Pharmaceutical Packaging Materials Quality Control and USP 661.1 Compliance: Agilent Cary 630 FTIR

Application Note

Pharmaceutical Testing and Research

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Introduction

The composition and quality of packaging materials can have a critical impact on the performance, function, and production cost of pharmaceutical medications or drugs. Improper packaging can cause the active pharmaceutical ingredients (API) in medications to degrade faster, and have shorter shelf lives. Detecting problems, impurities, or incorrect polymer compositions early in the packaging process can prevent a more costly failure of an end product that reaches the consumer.

Mid-infrared FTIR spectroscopy has a long history of identifying the chemical compositions of polymers, fillers, and additives used in the pharmaceutical, coatings, and chemical industries. The mid-infrared spectrum is often referred to as the chemical fingerprint of a material, due to its rich detail and specificity in reference to a known composition. FTIR spectroscopy is a rapid and easily implemented technique to screen polymers and other packaging materials at all stages of the packaging process. The Agilent Cary 630 FTIR spectrometer used in this work features Microlab software, which is available with an Agilent SCM/SDA compliance package that contains security and auditing features required for GMP by the 21 CFR part 11 regulation. This method-driven software package makes comparison between product polymers and known USP verified polymers easier than ever.

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This application note fosuses on the use of the Cary 630 FTIR spectrometer for analyzing polymers used in pharmaceutical packaging.

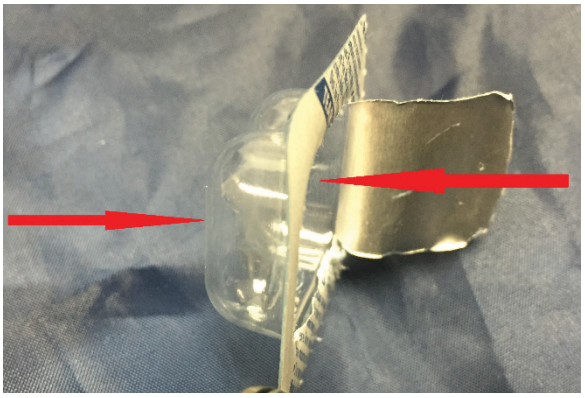
- Differences in the FTIR spectra of name brand and generic packaging in over-the-counter cold and flu medications are demonstrated. Discrepancies observed from the spectra of polymers used in blister packs illustrate how FTIR spectroscopy can aid in elucidating product quality control issues.
- The detection of pharmaceutical counterfeits by analysis of packaging material is discussed. Since high quality drug counterfeits are difficult to obtain from regulatory sources as they are connected to criminal investigations, the materials analyzed in this work are representative examples of potential compositional differences observed in the packaging between counterfeit and genuine products.
- The application of the Cary 630 FTIR system to the pharmaceutical packaging regulation, USP 661.1 is demonstrated. The USP chapter, 661.1, "Plastic Materials of Construction" [1], provides standards for characterizing plastic materials and components used to package pharmaceutical products, as well as addresses the safety and impact of interactions between packaging systems and the products they contact. The work described focuses specifically on polymer identification by FTIR spectroscopy. The USP has accepted the FTIR attenuated total reflectance (ATR) technique for active pharmaceutical ingredients (API) in USP general chapters <197> [3] and <851> [4].

Methods and Measurements

Over-the-counter cold and flu liquid cap blister packaged medications were purchased from various retailers. A total of five generic/store brand medications, and four name brand medications were purchased. One name brand medication was measured and compared to an identical product purchased five months prior. Similarly, another generic medication purchased in 2012 and again in 2016 was measured to compare for any spectral differences. The blister pack samples were measured on the inside and outside of the clear polymer blister (Figure 1A) and the white paper on the outer foil (Figure 1B).

These samples were measured using the Cary 630 FTIR spectrometer with KBr optics. Spectra consisted of 64 co-added interferograms recorded at 4 cm^{-1} resolution. The single reflection diamond ATR sample technology allows spectra to be collected with the full 4,000–400 cm^{-1} mid-infrared region.

