Product-Specific Guidances for New Chemical Entity (NCE) Drug Products

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Introduction

Background:

- The Office of Generic Drugs (OGD) publishes product-specific guidances for generic drug development. Each guidance, when finalized, describes the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs (RLDs).[1]
- The entrance of generics into the market depends on several factors, including unexpired new chemical entity (NCE) exclusivity for an 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 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). The NCE exclusivity period may also be extended with Pediatric Exclusivity (PED, 6 months added for 5.5 years total) or Generating Antibiotic Incentives Now Exclusivity (GAIN, 5 years added for 10 years total).
- Besides exclusivity protection, many new drug applications (NDAs) also have patent protection. Patent protection can impact ANDA approval but does not necessarily prevent approval (e.g., ANDAs that challenge patents and are not sued may not be blocked from approval).

Objective:

To evaluate NDAs with NCE exclusivity, patent data, and the availability of product-specific guidances.

Methods

Study Design:

A cross-sectional study using exclusivity and patent data from the electronic Orange Book published in December 2016 was conducted.

Data Resources:

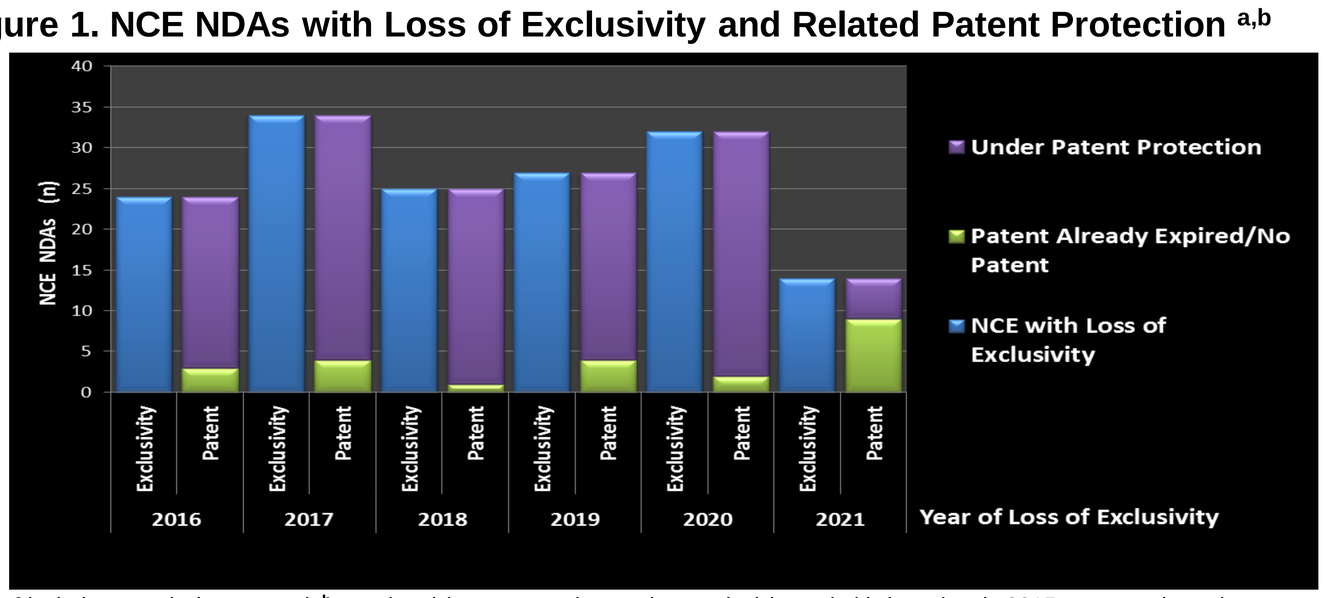
Data were retrieved from the publically available Orange Book[2], product-specific guidance website[1], Drugs@FDA[3], and National Drug Code (NDC) directory[4] databases (accessed in December 2016).

Analysis:

- Trends over time under the study period were examined.
- Number of NCE NDAs with "loss of exclusivity" (LOE), i.e., the expiration of all relevant exclusivity periods for the drug product that would prevent the submission of an ANDA, and proportion of published product-specific guidance coverage over time were examined.
- Proportion of NCE NDAs by dosage form, route of administration, and pharmacologic drug class were evaluated.
- Descriptive statistics and chi-squared tests were used.

