Application note

The Versatility of the iS50 FTIR Spectrometer: A Complete Vibrational Spectroscopy Solution

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Vibrational spectroscopy is a powerful analytical technique that is extensively used in a wide range of fields, from chemistry and materials science to biology and environmental science. The most common vibrational spectroscopy is infrared spectroscopy (IR), which can be further divided into near-infrared (NIR) spectroscopy (12,800 to 4,000 cm^{-1}), mid-infrared (mid-IR) spectroscopy (4,000 to 400 cm^{-1}), and far-infrared (far-IR) spectroscopy (400 to 10 cm^{-1}). Also included in the vibrational spectroscopy family is Raman spectroscopy, which involves the scattering of monochromatic light by molecules, resulting in energy changes that correspond to vibrational transitions. Each form of vibrational spectroscopy has its own strengths and limitations, and a brief comparison of different spectroscopy techniques is summarized in Table 1. The optimal technique to choose depends on the type of sample, the experimental conditions, and the information required. An instrument that can provide access to all these techniques on a single platform offers highly sought-after versatility that enables holistic sample analysis with improved confidence.

Information	Sampling Considerations
Mid-IR	
• Strong fundamental vibrations (stretching and bending). • Sensitivity to polar bonds and functional groups • Large number of libraries available • Information available for Identification and characterizing compounds	✓ Transmission, reflection, and ATR modes are available. ✓ Sensitive – Mid-IR can be used to analyze thin samples. × ATR is a surface technique and requires sample contact. × Transmission requires specialized windows. × Excessively thick samples can be over-absorbing.
Far-IR	
• Probes intermolecular interactions and low frequency vibrations • Limited spectral interpretation & libraries • Primarily used for analyzing the lattice dynamics and structural properties of materials, such as polymorphs, minerals, and crystalline solids	✓ Transmission, reflection, and diamond ATR are available. × ATR requires sample contact. × Limited window choices exist for far-IR. × Water vapor causes large interferences (purge is important).
Near-IR	
• Broad, overlapping combination bands and overtones • Can require chemometrics for analysis • Often used for quantitative analysis of bulk properties, such as physical characteristics, moisture content, and chemical composition	✓ Sampling through glass ✓ Greater penetration, allowing for thicker samples ✓ Good reflection data ✓ Fiber optics options × Weaker peaks (not ideal for thin samples)
FT-Raman	
• Sharp peaks based on fundamental vibrations • Sensitive to non-polar bonds (based on polarizability) • Emphasizes different structural aspects • Low-frequency peaks are standard with Raman	✓ Sampling through glass ✓ No sample preparation: just focus on the sample. × Mostly a surface technique × Small analysis spot size × Sample heating & fluorescence can be issues.

Table 1. Vibrational Spectroscopy Techniques: Information Provided and Sampling Considerations.

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The Thermo Scientific™ Nicolet™ iS50 FTIR Spectrometer provides easy access to and effortless switching between mid-IR, near-IR (NIR), far-IR, and FT-Raman in a single instrument.

- The FT-Raman module installs in the sample compartment and uses a 1,064 nm laser to produce Raman spectra. It also has a motorized stage that can be used for mapping.
- The built-in diamond ATR uses a dedicated detector with a diamond window providing access to both mid-IR and far-IR spectra.
- The near-IR module includes an integrating sphere and access to fiber optics.
- Automated switching of beamsplitters, detectors, and sources to suit different modes is possible.

In this application note, analyses of polymorphs of acetaminophen are used to illustrate the implementation of different forms of vibrational spectroscopy. Polymorphs are different crystalline forms of the same chemical compound where each polymorph has its own unique crystal structure, resulting in different vibrational modes and frequencies. Acetaminophen, a widely used antipyretic and analgesic pharmaceutical compound, has different polymorphic forms that have been studied extensively.[1] The most common and thermodynamically stable form of acetaminophen is the monoclinic Form I, a form that is commercially available and found in many solid pharmaceutical formulations. Two orthorhombic forms (II and III) are thermodynamically unstable but attainable using thermal (melts) and solution (recrystallization) methods. Figure 1 shows the different methods used in this study for producing these polymorphic forms. The various forms of acetaminophen were all verified using vibrational spectroscopy.