A



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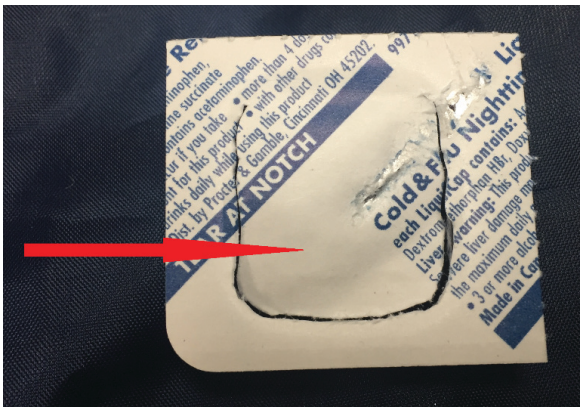

Figure 1. The blister pack areas measured from cold and flu liquid cap medications: the inside and outside of the clear polymer blister (A) and the white paper regions of the outer foil (B).

Results and Discussion

Comparison of the packaging used in a generic brand and name brand over-the-counter medicine using an Agilent Cary 630 FTIR

The clear plastic material of a blister pack is typically comprised of a bilayer (Figure 1A). The lid or foil paper (Figure 1B) is glued to the plastic blister using adhesives to seal the product in a dry stable environment. The composition of the bilayer polymers has a significant impact on the water vapor permeability of the blister pack. The degree of water vapor permeability is measured as the water-vapor transmission rate (WVTR). Rigid polyvinyl chloride (PCV) is an industry standard blister pack material that has a low WVTR, and has excellent thermoform characteristics. It was found in at least one layer in every blister pack tested. The most basic and lowest cost blister pack construction is a PVC/PVC bilayer, which was observed in one of the five generic cold medicines tested. Figure 2A shows a PVC blister polymer spectrum, and indicates ~2–3 % of a copolymer such a polyacrylate or polyvinylacetate, as determined by the presence of a weak ester carbonyl at 1,736 cm^{-1}. The concentration of this copolymer is variable from manufacturer to manufacturer (Figure 2A, maroon versus red), and could be used as a quality control check or as confirmation of genuine packaging material. Typically, generic blister packs have PVC as the outside layer and polyvinylidene chloride (PVDC, Figure 2B) as the inside layer facing the product and lidding. The layer of PVDC lowers the WVTR by a factor of 5–10 [5], but makes the blister packs more expensive to produce. One of the generic blister pack products was observed to have the PVDC coating on the outside layer, with PVC as the inside product facing layer. This was initially thought to be a possible manufacturing error. Since the product tested was manufactured in 2012, a new store branded sample was purchased from a local retailer (2016). The spectra indicated similar plastic blister composition in both the old and new samples. Any differences in the blister pack composition could easily be overlooked in a counterfeit repackaging operation, and used as evidence that a product is not genuine.