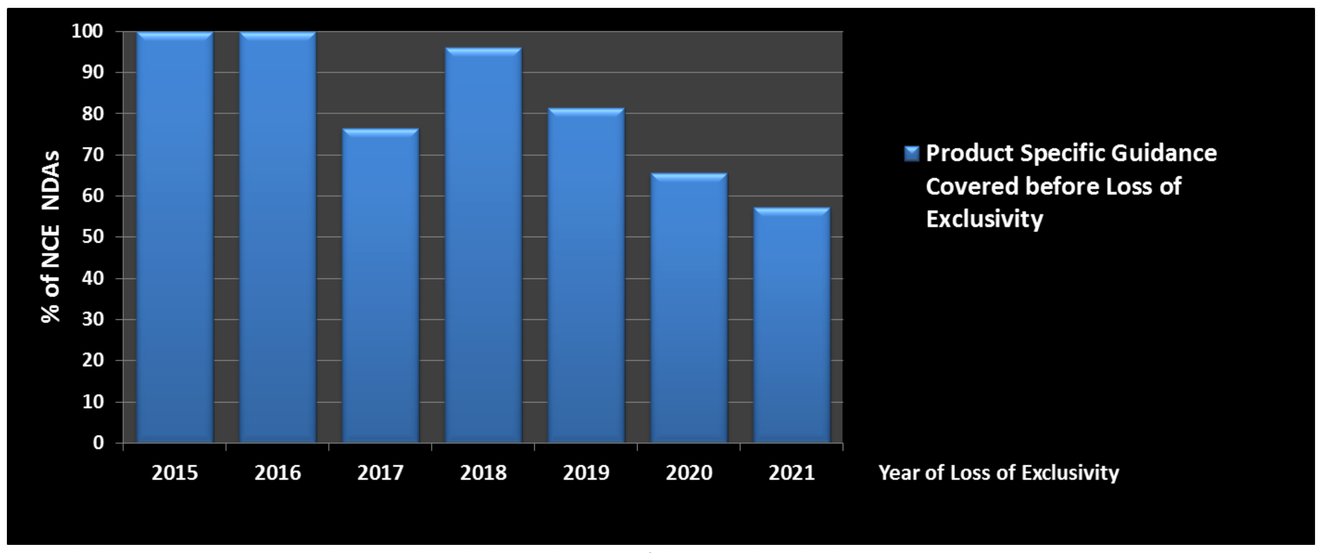
Results

Figure 1. NCE NDAs with Loss of Exclusivity and Related Patent Protection [a,b]



[a] includes tentatively approved; [b] year (x-axis) represented year when exclusivity period is lost; data in 2015 were not shown because it did not represent a full calendar year (only included from Jul 28, 2015-Dec 31, 2015.)

Figure 2. Proportion of Product-Specific Guidance Coverage Before Loss of Exclusivity [a,b]



[a] in 2015 the data only includes from Jul 28, 2015-Dec 31, 2015; [b] Product-Specific Guidance represented as those published by December 31 2016; $P<0.05$