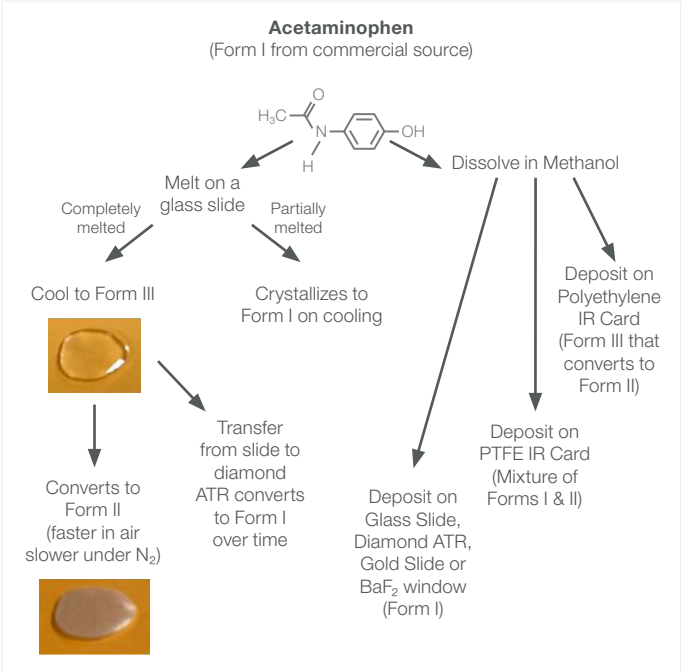

Figure 1. Routes to produce different polymorphic forms of acetaminophen.

ATR Mid-IR (4,000 – 400 cm^{-1})

Figure 2 shows the mid-IR spectra of the Forms I, II, and III of acetaminophen using the built-in diamond ATR. Form III is noticeably different from the other two. Many peaks appear broader and less defined. The differences between Form I and Form II are subtle but discernable upon close inspection, especially in the highlighted spectral regions. There is a prominent peak at 682 cm^{-1} in Form I but not in Form II. The peaks in the region 1,270-1,200 cm^{-1}, arising from C-O and/or C-N stretching; and 1,680-1,585 cm^{-1}, ascribed to the amide bonds, have distinct patterns for Forms I and II. In addition, some peaks in Form II are shifted to higher frequencies. For example, the peak at 3,162 cm^{-1} in Form I, attributed to hydrogen bonded O-H stretches, is shifted to 3,207 cm^{-1} in Form II.[2]

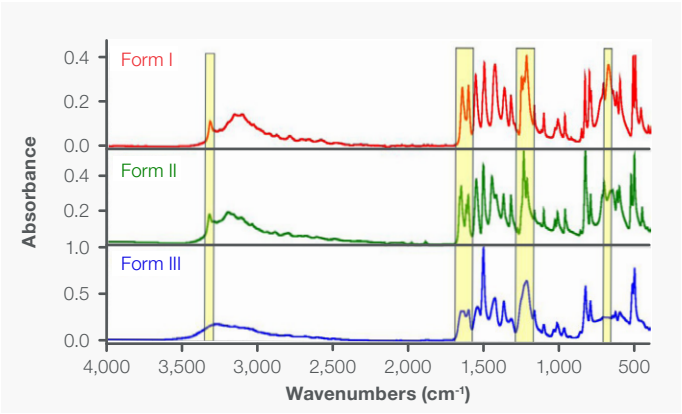

Figure 2. Mid-IR diamond ATR spectra of Forms I, II, and III. The regions highlighted in yellow show the difference between the spectra.

Transmission Mid-IR (4,000-400 cm^{-1})

Transmission mid-IR spectroscopy can also be used to analyze these polymorphs. Figure 3 shows the transmission IR spectrum obtained by depositing acetaminophen from a methanol solution on a polyethylene (PE) IR card. The PE contributions were subtracted, and the resulting spectrum was compared with the ATR spectra (Figure 2) to confirm the presence of Form II.

Interestingly, when depositing the methanol solution of acetaminophen onto a PE IR card, acetaminophen was in Form III initially, but converted to Form II over time. The conversion was complete in about 400 minutes. Figure 4 shows the peak area profiles tracking the Form III → Form II conversion using a time series. At the beginning, as shown by the spectrum at T2, acetaminophen was predominantly in Form III. Conversely, at T425, acetaminophen was almost exclusively in Form II.