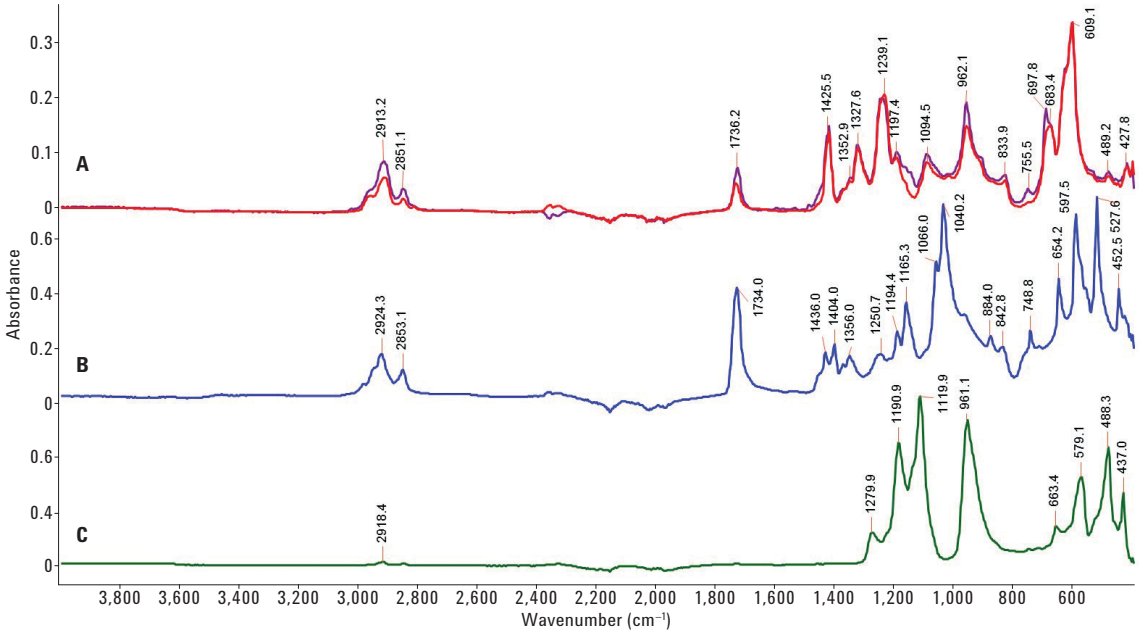

Figure 2. The stacked FTIR spectra, collected on an Agilent Cary 630 diamond ATR, of clear blister polymers from various over-the-counter cold medicines; PVC (A), PVDC (B), and PCTFE (C). The outer blister layer of generics (A, red) is overlaid with the inner layer of brand name blister polymers (A, maroon), and indicates PVC with additional SBR copolymer in the brand name material.

There was a third type of blister pack composition found in all the name brand cold medicines. Polychlorotrifluoroethylene (PCTFE, Figure 2C green spectrum) was used as the outer layer, and PVC as the inner layer. PCTFE can lower the WVTR by a factor of 15 when compared to PVC alone, but is 4–5 times more expensive than PVC/PVDC material with a comparable WVTR [6].

Another difference in the PVC composition was observed and shown in the maroon spectrum of Figure 2A. Styrene-butadiene copolymer was observed in some of the PVC layers, and was also variable in concentration between products. Styrene-butadiene copolymers are often referred to as styrene-butadiene rubber (SBR) or styrene-butadiene-styrene copolymer (SBS), and are likely added to the PVC formulation to improve the thermoforming or physical performance characteristics of the blister pack. The SBR bands in the PVC layer are easier to observe in the Figure 3 spectral overlay, with the name brand interior PVC (red) overlaid with the generic outside PVC (blue). Additional SBR absorbance bands in the red spectrum are observed at 3,026 cm^{-1}, 2,915 cm^{-1}, 2,850.5 cm^{-1}, 1,639 cm^{-1}, 1,601 cm^{-1}, 1,492 cm^{-1}, 964 cm^{-1}, 911 cm^{-1}, 755.5 cm^{-1}, and 698 cm^{-1}. The intensity of these absorbance bands is directly proportional to the concentration of SBR in the PVC, and can be measured with high precision with the MicroLab PC software on the Cary 630. Methods can be set up to measure the SBR component with green, yellow, or red thresholds to indicate the degree of difference of an unknown with warning levels as good, marginal, or critical for a QA/QC or counterfeit analysis. The ability of FTIR to detect a small amount of the SBR copolymer in the blister polymer is an example of how compounds with specific infrared signatures could be added, as an anticounterfeit measure, to the primary or secondary packaging of pharmaceutical products.

