What factors may impact the likelihood of first abbreviated new drug application (ANDA) submission for a reference product?

Saranrat Wittayanukorn[1], Matthew Rosenberg[2], Andreas Schick[2], Meng Hu[3], Zhong Wang[3], Andrew Babiskin[3], Liang Zhao[3]

[1]ORISE Fellow, Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, CDER, FDA
[2]Office of Program and Strategic Analysis, Center of Drug Evaluation and Research, U.S. Food and Drug Administration
[2]Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, CDER, FDA

Introduction

Background:

- The entrance of generics into the market depends on several factors, including unexpired new chemical entity (NCE) exclusivity for an reference listed drug (RLD). NCE exclusivity generally prevents the submission of an abbreviated new drug application (ANDA) for 5 years from the date of approval of the RLD; however, an ANDA may be submitted 4 years from the date of approval of the RLD if the ANDA contains a Paragraph IV certification of patent invalidity or noninfringement to a patent listed in FDA's Approved Drug Products With Therapeutic Equivalence Evaluations (the Orange Book) for the RLD)[1].
- In addition, factors such as patent protection, drug sales, and drug characteristics may also play a role in ANDA entering to the market[2] .
- Although previous studies have examined factors associated with generic drug entry to the market focusing on approval, little is known about factors that influence ANDA submissions. Understanding factors that have an impact on generic submission may help facilitate regulatory science prioritization and the availability of generic drugs into the market, increasing patient's accessibility and affordability to care.

Objective:

The purpose of this study was to examine factors associated with the likelihood of first ANDA submission for an RLD.

Methods

Study Design and Data Resources:

- A cross-sectional study was conducted using exclusivity and patent data from publicly available Orange Book database (03/2018). Other sources include FDA's Product-Specific Guidances (PSGs)[3] (03/2018), National Drug Code database, internal FDA ANDA submission data (7/01/2009-3/16/2018), Risk Evaluation and Mitigation Strategies (REMS) data, and IQVIA quarterly expenditure data[4] (01/2011-.12/2017), adjusted for inflation to 2011 US dollars.

Analysis:

- Unit of analysis across the study was the RLD, defined as all strengths, dosage forms, routes, and products associated with the new RLD.
- Two groups, i.e., RLDs with NCE exclusivity (i.e., NCE group) and without NCE exclusivity (i.e., non-NCE group), were categorized.
- Potential ANDA submission dates were defined as 4 years after RLD approval date (i.e., assuming Paragraph IV certification) for NCE group, and as the RLD approval date for non-NCE group. Sales were defined as US RLD revenue 1-year before actual ANDA submission dates or 1 year before potential ANDA submission date or sales in 2017 (if no ANDA submitted).
- RLDs with no sales information or had potential ANDA submission before 7/01/2009 and after 12/31/2017 were excluded from the analysis.
- Number of ANDA submission and distribution of sales among NCE and non-NCE group were examined using descriptive statistics. Two Cox (NCE and non-NCE) models with stepwise selection methods were used to determine factors associated with the likelihood of first ANDA submissions. All statistical analyses were conducted using SAS 9.4.

