INJECTABLE DRUG DEVELOPMENT

TECHNIQUES TO REDUCE PAIN AND IRRITATION

Edited by

Pramod K. Gupta and Gayle A. Brazeau

Interpharm Press Denver, Colorado





Invitation to Authors



Interpharm Press publishes books focused upon applied technology and regulatory affairs impacting healthcare manufacturers worldwide. If you are considering writing or contributing to a book applicable to the pharmaceutical, biotechnology, medical

device, diagnostic, cosmetic, or veterinary medicine manufacturing industries, please contact our director of publications.

Library of Congress Cataloging-in-Publication Data

Injectable drug development: techniques to reduce pain and irritation / edited by Pramod K. Gupta and Gayle A. Brazeau.

p. cm.

Includes bibliographical references and index.

ISBN 1-57491-095-7

- 1. Injections. 2. Injections—Complications. 3. Drug development.
- I. Gupta, Pramod K., 1959- II. Brazeau, Gayle A.

[DNLM: 1. Injections—adverse effects. 2. Pain—chemically induced.

3. Pain—prevention & control. 4. Pharmaceutical Preparations administration & dosage. WB 354 156 19991

RM169.149 1999

615'.6-dc21

DNLM/DLC

for Library of Congress

99-26911

CIP

10987654321

ISBN: 1-57491-095-7

Copyright © 1999 by Interpharm Press. All rights reserved.

All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Printed in the United States of America.

Where a product trademark, registration mark, or other protected mark is made in the text, ownership of the mark remains with the lawful owner of the ma/k. No claim, intentional or otherwise, is made by reference to any such marks

in this book.

While every effort has been made by Interpharm Press to ensure the accuracy of the information contained in this book, this organization accepts no responsibility for errors or omissions.

Interpharm Press 15 Inverness Way E. Englewood, CO 80112-5776, USA

Phone: +1-303-662-9101 Fax: +1-303-754-3953 Orders/on-line catalog:

www.interpharm.com



BIANE 0 354 T56 1999

Contents

Pre	reface	
	Acknowledgments	xiv
Edi	tors and Contributors	xv
	A: Background of Pain, Irritation, and/or Muscle Damage with Injectables	
1.	Challenges in the Development of Injectable Products	3
	Michael J. Akers	
	General Challenges	4
	Safety Concerns	5
	Microbiological and Other Contamination Challenges	6
	Stability Challenges	8
	Solubility Challenges	10
	Packaging Challenges	11
	Manufacturing Challenges	11
	Delivery/Administration Challenges	13
	References	14



iv Injectable Drug Development

2.	Pain, Irritation, and Tissue Damage with Injections	15
	Wolfgang Klement	
	Must Injections Hurt?	15
	Mechanisms of Pain and Damage	16
	Routes of Drug Injection	18
	Cutaneous/Subcutaneous Injections 18	20
	Intramuscular Injections 22	
	Intra-arterial Injections 24	
	Intravenous Injections 26	
	Conclusions and Perspectives	49
	Acknowledgements	50
	References	50
3.	Mechanisms of Muscle Damage with Injectable Products	57
	Anne McArdle and Malcolm J. Jackson	
	Abstract	57
	Introduction	57
	Mechanisms of Muscle Damage	58
	Elevation of Intracellular Calcium Concentration 58	
	Increased Free Radical Production 60	
	Loss of Energy Homeostasis 61	
	Methods of Assessing Drug-Induced Skeletal Muscle Damage	62
	Microscopic Analysis of Skeletal Muscle 62	-
	Muscle Function Studies 63	
	Leakage of Intramuscular Proteins 64	
	Microdialysis Studies of Individual Muscles 64	
	Cellular Stress Response 65	
	Techniques to Assess the Mechanisms of Muscle Damage	66
	Models of Muscle Damage 66	
	Techniques to Show Changes in Muscle Calcium Content 66	
	Markers of Increased Free Radical Activity 67	
	Methods of Measuring Cellular Energy Levels 67	
	Conclusions	67
	Acknowledgments	67
	References	68



B: METHODS TO ASSESS PAIN, IRRITATION, AND Muscle Damage Following Injections

4.	In Vitro Methods for Evaluating Intravascular Hemolysis	77
	Joseph F. Krzyzaniak and Samuel H. Yalkowsky	
	Significance	78
	In Vitro Methods for Evaluating Hemolysis	79
	Static Methods 81	
	Dynamic Methods 82	
	Comparison of In Vitro and In Vivo Hemolysis Data	85
	Summary of In Vitro Methods	86
	References	87
5.	Lesion and Edema Models	91
	Steven C. Sutton	
	Edema and Inflammation	91
	Lesion Models	92
	Rabbit 92	
	Mice 96	
	Rat 96	
	Biochemical Models	97
	Serum Glutamic-Oxaloacetic Transaminase 97	
	N-Acetyl-β-Glucosaminidase 97	
	Myeloperoxidase 97	
	Creatine Kinase 98	
	Edema Models	105
	Inducing Edema 105	
	Exudative Models of Inflammation 105	
	Vascular Permeability Models 105	
	Footpad Edema Models 106	
	Correlation of Models	107
	Rabbit Lesion Versus Rabbit Hemorrhage Score Model 107	
	Rabbit Lesion Versus Rabbit CK Model 108	
	Rabbit Lesion Versus Rat Footpad Edema Model 109	
	Rabbit Lesion Versus Rat CK Model 109	
	Rat and Human 110	



DOCKET

Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