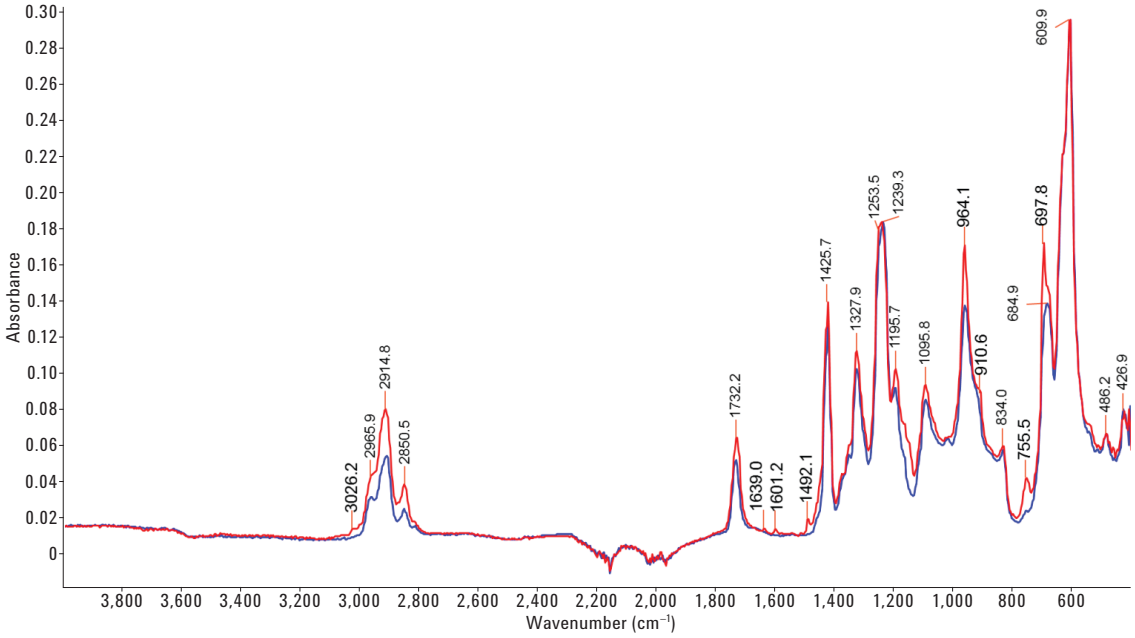

Figure 3. The FTIR spectral overlay of the PVC outer blister layer of generics (blue) overlaid with the name brand inner layer (red), indicating PVC with additional SBR copolymer in the name brand material.

One of the most powerful benefits of FTIR analysis is the ability to quickly measure multiple parts of a single sample. This allows for additional confirmation of quality on the manufacturing floor, or evidence of tampering in counterfeit applications. One example of this was the analysis of the paper backing of blister packs, shown in Figure 4. The backing of most blister packs, name brand or generic, use microcrystalline cellulose paper glued to an aluminum foil film (Figure 4, red). The IR analysis of one name brand blister pack (Figure 4, blue) indicated a polymer backing material with very high concentrations of fillers. The IR spectrum of the polymer backing material indicates a styrene-acrylate copolymer (3,060 cm^{-1}, 3,026 cm^{-1}, 1,729 cm^{-1}, and so forth) with high levels of calcium carbonate (1,420 cm^{-1} and 874 cm^{-1}) and kaolin clay (3,690 cm^{-1}, 1,026 cm^{-1}, 910 cm^{-1}, and so forth). The detection of the relatively small amount of styrene-acrylate copolymer is another indication of how small and thin IR-sensitive polymers can be to prevent counterfeit reproduction of blister packs. These obvious fingerprint-like distinctive differences in the IR spectra enable FTIR ATR spectra from different parts of the primary (that is, blister packs) and secondary (cold medicine box) packaging to be compared to known reference standards.