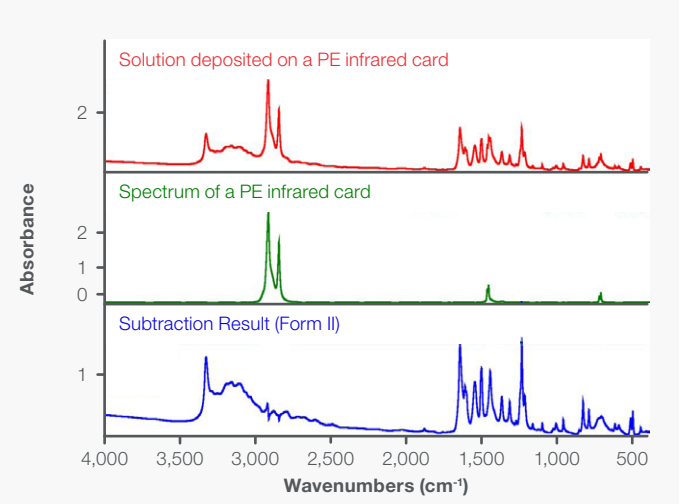

Figure 3. Mid-IR transmission spectra for a methanol solution of acetaminophen deposited on a PE IR card, a blank PE card, and the subtraction result (Form II).

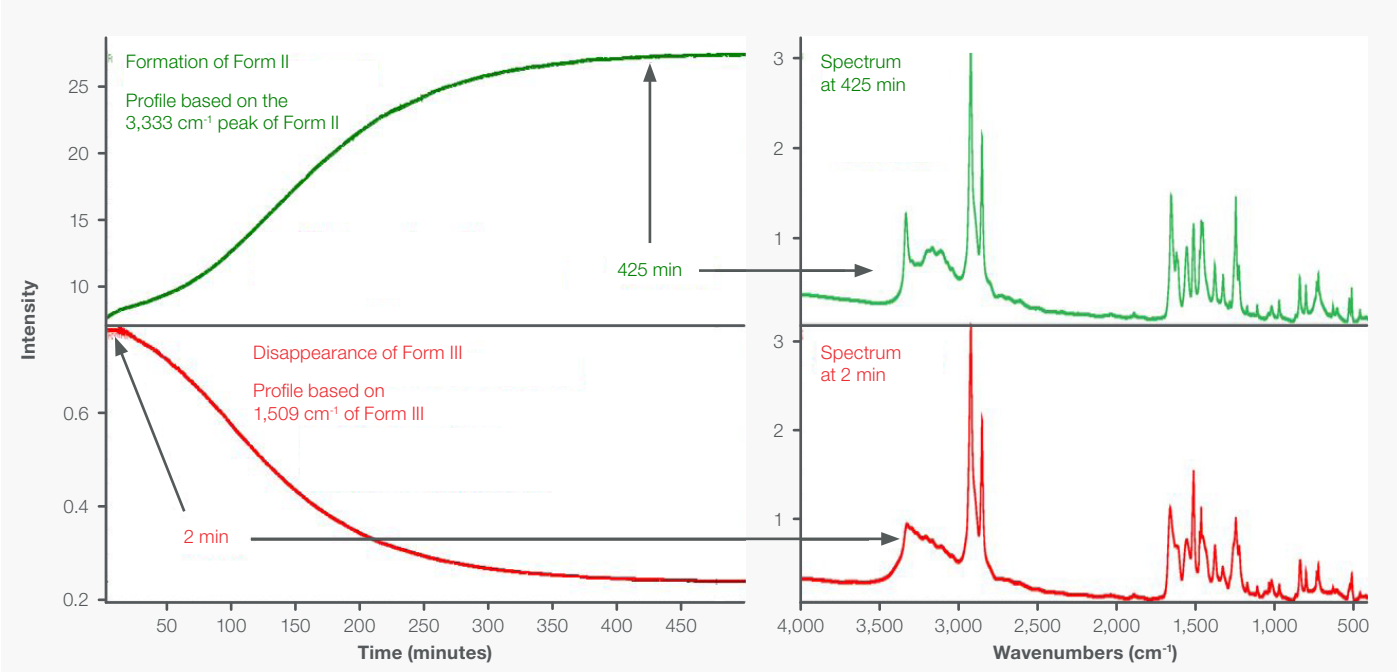

Figure 4. Times series peak area profiles showing the transformation of Form III to Form II for material deposited on a PE Card. Spectra are from 2 minutes (Form III) and 425 minutes (Form II).

