by P.Das and Gokul Das
7. Law and Drugs, Law Publications by S.N. Katju
8. Original Laws Published by Govt. of India
9. Websites: fda.org, wipo.int, patentlawlinks.com, hc-sc.gc.ca, ich.org

PAPER II : Regulation of Preclinical and Clinical Studies : 3hrs/week

1. **Developability of drug molecules**
   a. Drug properties (solubility, permeability), optimization and selection of lead candidates.
   b. BCS classification of drugs
2. **Regulation of preclinical studies**

a. Lead Molecule Selection: Pharmaceutical Profiling and Toxicity Assessments, Toxicity Evaluations, Utilizing the Preclinical Database to Support Clinical Drug Development
b. Regulations and issues related to preclinical evaluation of drugs and biologics in animal models/alternate to animal models, ICH Guidelines and Current Practices

3. **Regulation of Good Laboratory Practices:**
   FDA GLP regulations, Indian, and International (OECD) regulation, Regulation of Computer systems, Implementing GLPS in non- GLP analytical Laboratory, Controlling the good laboratory practices inspection process.
4. **Product development and clinical supplies**

a. Preformulation studies (compatibility, polymorphism), Formulation and Production Strategies for Enhancing Bioavailability of Poorly Absorbed Drugs first in man (FIM) formulation and formulations for late stage clinical trials
b. Clinical supplies – manufacturing, labeling and management

5. Design of clinical studies

a. Study design and methodology in clinical trials, ethical aspects of design and methodology, responsibilities of sponsor, monitor and investigator
b. Enrollment strategy, study completion best practices, detection of fraud and misconduct.

6. Regulation of clinical studies

a. Efficacy & safety assessment in clinical trials, Adverse Events (AEs) versus Serious Adverse Events (SAEs). Assessment, recording and medical management of AEs, Unblinding because of an AE, expedited reporting of SAE and handling a subject death in a clinical trial (Phamacovigilance strategies and reporting).

b. Global regulations for Good Clinical Practices (GCPs): CFR/ICH/EU GCP Obligations of Investigators, Sponsors, and Monitors, Quality Assurance, Managing and Monitoring Clinical Trials, European CT Directive: Implementation and Update.

Text Books:

1. Drug Discovery and Evaluation Safety and Pharmacokinetic Assays _by H. GerhardVogel (Ed.)
2. Franz Jakob Hock, Jochen Maas,Dieter Mayer Springer-Verlag Berlin Heidelberg New York 2006, Printed in Germany
3. Hand Book of Drug Screening by Ramakrishna S, and Prabavathi B F volume 114, 2001 ,
4. Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016
5. Clinical Drug Trials and Tribulations Second Edition\Clinical Drug Trials and Tribulations Second Edition, M eedited by Allen Cato, Lynda Sutton, Cato Research Ltd. Durham, North Carolina, Allen Cato III, Cato Research Ltd.San Diego, California2002Marcel Dekker, Inc.Marcel Dekker, Inc. New York • Basel
6. Clinical Research in Pharmaceutical Development, edited by Barry Bleidt and Michael Montagne c 2002 Marcel Dekker, Inc. Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016
7. Drug Products for Clinical Trials: An International Guide to Formulation, Production, Quality Control, edited by Donald C. Monkhouse and Christopher T. Rhodes Marcel Dekker, Inc. New York.

REFERENCES:

1. FDA regulatory affairs : a guide for prescription drugs, medical devices, and biologics edited by Douglas J. Pisano, David Mantus. © 2004 by CRC Press LLC CRC Press LLC, 2000 N.W. Corporate Blvd., Boca Raton, Florida 33431, Printed in the United States of America
2. Global Regulatory Issues for the Cosmetics Industry Volume 1Edited by C. I. Betton Delphic HSE Solutions Ltd, England, Copyright © 2007 by William Andrew Inc Published by: William Andrew Inc. 13 Eaton Avenue, Norwich, NY 13815
3. New Drug Development: A regulatory Overview by Mark Mathieu
4. FDA Regulatory: A guide for prescription drugs, Medical Devices, & Biologics. Douglas J. Pisano, David Mantees. CRC Press
5. Good Drug Regulatory Practices-A Regulatory Affairs Quality Manual by Heleene Dumetriu. CRC Press
6. US FDA guidelines - www.**fda**.gov
7. CDSCO guidelines - www.**cdsco**.nic.in
8. EMEA guidelines - www.**emea**.europa.eu
9. ICH guidelines - www.**ich**.org