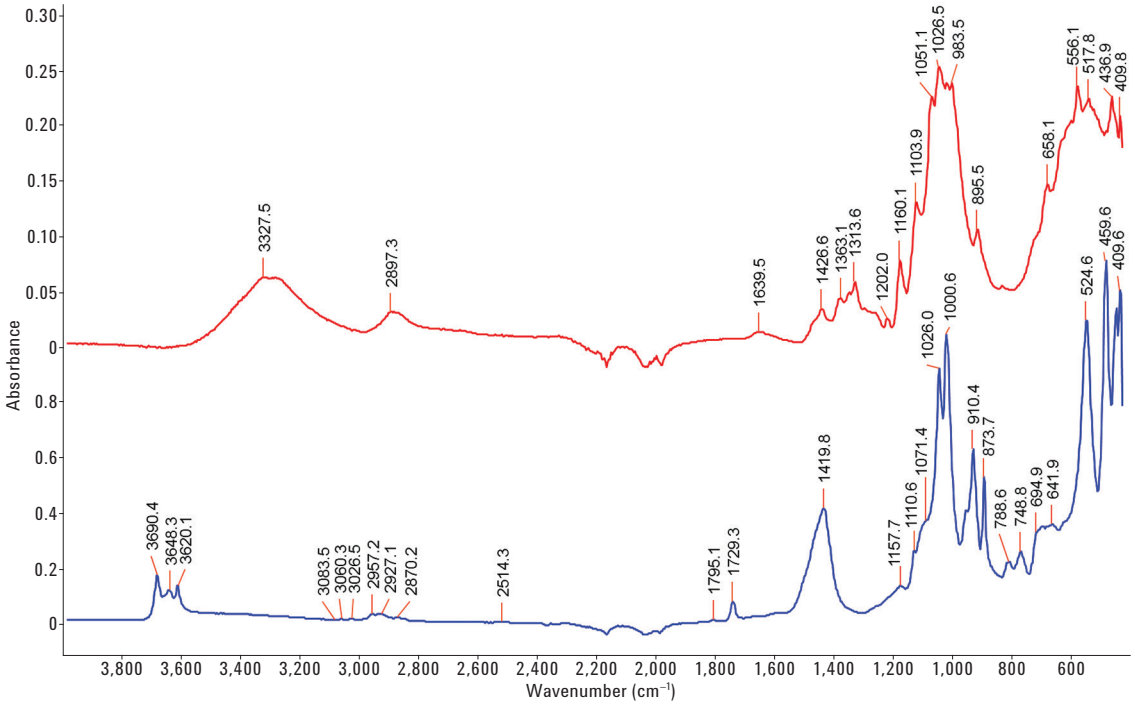

Figure 4. Overlaid FTIR spectra, collected using an Agilent Cary 630 diamond ATR, of the paper backing from cold medicine blister packs: microcrystalline cellulose (red) and styrene-acrylate copolymer (blue). Most blister packs use the microcrystalline cellulose backing (red), however, one name brand product used the styrene-acrylate copolymer material (blue), which contains very strong bands for calcium carbonate and kaolin clay.

Agilent Cary 630 FTIR and USP 661.1 compliance

USP recognizes that "the use of well-characterized materials to construct a packaging system is a primary means of ensuring that the packaging system is suited for its intended use because the properties and characteristics of the materials can be matched to the performance requirements of the packaging system" [1]. USP Chapter 661.1 prescribes methodology for characterizing packaging materials, based on:

- Base polymer identity
- Material biocompatibility (bioreactivity)
- General physicochemical properties of materials
- Additives
- Extractable metals [1,2]

USP 661.1 requires that polymers will be identified in either transmission or ATR modes [2].

USP 661.1 also lists polymers that have reference standard materials available for purchase. Material screening requires identification by infrared (IR) spectroscopy of the following base polymers: PVC, polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), polyethylene terephthalate G (PETG), polyamide (nylon), polyurethane (PUR), polyethylene vinyl acetate (PVA), acrylonitrile butadiene styrene (ABS), silicones, polytetrafluoroethylene (PTFE), polycarbonate (PC), polystyrene (PS), poly methyl methacrylate (PMMA), polysulfone (PSO), and PVDC. These standard polymers can be measured by FTIR, and compared to unknowns for identification. If the spectrum of the unknown matches the spectrum of the USP reference material and has no additional peaks, it would comply with the polymer ID test in USP 661.1.

The application of the USP 661.1 polymer identification procedure is accomplished by adding the FTIR ATR spectrum of the USP qualified standard polymer to a spectral library. The IR spectrum of the unknown polymer is then measured and searched against the USP 661.1 library. The library search method then overlays the IR spectrum of the unknown with the USP 661.1 library spectrum (Figure 5, red and blue respectively). The quality of the match is quantified with an automated algorithm that determines how well the peaks match up, with a hit quality index between 0–1. The idealized perfect match would be 1.000, however, identical polymers typically report a hit quality >0.98, as shown in Figure 5. The PVC sample measured in Figure 5 is from the interior blister polymer layer from a name brand cold medicine, and the near perfect match index of 0.996 indicates PVC + SB copolymer. Small differences, such as additives or copolymer formulations, between the test sample and the reference standard will cause the hit quality value to decrease. For example, the PVC blister pack polymer without SBR is shown as the second hit on the list, with a significantly lower hit quality index of 0.964. The PVC polymer spectrum from the Agilent polymer library is the third hit down, with a hit quality of 0.944. If a polymer, such as PCTFE or PVDC, that is not on the USP 661.1 standards list needs to be added to the IR library, then full USP 661 physicochemical and biological tests should be performed. If the polymer passes the extractable and biological tests, it can be qualified by USP as a customer reference polymer material, and the spectrum can be added to the customer's USP 661.1 reference IR library.