Far-IR transmission (600-100 cm^{-1})

Far-IR is particularly useful in the analysis of polymorphs due to its ability to probe the lattice vibrations of molecules. Far-IR can be performed as a transmission experiment. PE is often used for supporting samples (windows, pellets), as well as detector windows, owing to its far-IR transparency. Figure 5 shows the far-IR transmission spectra of Forms I, II, and III on PE cards. The spectra differ in frequencies and relative intensities. The most conspicuous difference is that the 217 cm^{-1} peak in Form I appears at 189 cm^{-1} in Form II.[3] Form III has a peak at 225 cm^{-1}, but the overall spectrum is substantially different from Form I.

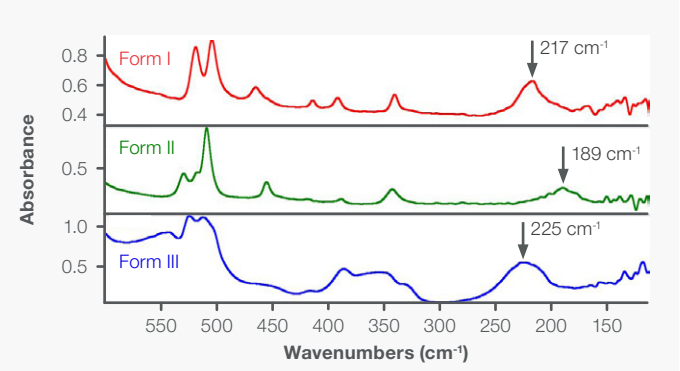

Figure 5. Far-IR transmission spectra of Forms I, II, and III of acetaminophen on PE IR cards.

Far-IR ATR (1,800-100 cm^{-1})

Transmission far-IR can be complicated by the interferences of water vapor peaks in the far-IR region. To that end, the iS50's built-in diamond ATR, along with a dedicated detector with diamond windows, offers a viable alternative. Diamond is transparent across both mid-IR and far-IR regions. Furthermore, this ATR is housed inside the instrument, so it maintains a very stable atmosphere and thereby mitigates the water vapor interference. Figure 6 shows the far-IR spectra of Forms I, II, and III using the built-in diamond ATR. The spectra include the far-IR region (400-100 cm^{-1}) and part of the mid-IR region (1,800-400 cm^{-1}) where there is no interference from the diamond.

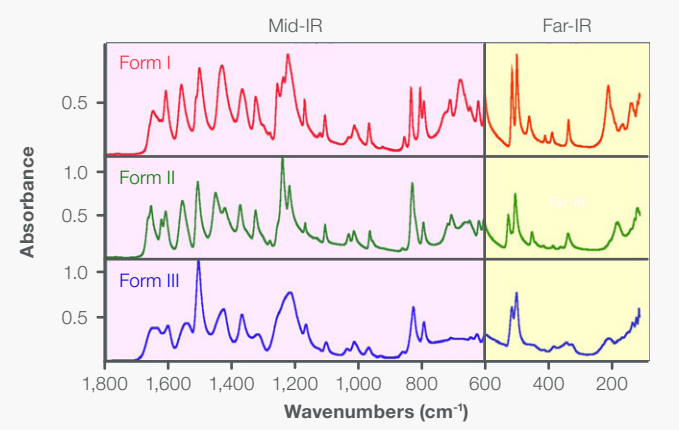

Figure 6. Far-IR diamond ATR spectra of the three polymorphic forms of acetaminophen.

NIR Transmission (10,000 - 4,000 cm^{-1})

NIR spectroscopy is based on molecular overtone and combination vibrations. It offers some unique sampling advantages, such as direct sampling through glass containers. The transmission spectra of Forms I and II (Figure 7) were collected as material melted and cooled on glass microscope slides. The glass does not interfere with NIR measurements. The areas highlighted (6,200-5,775 cm^{-1} and 5,000-4,830 cm^{-1}) are where the most distinct differences can be found. Despite the broader overlapping peaks, it is still possible to distinguish the two polymorphs. It is worth mentioning that compared to mid-IR, much thicker samples can be used for NIR transmission measurements because reduced absorption allows for greater penetration. The ability to analyze thicker samples allows for more representative sampling and improved accuracy in quantitative measurements.