PAPER III : GOOD MANUFACTURING PRACTICES : (THEORY) 3hrs/week

1. **GXPs in pharmaceutical industry**
   a. Concepts of GXP, importance of documentation, good laboratory practices (GLPs), good clinical practices (GCPs) and good manufacturing practices (GMPs).

b. **Good Laboratory Practices:** The History of GLP, The Idea behind GLP, The Areas of Application, The Pillars of Good Laboratory Practice, Where Can GLP be Profitably Applied?

2. Quality Management Systems.

a. ISO : Introduction to ISO certification procedure.
b. TQM: Principles of TQM.
c. Role of Quality Assurance in Manufacturing and compliance.

3. GMPs

Good manufacturing practices for active pharmaceutical ingredients (bulk drug substances), pharmaceutical excipients, pharmaceutical products, sterile pharmaceutical products, biological products, manufacture of herbal medicines and radiopharmaceutical products

1. Inspections

Pre-approval inspections, Inspection of pharmaceutical manufacturers, Inspection of drug distribution channels, Quality systems requirements for national good manufacturing practice inspectorates, inspection report, model certificate of good manufacturing practices

2. Audits

GMP compliance audit, Definition Summary, Audit policy, Internal and External Audits, Second Party Audits, External third party audits, Preparation for Audit, Conducting audit, audit analysis, audit report, audit follow up.

Text Books:

1. Good Clinical, Laboratory and Manufacturing Practices Techniques for the QA Professional, Edited by PA Carson,and N Dent,, The Royal Society of Chemistry 2007, Published by The Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 0WF, UK
2. Good laboratory practice: the why and how by Seiler Publisher: Springer; 2ndedition
3. GMP/ISO Quality Audit Manual for Healthcare Manufacturers and Their Suppliers, VOLUME 2
4. Regulations, Standards, and Guidelines, by Leonard Steinborn, © 2005 by CRC Press, CRC Press, 2000 N.W. Corporate Blvd., Boca Raton, Florida 33431
5. Quality assurance of pharmaceuticals : a compendium of guidelines and related materials. Vol. 2, Good manufacturing practices and inspection. – 2nd ed. © World Health Organization 2007 WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.
6. Good Manufacturing Practices for Pharmaceuticals Sixth Edition edited by Joseph D. Nally *Nallianco LLC New Vernon, New Jersey, U.S.A.*

REFERENCES:

1. Good manufacturing practices of Pharmaceuticals by Willig Publisher: C B S Publishers & Distributors
2. cGMP current good manufacturing practices for Pharmaceuticals by Potder
3. Good manufacturing practices for pharmaceuticals by Manohar A Potder
4. How To Practice Glp Good Laboratory Practice Publisher: Vandana Publications
5. A WHO guide to good manufacturing practice (GMP) requirements , New York
6. GMP Audit Template, EU Guidelines, (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4 en.htm)
7. "Frontmatter" CRC handbook of laboratory Safety Edited by A. Keith Furr 5th edition CRC Press, BOCARATON, Florida.

PAPER IV : PHARMACEUTICAL PRODUCTION AND MANAGEMENT: (THEORY)
3hrs/week

1. **Pilot plant scale-up technique**

a. Pharmaceutical pilot plant, pilot plant design, case studies for tablets, capsules, aerosols, liquid orals, parenterals, sustained release preparations and semi solids preparations.
b. Basic requirements-design of product, facility, equipment selection and personnel.

