Assessment of Manufacturing Related Deficiencies for Modified Release Tablet in Abbreviated New Drug Applications

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Abstract

Generic drugs have played an important role for public health. However, the first cycle approval rate is low for original abbreviated new drug applications (ANDAs). To identify the potential root cause, we conducted this research project to collect and analyze the cited deficiencies for modified-release tablets in abbreviated new drug applications. The study results revealed that most applications received Complete Response (CR) were caused by multiple review disciplines being inadequate. Common deficiencies were found for manufacturing. Avoiding common manufacturing deficiencies can improve the quality of the applications which can improve the first cycle approval rate for generic drug applications.

Introduction

Generic drugs have played an important role for public health. However, the first review cycle approval rate for ANDAs is generally low. During FY18-FY19, 18% of the original ANDAs were approved during the first review cycle. To facilitate the communication and address deficiencies during the review cycle, FDA issued 6065 original information requests (IRs), 5045 discipline review letters (DRLs), and 4958 complete responses (CRs) for all generic applications to the applicants. To identify if manufacturing related deficiencies are the potential root cause of relatively low first cycle approval rate in the modified release (MR) tablet ANDAs, we collected and analyzed the review recommendations from each review discipline and the manufacturing related deficiencies.

Materials and Methods

FDA CDER informatics platform was queried for information related to original modified-release tablets ANDAs submitted from January 1, 2017 to December 31, 2019 excluding refuse-to-receive and withdrawn applications. The recommendation was recorded for each review discipline including bioequivalence, labeling and pharmaceutical quality (drug substance, drug product, process, facility and biopharmaceutics) after completing first review cycle. The first cycle approval rate was calculated for the identified applications. The percentage of inadequacy was calculated for each review discipline for the applications received CRs. Deficiencies corresponding to manufacturing assessments cited in the IRs, DRLs and CRs were collected, classified and analyzed.

Table 1. Summary of the studied applications.

Categories	ER Tablets*	DR Tablets*	Total
Identified applications	170	16	186
Complete Response applications	149	13	162
First review cycle approved applications	18	3	21
Tentative approval applications	3	0	3
Complete response rate	88%	81%	87%
First cycle approval Rate	12%	19%	13%

*ER Tablets: Extended-Release Tablets

*DR Tablets: Delayed-Release Tablets

First Cycle Approval Rate = (First Cycle Approvals+ First Cycle Tentative Approvals)/All Identified Applications x 100%

Results and Discussion

We identified 186 modified release tablet ANDA original applications including 170 ER tablet ANDAs and 16 DR tablet ANDAs. The study shows the first cycle approval rate was 13% with 87% CR rate. 1285 manufacturing related deficiencies were cited during the first review cycle which included 275 cited in the CR letter. In the 162 CR applications, 51% applications were cited with process inadequate recommendations. 33% applications were cited with facility inadequate recommendation. However, only 4% CR applications caused by manufacturing inadequate while other disciplines are adequate. 90.7% of the CR applications were caused by multiple review disciplines being inadequate. Manufacturing related deficiencies were classified and analyzed. 70% of the cited manufacturing deficiencies were unit operations related.

Table 2. Summary of the CR classification for each review discipline in first review cycle...

	ER Tablets		DR Tablets		MR Tablets	
Disciplines	Major	Minor	Major	Minor	Total #	%
Bioequivalence	31	14	4	1	50	31
Labeling	0	56	0	6	62	38
Drug Substance	11	70	3	4	88	54
Drug Product	28	97	4	8	137	85
Process	11	63	0	8	82	51
Facility	51	0	3	0	54	33
Biopharmaceutics	11	65	0	6	82	51

Table 3. Summary of the manufacturing process deficiencies cited in first review cycle.

	ER tablets		DR tablets	
Categories	# of Deficiencies	% Cited Deficiencies	# of Deficiencies	% Cited Deficiencies
Batch Formula	48	4	3	3
Commercial Process Flow Diagram	33	3	6	6
DS Attributes / DP Design Factors Impacting DP Manufacturing	28	2	7	7
Unit Operation Assessment	835	71	69	65
Executed and master batch records	36	3	3	3
Yield and reconciliation	56	5	8	8
Hold Time	77	7	6	6
Microbiological Controls	42	4	2	2
Process validation comments	24	2	2	2
Total cited deficiencies	1179	100	106	100

Conclusion

The first cycle approval rate is 13% for modified-release tablet ANDAs submitted between 2017 to 2019. Deficiencies identified in multiple review disciplines are responsible for the low first cycle approval rate. Most of the cited manufacturing process related deficiencies are unit operations. Avoiding the most common manufacturing deficiencies can improve the quality of applications which can improve the first cycle approval rate.