Results

Figure 1. Distribution of Number of ANDA Submissions by NCE

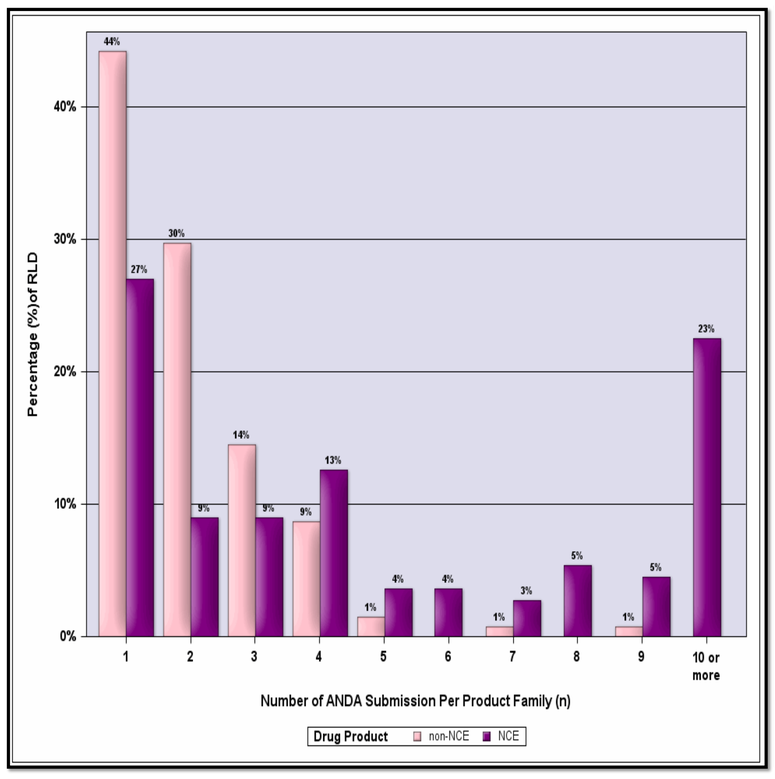


Figure 2. Distribution of Sales before ANDA submission by NCE[a]

[a] Expenditure data were adjusted for inflation to 2011 US dollars

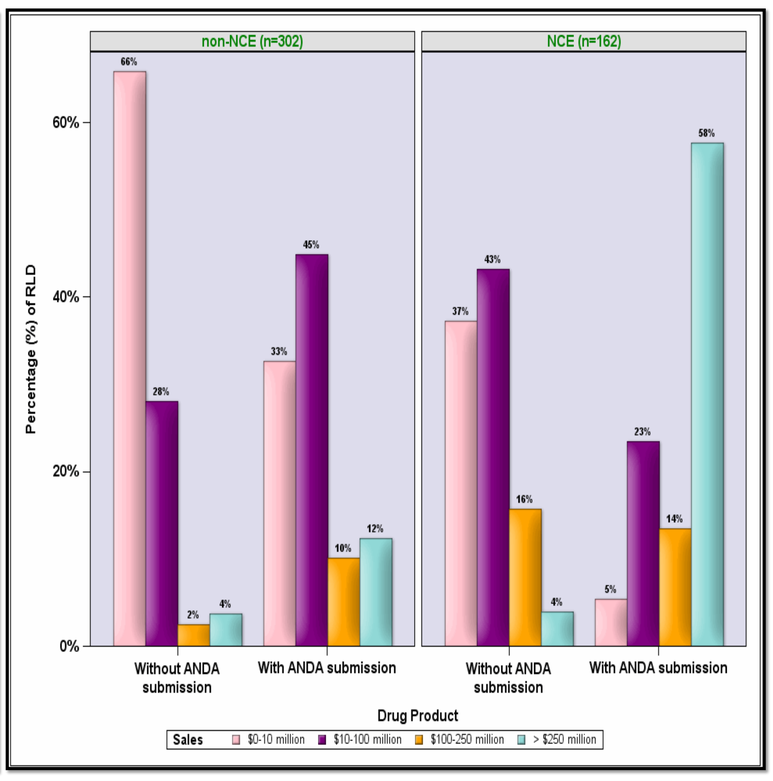
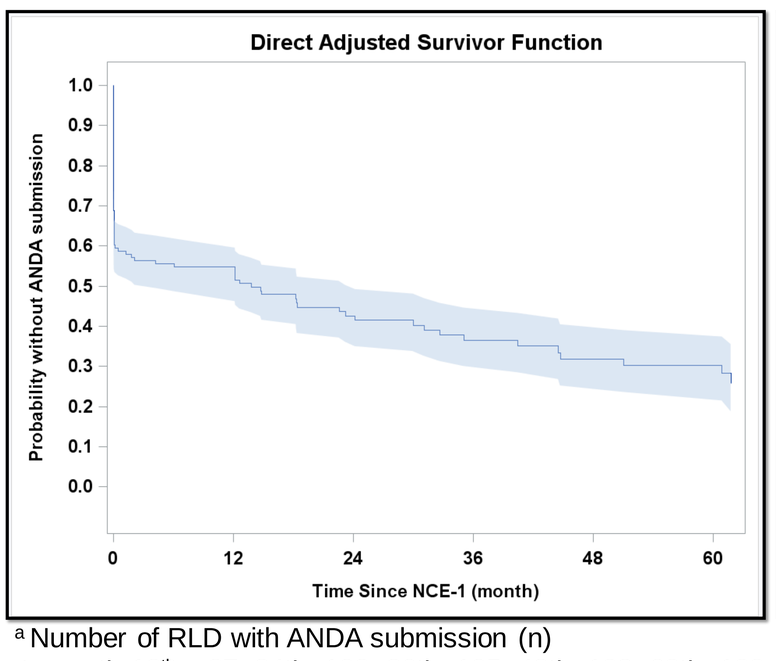