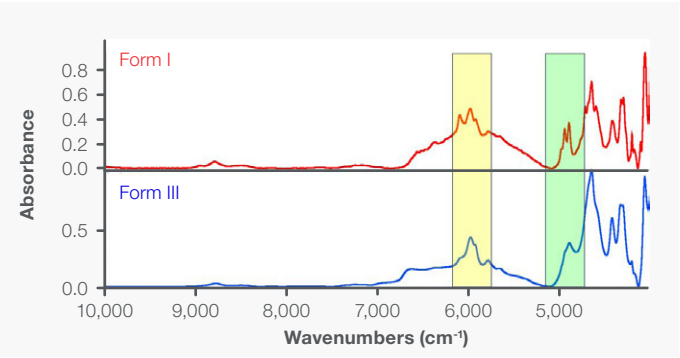

Figure 7. NIR transmission spectra of Forms I and II of acetaminophen on glass slides.

NIR Reflection (10,000 - 4,000 cm^{-1})

Figure 8 shows NIR reflection spectra collected with the NIR integrating sphere of an iS50 NIR module. The spectrum of Form I was obtained with the material in a vial. The spectra of Forms II and III were measured through the back side of the glass microscope slide that the sample was melted on. The tablet was placed directly on the integrating sphere window. The spectrum of the commercial acetaminophen tablet confirms that the acetaminophen is in Form I, indicated by the characteristic peak patterns in the highlighted regions.

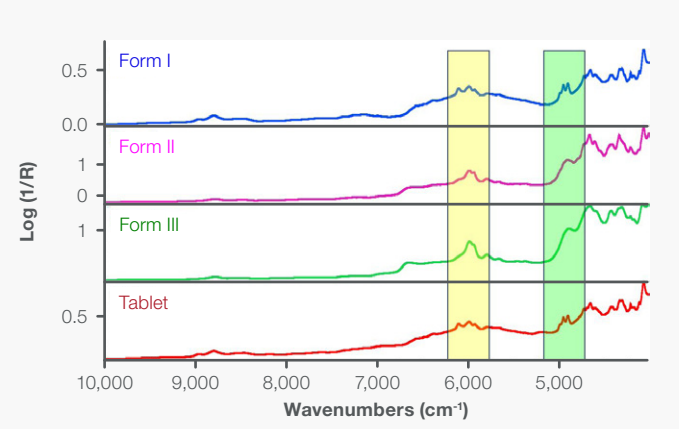

Figure 8. NIR diffuse reflection spectra of Forms I, II, and III of acetaminophen and a commercial acetaminophen tablet.

Raman (3,700-100 cm^{-1})

Raman is a different form of vibrational spectroscopy. Like mid-IR, a Raman spectrum is often comprised of sharp peaks arising from fundamental molecular vibrations. However, Raman is based on different selection rules than mid-IR and therefore it is highly complementary to mid-IR. Furthermore, Raman shares many sampling advantages of NIR, such as sampling through glass. It also provides information in the low frequency region, similar to far-IR. Raman spectra of Forms I, II and III are shown in Figure 9. There are noticeable frequency shifts and intensity differences for the peaks from the different polymorphs. The most indicative peak is the lattice phonon peak at 121.5 cm^{-1} that appears in the spectrum of Form II but not present in the other two forms. The large shoulder at the edge of the spectrum of Form I comes from a peak at 89 cm^{-1} which is just outside the spectral range of the FT-Raman module.[4] Form III does not have either of these peaks but does have a large shoulder that extends down past 50 cm^{-1}. Form III is significantly different from Form I in other parts of the spectrum so they can be easily distinguished.