2. API – Synthesis, Pilot study, Technology transfer and bulk drug production, ICH guidelines with respect to API, stability testing. GMP and WHO guidelines.
3. Nature and scope of production management: locating production and service facilities: Layout planning and analysis: Types of Manufacturing systems and layout – mass production, batch production and selection: Process planning: Aggregate planning and Master production scheduling: Project management – project planning project scheduling PERT and CPM use.
4. Materials Management: An introduction to materials management . Material requirement Purchase management, Inventory control, Material handling: Vendor selection Make or buy decision Negotiation: Cost-reduction techniques – Standardization codification and variety reduction: waste management : Value analysis: Determination and description of material quality acceptance sampling plan.
5. **Optimization techniques in Pharmaceutical Formulation and Processing:**

Introduction, Optimization parameters, classical optimization, statistical design, applied optimization methods like EVOP, Simplex, Langrangian techniques.

6. **Formulation and production management**

Plant site selection and layout.
Material handling for various pharmaceutical products, service facilities and preventive maintenance in pharmaceutical companies-Group and individual replacement

7. **Safety**

Industrial hazards due to fire, accident, mechanical, electrical equipment, monitoring and preventive system (Safety measures including insurance).
Effluent testing, treatment and waste management.

BOOKS:

1. The theory and practice of Industrial Pharmacy Leon Lachman, Ph.D., Lachamn Consultant Services, Inc. Garden City, New York. Herbert A. Lieberman, Ph.D., H.H. Lieberman Associates Inc. Consultant Services, Livingstom, New Jersey, Joseph L. Kanig, Ph.D, Kanig Consulting and Research Associates, Inc Ridgefield Connecticut. Third Edition (Indian Edition) Varghese Publishing House, Hind Rajasthan Building, Dadar Bombay 400017.1987.

2. Pharmaceutical Dosage Forms and Drug Delivery Systems Fifth Edition Howard C. Ansel, Ph.D., Professor and Dean, College of Pharmacy, The University of Georgia. Nicholas G. Popovich , Ph.d., Professor, School of Pharmacy and Pharmaceutical Sciences, Purdue University. Published by Lea & Febiger, Philadelphia, London. 1990.

3. Industrial Pharmacy, Dr. N. Udupa, 1992, II Edition Varghese Publishing House, Bombay.
4. Admn. E.E. and Ebert RJ: Production and Operations Management, 6th Edition, New Delhi prentice Hall of India 1995.
5. Chunawalla and Patel: Production and Operations Management, Himalaya Publishing House.
6. Gopalakrishnan.P and Sundarshan M Hand Book Materials Management New Delhi Prentice Hall of India. 1994.
7. Dutta A.K. Integrated Materials Management New Delhi PhI1986.
8. Buffa E.S. and Sareen: Modern Production Management, New York, John Wiley 2002.
9. GMP for Pharmaceuticals forth edition by S. Willing, J. Stocker Marcel Decker series 1997.
10. I.P.., B.P., U.S.P. International Pharmacopoeia.
11. Pharmaceutical Production and Management by C.V.S.Subrahmanyam

II – Semester

(PRACTICALS)

PAPER I. Drug Development & Approval Process (Practicals) 9 hrs/ week

Practical shall be based on theory Paper I and II. Example experiments:

1. IND protocols
2. NDA protocols
3. Developing a plan that will be suitable from development to approval for new compounds
4. Developing a plan that will be suitable for generic drugs.
5. SUPAC protocols

PAPER II. PHARMACEUTICAL PRODUCTION AND MANAGEMENT (Practicals) (9 hrs/ week)

Practicals

Student shall carry out a project and submit an assignment consisting of a write up on project suggested for the year which may include.

Organization/ Business case presentations.

Survey of market research to collect information regarding management of a given diseases and disorder (disease management is not there in the theory)

Group discussions and case studies based on theory.

Layouts for API (Tablets, capsules, ophthalmic, parenteral and other formulations)

Evaluation of rubber as packing material.

Evaluation of Glass as packing material.

Evaluation of Plastic as packing material.