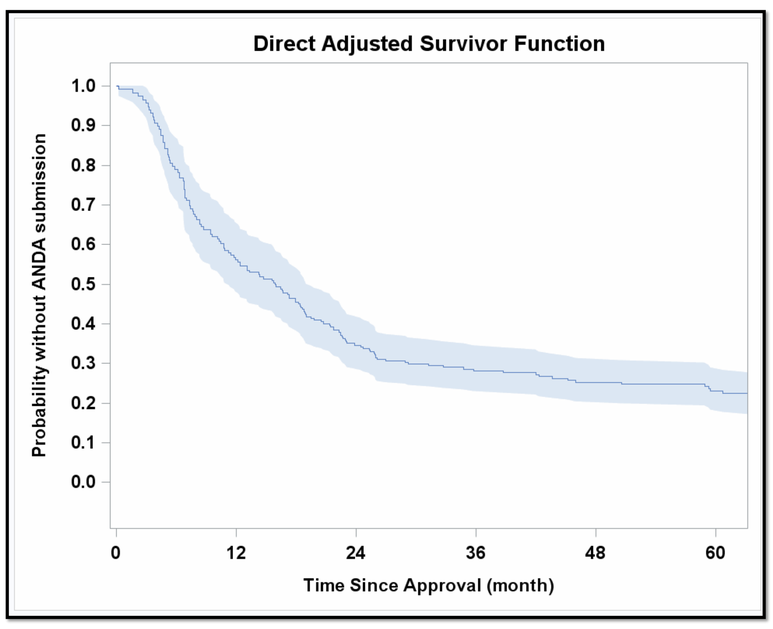
Figure 3. Overall survival among RLDs for first ANDA submission

Figure 3A. NCE Group[a]



[a] Number of RLD with ANDA submission (n) at month 12th: : 87; 24th: 100; 36th: 105; 48th: 108; 60th: 109

Figure 3B. Non-NCE Group[b]



[a] Number of RLD with ANDA submission (n) at month 12th: 61; 24th: 107; 36th: 123; 48th: 129; 60th: 133

Figure 4. Forest Plots of Factors that Have an Impact on First ANDA Submission[a]