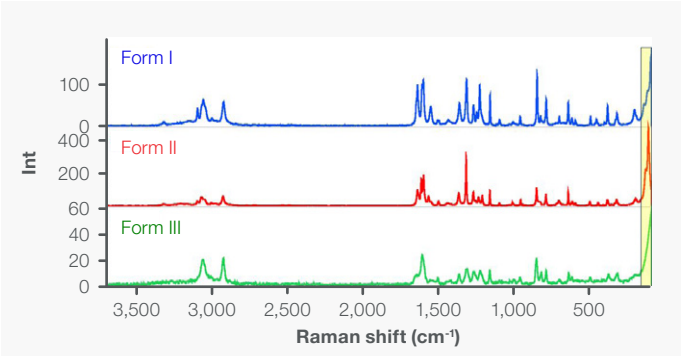

Figure 9. FT-Raman spectra of Forms I, II, and III of acetaminophen.

An FT-Raman accessory can be used to map samples. Figure 10 shows an example where five regions on a migraine tablet were mapped. The multivariate curve resolution (MCR) images show the spatial distribution of the two most abundant components in the tablet. The green regions represent acetaminophen in Form I and the blue regions represent aspirin.

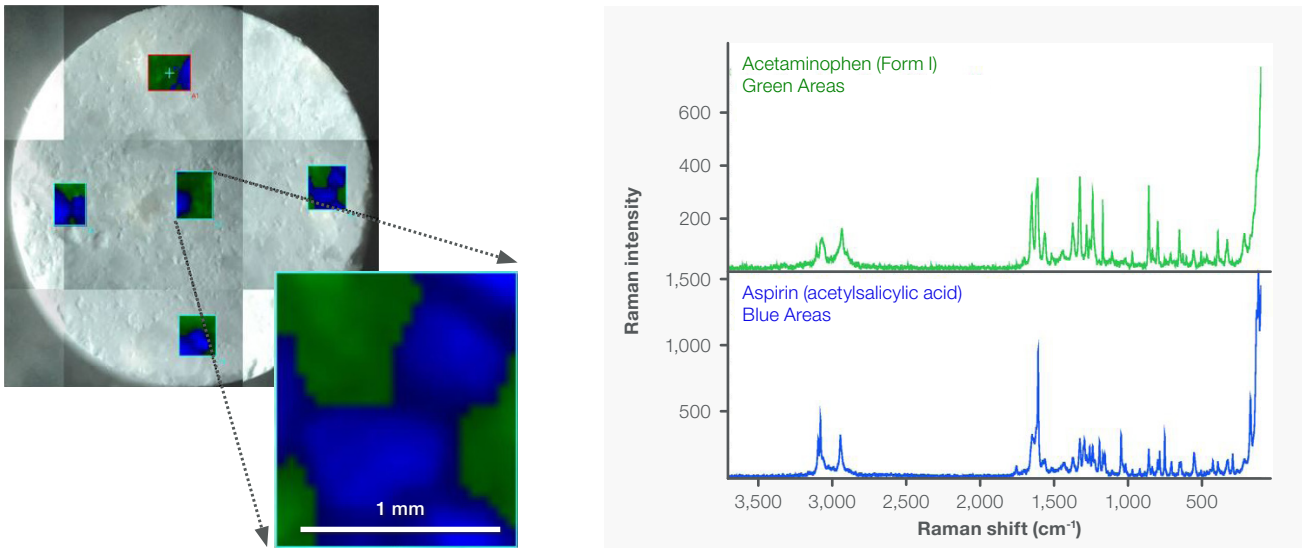

Figure 10. FT-Raman mapping of 5 regions on a commercially available migraine tablet. The MCR images show the distribution of the two largest components (acetaminophen – Form I (green) and aspirin (blue)).

Conclusions

In this application note, polymorphs of acetaminophen were analyzed via mid-IR, far-IR, NIR and Raman using an iS50 FTIR spectrometer. With each spectroscopic technique, the three polymorphs were successfully differentiated. Different vibrational spectroscopy techniques offer complementary information about molecular structures, dynamics, and interactions. By integrating multiple vibrational spectroscopy techniques, researchers can obtain a more comprehensive understanding of the materials and confirm analysis results.

The Thermo Scientific Nicolet iS50 FTIR Spectrometer accommodates mid-IR, far-IR, NIR, and Raman spectroscopy in a single platform with software selectable, automatic switching of beamsplitters, detectors and light sources to suit different modes. The system offers unrivaled versatility and flexibility that allows a synergistic approach to reveal deeper insights into the properties and behavior of a wide range of materials and compounds.

References

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