Figure 3. Proportion of NCE NDAs by Dosage Form and Route of Administration

Figure 3A. Route

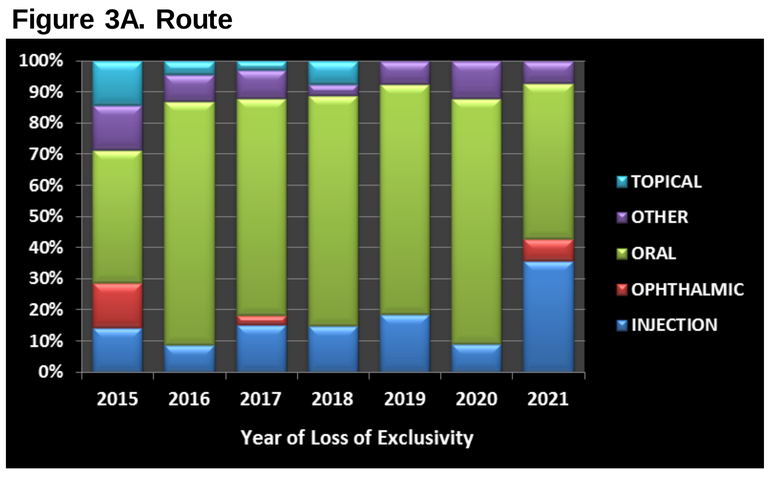


Figure 3B. Dosage Form

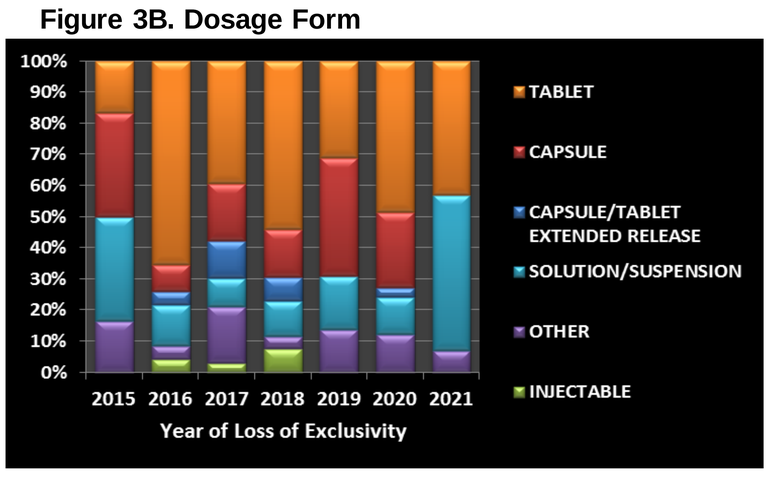
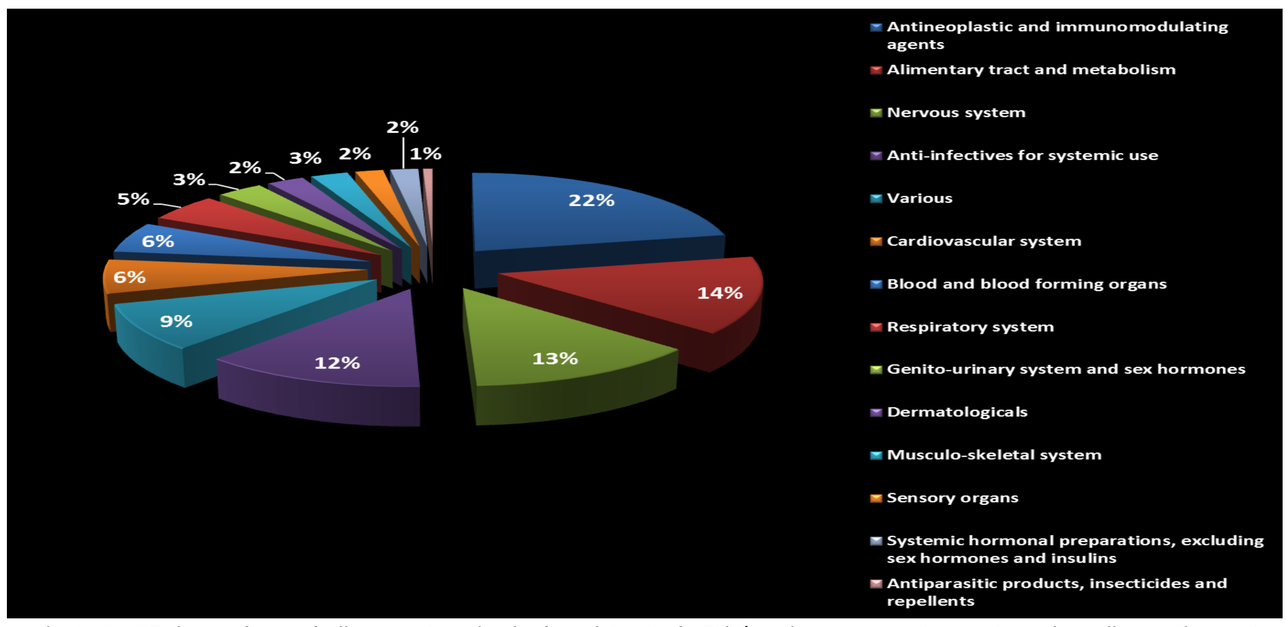


Figure 4. Proportion of NCE NDAs by Pharmacologic Drug Class[a,b]



[a] Representing160 NCE drugs after excluding uncategorized values (11 out of 171); [b] Various represents agents such as diagnostic agents or contrast media

Main Findings

- A total of 171 NCE NDAs with a projected LOE between 7/28/2015-3/06/2027 were identified as of December 2016.
- Figure 1 demonstrated the number of NCE NDAs with LOE in that year and the proportion of NCE NDAs still under patent protection. The number of NCE NDAs with LOE was highest in 2017 (n=34). As of December 2016, the exclusivity period(s) for 33 NCE NDAs have expired; whereas 138 NCE NDAs are still protected by an exclusivity period.
- Product-specific guidances were generally published prior to expiration of the exclusivity period(s) for NCE NDAs. Product-specific guidances have been published for an average of 82.39% (±17.13%) of all NCE NDAs ($p<0.05$) (Figure 2).
- Drug products intended for the oral route of administration, particularly in tablet dosage form, comprised the highest proportion of NCE NDAs (Figure 3A,B).
- Antineoplastic and immunomodulating agents (e.g., kinase inhibitor; 20.47%), Alimentary tract and metabolism (e.g., diabetic agents; 13.45%), Nervous system (e.g., anti-epileptic agents; 12.28%), and anti-infectives (e.g., anti-viral agents) were pharmacologic classes with a high proportion of NCE exclusivity (Figure 4).

Conclusion

- Exclusivity and patent protection are important considerations for submission and approval of ANDAs.
- Product-specific guidances have been published for the majority of NCE NDAs for which LOE will occur in the next 4 years.
- Findings support the continuing need for product-specific guidance development. Availability of product-specific guidances assist applicants with developing generic products.

References

1. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
2. https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
3. https://www.fda.gov/Drugs/InformationOnDrugs/ucm135821.htm
4. https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm

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