Figure 4A. NCE Group

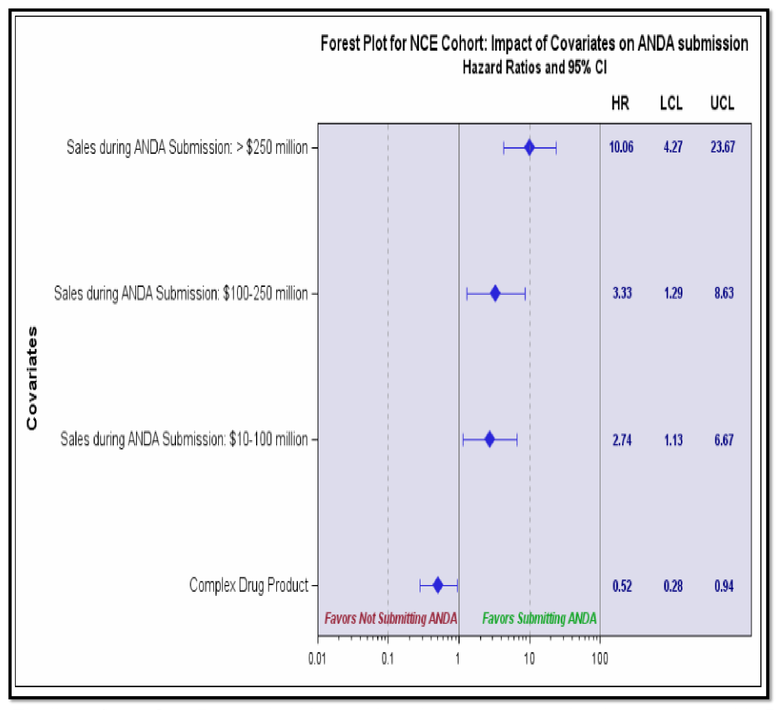
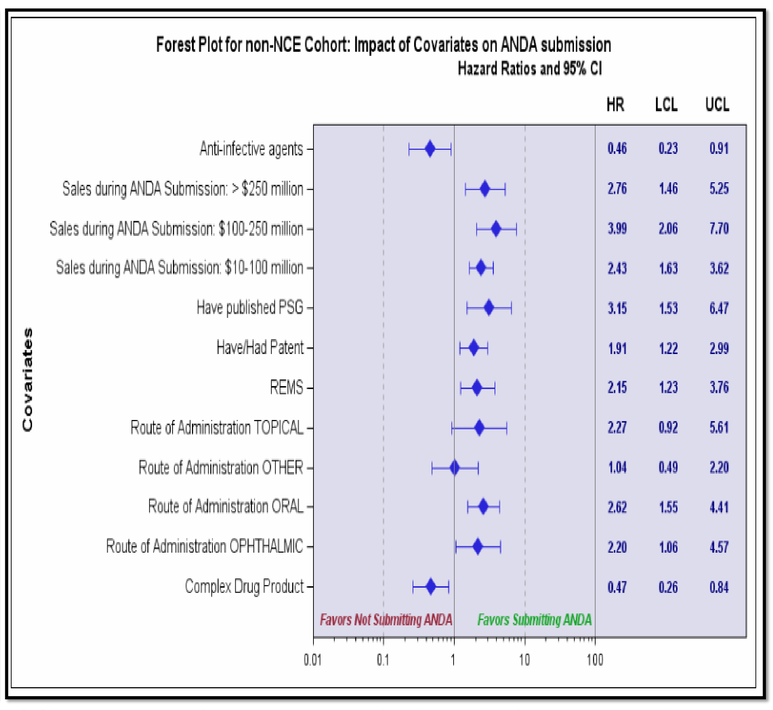


Figure 4B. Non-NCE Group



[a] Findings from Cox Proportional models using stepwise selection method with $P<0.05$, representing factors retained in final models after stepwise selection.

Main Findings

- We analyzed a total of 464 RLDs with potential ANDA submission dates after the exclusion criteria.162 RLDs (34.91%) have/had NCE exclusivity. Results from descriptive analyses have shown that number of ANDA submissions per family and sales were typically higher in NCE group (Fig1 and 2, respectively).
- For NCE group, 53.70% (87/162)) of RLDs had an ANDA submission occur within the fifth year after RLD approval (Fig 3A). Annual sales were the only factor associated with increased likelihood of occurrence of first ANDA submission (Fig 4A). Specifically, adjusted hazard ratio for RLDs with sales > $250 million was approximately 10 times higher than those with sales <$10 million (HR;10.06, 95%CI;4.27-23.67), suggesting RLDs with higher sales are more likely to have ANDA submissions. Complex drug product[5] was associated with decreased events of first ANDA submission (HR;0.52, 95%CI;0.28-0.94), (all P<0.05).
- For the non-NCE group, around 20% (61/302) of RLDs have an ANDA submission occur within the first year, which is slower than NCE-group (Fig 3B). Factors associated with increased likelihood were: annual sales, (adjusted hazard ratio for RLDs with sales > $250 million was approximately 2.76 times higher than those with sales <$10 million [HR;2.76, 95%CI;1.46-5.25]); having REMS; having PSG; having unexpired patent(s) at the time of ANDA submission ; and having oral or ophthalmic route of administration (Fig 4B). Factors associated with decreased likelihood were being complex drug products[5] and anti-infective/antiviral therapeutic class (all P<0.05).

Conclusion

- Several factors may impact the likelihood of first ANDA submissions, e.g., sales and PSG availability appear correlated with high likelihood of ANDA submissions. Research on standards for complex drug products may facilitate ANDA submissions in this category.
- Findings support the continuing need for PSG development, as availability of PSGs assist applicants with developing generic products, particularly for complex drug products.
- Interpretation of the impact of variable of PSG availability may be confounded with other complexity variables (e.g., variables for drug complexity).

References

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2. Fiona MSM. Entry Decisions in the Generic Pharmaceutical Industry. The RAND Journal of Economics. 1999;30(3):421-440.
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4. IQVIA National Sales Perspectives, IQVIA Institute, Calendar Year 2011-2017, data extracted March 2018
5. https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

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