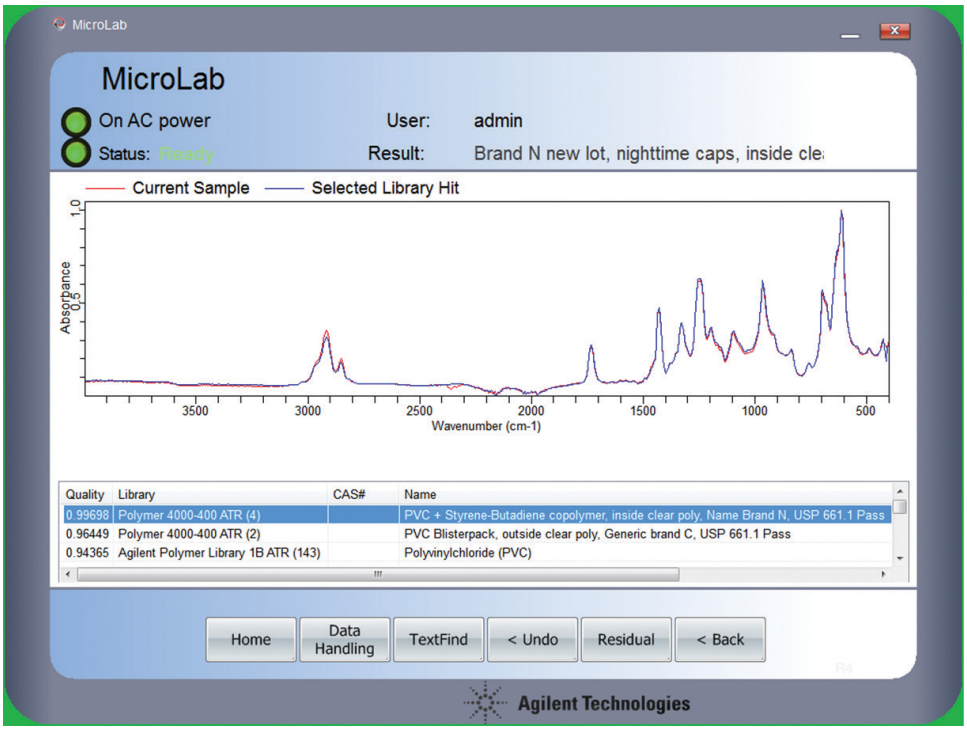

Figure 5. The FTIR ATR library search result from the Agilent Cary 630 FTIR; the current sample (red) is the example unknown blister polymer, which was searched against the library of known USP 661.1 passed polymers made from name brand and generic blisters. The top hit is a nearly perfect match to the correct library material, PVC + SBR copolymer (blue spectrum).

Conclusion

The Agilent Cary 630 FTIR equipped with a diamond ATR accessory can quickly and easily identify differences between blister pack materials from name brand and generic cold medicine products. We observed that primary packaging in name brand medicines uses a more expensive blister polymer bilayer composition compared to the standard PCV used in generic blisters. Even similar PVC materials, used in different name brand blisters, incorporate different amounts of styrene-butadiene copolymer, which can be detected and measured precisely with the Cary 630 FTIR. The paper backing of the cold medicine blister packs were compared as an example of the many other components of the primary and secondary packaging that can be measured in a test sample.

The polymer identification capability of the Cary 630, by means of the library search methods in the MicroLab PC software, was demonstrated for polymer screening as per USP 661.1. In this example, the FTIR spectrum of a polymer test sample was compared to spectra contained in a library of the reference materials described in USP 661.1. The resulting hit quality index value is an objective, quantifiable measure of how well the sample matches the reference USP polymers.

The spectral differences observed in this work are often subtle, but quite important. They can be indicative of unintentional differences in the polymer used in packaging, which in turn may result in product quality issues. They may also be indicative of a counterfeit pharmaceutical. If the packaging material is not consistent with the manufacturer's standard, then the drug may not be either. The Cary 630 FTIR demonstrates the capability and flexibility to solve counterfeit pharmaceutical, quality control, and USP 661.1 compliance issues.

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Printed in the USA
June 9, 2016
5991-6978EN

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